Lead Article

Microbiome and nutrition in autism spectrum disorder: current knowledge and research needs

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Autism spectrum disorder (ASD) is the fastest growing neurodevelopmental disorder in the United States. Besides genetic risks, environmental factors have been suggested to contribute to the increase in ASD diagnosis over the past decade. Several studies have reported abnormalities in microbiota composition and differences in microbial metabolites in children with ASD. Gastrointestinal discomfort is commonly reported in children with ASD. Additionally, food selectivity and picky eating patterns are commonly reported. A number of mechanisms underlying the interaction between nutrition, the gut microbiota, and ASD symptoms via the microbiota–gut–brain axis have been proposed, including immune, hormonal, or neuronal pathways. Here, the current evidence base regarding the gut environment and nutritional status of children with ASD is reviewed. Potential underlying mechanisms of the microbiota–gut–brain axis in ASD and the interplay between nutrition, microbiota, and ASD symptoms are also reviewed. Future studies investigating the microbiota in the context of dietary intake are needed to increase understanding of the interplay between diet and the gut microbiota in ASD and to identify potential dietary, probiotic, or prebiotic intervention strategies.

INTRODUCTION

Autism spectrum disorder (ASD) is typified by deficits in social communication skills and the presence of repetitive or restrictive behaviors.[1] Conditions that fall onto the spectrum of ASD include autistic disorder, pervasive developmental disorder not otherwise specified, and Asperger syndrome. Autism spectrum disorder is a clinically heterogeneous disorder, and severity of symptoms varies widely among affected individuals. Between 2000 and 2010, ASD diagnoses have doubled from 6.7 to 14.7 per 1000 children aged 8 years and under.[2] In 2010, 1 in 68 children in the United States were diagnosed with ASD,[2] and there is a continuing upward trend in the number of children being diagnosed with ASD.[2,3] The healthcare cost for a child with ASD is 6 times higher than that for a healthy child.[4]

Identifying causes for the development of ASD is difficult. Studying the ASD population is complicated by the phenotypic heterogeneity of the disease and comorbidities (eg, anxiety, hyperactivity). Genetic as well as environmental factors are suggested to play a role.[5] However, genetic factors might account for only 10% to 20% of the observed ASD cases, and the concordance rate of monozygotic twins is less than 100% (77% for male pairs and 50% for female pairs), suggesting an important contribution of environmental elements in ASD development.[6] Prenatal and perinatal environmental exposures (eg, dietary factors, maternal diabetes, stress, medications, or infections) are associated with an increased risk of ASD.[7] Proposed dietary risk factors include maternal prenatal and perinatal folate and iron status or polyunsaturated fatty acid intake.[8–10] Food selectivity, food neophobia, and "picky

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eating" are prevalent among children with ASD and can contribute to the development of nutrient deficiencies.[11] Indeed, vitamin, mineral, and fatty acid deficiencies have been observed in children with ASD, including deficiencies in vitamin D and calcium.[12] Because parents are concerned about the nutritional status of their children and side effects of traditional medication, complementary and alternative medicine is commonly used by parents of children with ASD.[13]

The microbiota–gut–brain axis has been described as a way of communication between the gut microbiota and the brain.[14] Functional and inflammatory gastrointestinal (GI) diseases show a high comorbidity (94%) with psychiatric diseases, such as depression or anxiety.[15] On the other hand, compositional differences in the gut microbiota of patients with neurodevelopmental disorders, including ASD, have been reported.[16,17] Alleviation of ASD symptoms after probiotic treatment highlights the potential of the gut microbiota to influence the behavioral consequences and, potentially, the etiology of ASD.[18] The goal of this review is to summarize the current evidence base regarding the gut environment and the nutritional status of children with ASD. Potential underlying mechanisms of the microbiota–gut–brain axis in ASD and interplay between nutrition, microbiota, and ASD symptoms will also be reviewed.

GUT ENVIRONMENT IN ASD

Gut microbiota

The word *microbiota* is defined as a collection of microbes, including bacteria, viruses, and fungi. The human GI tract is inhabited predominantly by bacterial species and contains approximately 3 million genes, or approximately 150 times as many genes as the human genome.[19] Increasing evidence supports a role of the gut microbiota and its metabolic products in host health, in part by influencing the immune system and metabolism, providing protection against pathogens and affecting neurodevelopment.[20–23] Recent findings generated from studies using germ-free rodents were fundamental in establishing the essentiality of communication between the gut microbiota and brain for normal cognitive and behavioral development. For example, germ-free mice showed reduced anxiety-like behavior and nonspatial memory, altered neurotransmitter levels in the brain, and altered hypothalamic–pituitary–adrenal (HPA) axis activity.[24–27] Especially intriguing for ASD is the influence of gut microbiota on the development of social behavior.[28,29]

Brain development extends into postnatal life, providing a window of vulnerability to external insults that could have lasting effects on cognition and behavior.[30] Because the gut microbiota develops primarily during infancy and parallel to brain development, it could play a principal role in neurodevelopment. Indeed, studies using germ-free mice showed a critical phase in the prenatal period in which the gut microbiota significantly influences neurodevelopment.[24,31] Early-life events that can alter the composition of the microbial community (eg, antibiotic use, hospitalization, formula feeding, or cesarean delivery) are associated with higher incidences for developing ASD, suggesting that early-life disturbances in the gut microbiota could contribute to the development of ASD.[32–34] No studies thus far have assessed the early microbiota composition of children at risk for developing ASD. More research is necessary to determine the correlation between early microbiota composition and the risk of developing ASD.

A number of studies have revealed that dysbioses are present once a child is diagnosed with ASD. Kang et al.[35] showed that the presence of ASD was a predictor of an overall less diverse microbiota. Several studies have shown changes in the relative abundance of Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, and Verrucomicrobia.[16,35–37] Specifically, a higher abundance of Bacteroidetes and Proteobacteria, but a lower abundance of Firmicutes and Actinobacteria, was observed in a subset of children with ASD. Additional studies have revealed differences in bacteria at the genus level, including significant reductions in the relative abundance of *Prevotella*, *Coprococcus*, *Enterococcus*, *Lactobacillus*, *Streptococcus*, *Lactococcus*, *Staphylococcus*, *Ruminococcus*, and *Bifidobacterium* species in children with ASD compared with nonaffected controls.[35,37,38] Conversely, Clostridia, *Sutterella*, and *Desulfovibrio* bacteria were found to be increased in children with ASD.[16,17,35] A higher abundance of Clostridia and *Desulfovibrio* bacteria and a lower ratio of Bacteroidetes to Firmicutes were associated with ASD severity in 2 studies.[16,39] How changes in microbial composition are related to ASD symptom onset is not well understood but may be correlated with the hormones and metabolites produced by the bacteria. Offspring of the maternal immune activation mouse model of ASD display microbial dysbiosis, suggesting that the gut microbiota could contribute to the development of ASD.[36]

Bacterial metabolites

Besides differences in the microbial composition of the gut microbiota of ASD patients, significant deviations have also been seen in the bacterial metabolites present in the feces and urine of children with ASD.

Short-chain fatty acids. Short-chain fatty acids (SCFAs), ie, acetate, propionate, and butyrate, are the end-products of microbial fermentation of carbohydrates in the colon and have been suggested to have various health benefits to the host (related to, for example, weight control, lipid profiles, and colon health).[40] The accumulation of SCFAs, however, specifically propionate, has also been shown to have broad effects on the nervous system physiology, causing developmental delay or seizures.[41] For example, in animal studies, propionate can cause neurobiological changes similar to those observed in ASD, and administration of propionate can provoke ASD-like behavior.[42–44] Elevated levels of SCFA concentrations in stool and serum of children with ASD have also been reported, and SCFA-producing bacteria, eg, Clostridia, *Desulfovibrio*, and *Bacteroides*, are increased in feces of children with ASD.[37,45,46] Thereby, translocation through the blood–brain barrier by transporters present on the blood–brain barrier or by passive diffusion could cause potential effects on the brain and lead to development of ASD symptoms.[47]

Neurotransmitters. Although most serotonin, or 5-hydroxytryptamine (5′-HT), is produced in the GI tract, it modulates neurodevelopment and might be important in social function and repetitive behavior.[48] Some bacterial species that are known to influence 5′-HT metabolism (eg, *Clostridium* species, *Lactobacillus* species) were increased in the stool of affected children. In patients with ASD, altered function and metabolism of neurotransmitters, such as 5′-HT and catecholamines, and dysfunction of the serotonergic system have been reported to contribute to symptomatology.[48–53] 5′-HT is elevated in whole blood and platelets in approximately 30% of children with ASD, making it a potential candidate as a biomarker for ASD.[50]

Gastrointestinal symptoms

In addition to abnormal microbial composition and changes in metabolites, GI distress, such as diarrhea, constipation, or abdominal pain, is prevalent among children with ASD and has been suggested to contribute to behavioral problems and to correlate with symptom severity.[39,46,54–58] In a prevalence study with over 14 000 individuals, a significant difference in the occurrence of bowel disorders was observed between children with ASD and nonaffected children.[59] High-risk infants (infants with siblings diagnosed with ASD) showed a greater prevalence of GI symptoms, and children with ASD were more likely to report GI symptoms (eg, constipation, food allergy/intolerance, diarrhea) in the first 3 years of life.[60,61] Likewise, maternal immune activation offspring displayed GI symptoms similar to symptoms observed in human ASD.[36]

Determining an exact prevalence of GI disorders in the ASD population is challenging because of social communication difficulties in individuals with ASD and discrepancies in interpreting GI problems.[62] The link between GI dysfunction and ASD symptoms is not well understood, but it is hypothesized to include intestinal inflammation, mitochondrial dysfunction, and microbial dysbiosis. Mitochondrial dysfunction (eg, dysfunction of mitochondrial enzymes or carriers) is prevalent in the ASD population, and many mitochondrial diseases are associated with GI disorders.[63,64] Frye et al.[64] also hypothesized that microbial dysbiosis could induce mitochondrial dysfunction and GI symptoms. For example, propionate, a product of microbial fermentation, is known to influence mitochondrial metabolism, and abnormalities in mitochondrial metabolism were observed in a propionate rodent model of ASD.[64]

Additionally, in children with ASD and comorbid GI symptoms, reduced messenger RNA expression of carbohydrate digestive enzymes (sucrase isomaltase and maltase glucoamylase) and hexose transporters (sodium-linked glucose transporter 1 [SGLT1] and glucose transporter 2 [GLUT2]), which can cause carbohydrate maldigestion and malabsorption, is also associated with an increased abundance of Bacteroidetes, Firmicutes, and Betaproteobacteria in the mucoepithelium.[65] The resulting accumulation of nondigested carbohydrates in the intestine, in turn, could lead to intestinal inflammation and potentially contribute to ASD behavioral problems.[65] Although changes in the intestinal microbiota are suggested to contribute to the development of GI disorders in individuals without ASD,[66] Gondalia et al.[67] found no differences in microbiota composition between ASD children with GI dysfunction and those without GI dysfunction.

In summary, more studies are needed to unequivocally establish a role of the GI tract in the development of ASD. Although not observed consistently, the potentially decreased risk of developing ASD associated with breastfeeding is especially intriguing, given that the fecal microbiota of breastfed infants differs from that of formula-fed infants.[34] Longitudinal studies investigating GI disorders and the microbiota in at-risk children before the onset of ASD symptoms are warranted to elucidate whether microbial dysbioses could be classified as a risk factor for developing ASD.

NUTRITION AND ASD

Achieving adequate nutritional intake presents a considerable challenge in children with ASD, owing to GI symptoms, food allergies, metabolic abnormalities, or

problematic eating behaviors. Approximately 90% of children with ASD experience some sort of feeding-related concern.[68] Children with ASD are more likely to present with food allergies, and parental reports of allergies include milk/dairy, nuts, and fruits.[69,70] Picky eating, food refusal, and food selectivity are commonly reported problematic eating behaviors in children with ASD, and food selectivity was associated with higher rates of ASD symptoms.[71] Food selectivity is usually based on color, shape, texture, or temperature of the food.[11] A strong preference for starches, snacks, and processed foods, along with a rejection of fruits, vegetables, or protein, is most common in children with ASD.[72,73] Increased consumption of snack foods and calorie-dense foods can lead to excessive weight gain, and research suggests higher rates of obesity in children with ASD than in unaffected children.[74] Obesity-related complications (eg, hypertension, diabetes) are also more prevalent among adults with ASD.[75]

Parents have reported food refusal and difficulty introducing new foods as common problems and have expressed concerns about little or no fruit or vegetable intake.[76] Comparing fruit and vegetable intake of children with ASD with that of healthy controls showed that daily servings of fruits and vegetables were significantly lower in children with ASD.[77] Because of feeding difficulties, parents are concerned about the nutritional status of their children and often use nutritional supplements to compensate for the believed inadequate intake.[78] The most commonly used supplements among the ASD population are multivitamin/mineral supplements,[79] yet most such supplements do not provide adequate amounts of the micronutrients most typically deficient in children with ASD (eg, choline, potassium).[79]

Although dietary problems are commonly observed in children with ASD, data on the extent and types of nutrient deficiencies are inconclusive. Biochemical and dietary assessment have both been used to assess nutrient adequacies and inadequacies in children with ASD. Vitamin, mineral, and fatty acids deficiencies are most commonly observed. Decreased concentrations in whole blood, serum, or plasma levels were found for pantothenic acid, folate, biotin, vitamin B_{12}, vitamin D, and vitamin E.[12] Circulating concentrations of calcium, magnesium, iodine, iron, chromium, and selenium were also lower in children with ASD than in nonaffected controls.[12] Concentrations of plasma n-3 fatty acids (docosahexaenoic acid, arachidonic acid) are lower in children with ASD, whereas plasma n-6 fatty acid concentrations were reported to be higher, suggesting a potentially more proinflammatory state in children with ASD.[12]

Diet has been suggested as a therapeutic measure for ASD symptoms, and one-third of children have been treated with some dietary intervention at time of ASD diagnosis.[80,81] A number of nutrition intervention strategies, including gluten-free/casein-free diets, ketogenic diets, or supplementation with n-3 fatty acids, minerals, or multivitamins, have been explored to treat behavioral symptoms and comorbid GI distress. Some diets (eg, gluten-free/casein-free diet, antioxidant diet, or ketogenic diets) have resulted in an alleviation of symptoms associated with ASD, whereas others resulted in no behavioral differences compared with control diets or even led to insufficient or excessive nutrient intake in response to interventions.[78,81–83]

Some improvements have been observed with other dietary interventions, including FODMAP (fermentable oligo-di-mono-saccharides and polyols) diet, elimination diets, avoidance of food coloring/food additives, or specific carbohydrate diet, but the evidence to support specialty diets as a therapeutic measurement is inconclusive.[74] An expert panel has set guidelines for the nutritional management of GI symptoms in children with ASD.[74] Specific considerations are required when working with children with ASD because of the high prevalence of food selectivity and general feeding problems. For example, if a child suffers from constipation, the types of fruits, vegetables, and whole grains that the child will accept in the diet need to be evaluated.[74] In-depth dietary assessment and individualized dietary recommendations by a trained dietitian are warranted for appropriate interventions. More research is needed to make general recommendations about diet as a therapeutic remedy for ASD.

PRE- AND PROBIOTICS AND ASD

Animal studies provide evidence that pro- and prebiotics can influence the serotonergic system, and *Lactobacillus* and *Bifidobacterium* administration has been shown to reduce intestinal permeability.[84–87] On the basis of health benefits commonly reported with pro- and prebiotics intake and new data suggesting a role of the microbiota in ASD etiology, some clinical studies have explored the effect of probiotic supplementation on ASD symptoms (Table 1). Some improvement in symptoms as well as in microbial and metabolite imbalances were observed in children with ASD and in animal models after probiotic treatment.[36,39,88–90] For example, West et al.[90] showed that 6 months of supplementation with a probiotic mixture containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus delbrueckii*, *Bifidobacterium longum*, *and Bifidobacterium bifidum* decreased the severity of GI and ASD symptoms. Similarly, supplementation with *Lactobacillus acidophilus* (strain Rosell-11) led to decreased concentrations of the bacterial metabolite D-arabinitol.[89] D-arabinitol is a metabolite of *Candida* species. However, microbiota changes were not analyzed after probiotic supplementation, making it difficult to draw

Table 1 **Studies investigating the effectiveness of probiotic supplementation on the symptomatology of autism spectrum disorder (ASD)**

Reference	Cohort population	Probiotic strain studied	Dose used	Key findings	Dietary information	Limitations
Human studies						
Sandler et al. (2000)[88]	11 ASD subjects (10 boys, 1 girl); age 3.5–7 y; regressive-onset autism	*Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Bifidobacterium bifidum*	Vancomycin 500 mg/d for 8 wk, followed by probiotics 40×10^9 CFU/mL/d for 4 wk	Short-term improvement in communication and behavior; no long-term improvement after discontinuation of vancomycin treatment; absence of *Peptostreptococcus* species and other anaerobic cocci in feces of children with ASD	No dietary information collected	Poor compliance with probiotic treatment. No control subjects (microbiota was compared with adult microbiota)
Kałużna-Czaplińska & Błaszczyk (2012)[89]	22 ASD subjects (2 females, 20 males); age 4–10 y; severe GI symptoms	*L acidophilus* (strain Rosell-11)	5×10^9 CFU/g, 2 times/d for 2 mo	Probiotic supplementation decreased D-arabinitol concentration and ratio of D-arabinitol to L-arabinitol in urine	ASD subjects were on sugar-free diet and consumed either a varied or a restricted diet. Other dietary supplements were used (magnesium, cod liver oil, vitamins B_2, B_6)	Microbiome composition was not analyzed. No control subjects
West et al. (2013)[90]	33 ASD subjects; age 3–16 y	Delpro (*L acidophilus, Lactobacillus casei*, *Lactobacillus delbrueckii*, *Bifidobacterium longum*, *B bifidum*); formulated with immunomodulator Del-Immune V (*Lactobacillus rhamnosus* V lysate)	1×10^{10} CFU, 3 times/d for 6 mo	Decreased severity of ASD symptoms; improvement of GI symptoms	Lack of information on diet	Microbiota composition was not analyzed. No control subjects
Tomova et al. (2015)[39]	10 ASD subjects (9 boys, 1 girl; 2–9 y) vs 9 non-ASD siblings (7 boys, 2 girls; 5–17 y) vs 10 non-ASD controls (10 boys; 2–11 y)	"Children Dophilus"; 3 species of *Lactobacillus* (60%), 2 species of *Bifidobacterium* (25%), 1 strain of *Streptococcus* (15%);	1 capsule 3 times/d for 4 mo; dose per capsule not indicated	GI dysfunction was higher in ASD children and siblings compared with controls at baseline; strong positive correlation between GI symptoms and ASD severity; increased ratio of Bacteroidetes to Firmicutes after probiotic supplement; decreased Firmicutes abundance after probiotic treatment; decreased *Bifidobacterium* and	Lack of information on dietary habits	Lack of information on exact dose of probiotic species. Only ASD group received probiotic treatment. Changes in ASD symptoms after probiotic treatment were not reported

(continued)

Table 1 **Continued**

Reference	Cohort population	Probiotic strain studied	Dose used	Key findings	Dietary information	Limitations
				Desulfovibrio counts after probiotic treatment; children with more severe ASD had higher Clostridia and *Desulfovibrio* counts and lower Bacteroidetes/Firmicutes ratios; correlation between TNF-α levels and GI symptoms and trend toward correlation between TNF-α and ASD severity; probiotic supplementation decreased TNF-α levels		
Russo (2015)[91]	49 ASD subjects (39 males, 10 females, mean age 11.4 y; 17 diagnosed with GI disease; 36 receiving probiotic therapy) and 36 neurotypical control subjects (29 males, 7 females, mean age 10.2 y)	No information provided	No information provided	Children with ASD taking probiotic therapy had decreased plasma myeloperoxidase and decreased plasma copper but not decreased plasma zinc	Dietary information was not collected	Microbiome was not analyzed. No information on which probiotic was used by subjects. Controls were not assessed for GI disease
Animal studies						
Hsiao et al. (2013)[36]	Maternal immune activation in mouse model of ASD	*Bacteroides fragilis* (ATCC 9343)	1×10^{10} CFU, every other day for 6 d at weaning	Corrected GI barrier integrity; corrected alterations in tight junctions and cytokine expression; corrected relative abundance of specific groups of microbes in Lachnospiraceae family and in unclassified Bacteriodales; amelioration of maternal immune activation–associated dysbiosis; amelioration of ASD-like behaviors (improvements in communicative, repetitive, anxiety-like, and sensorimotor behavior but not sociability or social preference)		

Abbreviations: CFU, colony-forming units; GI, gastrointestinal.

definite conclusions from the study.[89] Antibiotic treatment in combination with probiotic supplementation also improved some ASD symptoms in a subset of affected children.[91] Because of significant differences in the dose and intervention length between these studies, it is difficult to provide firm recommendations on the amount and kind of probiotic to use. In addition, no dietary information was collected, and not all groups analyzed microbiota changes after the probiotic treatment or included a control cohort. Tomova et al.[39] showed a normalization of microbiota after supplementation with a probiotic mixture containing *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* species. However, no reports on improvement of ASD symptoms after probiotic therapy were provided. Despite the evidence provided by these preliminary studies, it still not known if probiotic supplementation is efficacious in the management of ASD symptoms. Nevertheless, the use of probiotics in the management of ASD symptoms is highly discussed in the literature and, according to a physician survey, is recommended by one-fifth of physicians for treatment of ASD symptoms.[18,92,93]

MECHANISMS AND PATHWAYS OF GUT–MICROBIOME–BRAIN COMMUNICATION IN ASD

Emerging evidence suggests that the gut microbiota plays a critical role in ASD, but research on the routes of the communication between the gut and brain is limited. In general, proposed mechanisms of the microbiota–gut–brain axis include neural, hormonal, immune, and metabolic pathways. Neuroimmune pathways have been suggested to contribute to ASD symptomatology via the gut–brain axis.[62] De Theije et al.[62] proposed that ASD-associated cytokines originating from an inflamed GI tract can cross the blood–brain barrier and elicit an immune response in the brain, thereby influencing behavior. In a mouse model of psychosocial stress, immunization with the bacterium *Mycobacterium vaccae* promoted better coping in a social stress environment, potentially through activation of regulatory T cells.[94] Because the microbiota has been shown to be involved in the regulation and development of the immune system, altered gut microbiota associated with GI inflammation might not only contribute to GI disturbances in children with ASD but also influence behavioral problems through translocation of immune cells into the circulation.[20,95]

Animal models provided initial evidence for the ability of the gut microbiota to influence cognition and neurochemistry.[24–26] Additionally, behavioral changes observed in human subjects after probiotic supplementation suggest that the microbiota can influence neurological functions and neurochemistry in humans.[96,97] For example, Tillisch et al.[96] showed that a 4-week administration of 125 g of a fermented milk product containing *Bifidobacterium animalis* subsp *lactis* CNCM I-2494, *Streptococcus thermophilus* CNCM I-1630, *Lactobacillus bulgaricus* CNCM I-1632 and I-1519, and *Lactobacillus lactis* subsp *lactis* CNCM I-1631 to healthy women affected activity of brain regions that control processing of emotions and sensation. Additionally, consumption of 1.5 g of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 per day by healthy men and women alleviated general signs of anxiety and depression.[97]

The gut microbiota can influence brain development and cognitive function directly by modulating the permeability of the blood–brain barrier and affecting neurochemical concentrations (eg, brain-derived neurotrophic factor and 5′-HT).[98,99] On the other hand, the gut microbiota can use undigested food in the distal colon, such as indigestible carbohydrates and proteins, as an energy source and, in turn, release biologically active metabolites and precursors that can be transported by the blood or lymphatic system and act at distal sites such as the brain. Neural signals from the GI tract to the brain can be transmitted via the vagus nerve, the dorsal ganglia root, or somatosensory afferents.[100] Evidence for vagal-mediated signaling from the gut microbiota to the brain comes from studies in which behavioral and neurochemical changes induced by some bacterial species (eg, *Lactobacillus rhamnosus, Bifidobacterium longum*) were abolished in vagotomized animals.[101,102] Two potential mechanisms for the effect of neuroactive bacteria on behavior and neurochemistry were proposed. First, vagal chemoreceptors that are innervating mucosal villi could be activated by bacterial metabolites, such as SCFAs or 5′-HT, that can be transported across the epithelial barrier.[103] Second, vagal mechanoreceptors (ie, intramuscular arrays and intraganglionic laminar endings) could sense intestinal motility changes induced by some beneficial bacteria.[103] Although to date little is known about the effect of the microbiota on hormones involved in gut–brain communication, it seems plausible that the gut microbiota can modulate hormonal signaling in the gut–brain axis. The release of gut hormones and neuropeptides from enteroendocrine cells can be regulated by the gut microbiota, and gut hormones were proposed to influence cognitive processes.[104–107] For example, the release of peptide YY, which shows anxiolytic effects in rats, from intestinal L cells is stimulated by SCFAs.[107,108] On the other hand, accumulating evidence supports the role of microbially produced neurotransmitters (eg, 5′-HT, brain-derived neurotrophic factor) in the gut–brain communication.[24,109] In an animal model of ASD, specific bacterial metabolites (4-ethylphenylsulfate) caused ASD-related behaviors, suggesting that bacterial

metabolites could be a pathway of communication between the gut microbiota and brain in ASD.[36,37,110,111] Of specific interest with regard to microbiota-to-brain communication in ASD are serotonin, SCFAs, and the HPA axis, which are examined below.

Serotonin

Genetic, GI, or immune changes have been proposed as potential contributing factors to the hyperserotonemia observed in children with ASD[112–114]; however, not all cases of hyperserotonemia in children with ASD can be explained by genetic variations. Interestingly, administration of *Bacteroides fragilis* normalized plasma levels of 5′-HT in an animal model of ASD, and a recent report found that higher whole-blood 5′-HT levels were correlated with more GI symptoms.[115,116] Likewise, changes in serotonergic signaling were proposed to contribute to altered anxiety-like behavior in germ-free mice, and ingestion of *Bifidobacterium infantis* by conventional rats resulted in changes of 5′-HT metabolism in the brain stem and increased total plasma tryptophan levels.[24,117] These data indicate that the gut microbiota could be involved in higher 5′-HT production, thus identifying 5′-HT as a potential pathway through which the gut microbiota and brain communicate in ASD. Clinical and preclinical studies have shown that the gut microbiota can influence peripheral and central tryptophan and 5′-HT levels, which have the potential to regulate mood and cognition.[118] In ASD, abnormal intestinal permeability could allow 5′-HT to translocate into the systemic circulation, leading to elevated levels of blood 5′-HT.[50,119–121] In addition, 5′-HT cannot cross the blood–brain barrier and thus must be produced in serotonergic neurons from tryptophan. Increased 5′-HT production by some species of the gut microbiota in ASD could deplete peripheral tryptophan availability. This corresponds to data showing decreased capacity for 5′-HT synthesis in children with ASD as well as to reports showing a worsening in repetitive behaviors in individuals with ASD after tryptophan depletion.[122,123] Lastly, higher levels of 5′-HT in children with ASD can be linked to intestinal inflammation, often observed in children with ASD. 5′HT has been described to play an important role in intestinal inflammatory responses.[124] Although the cause-and-effect relationship between dysbiosis and intestinal inflammation is not yet fully understood, intestinal inflammation is associated with alterations in the gut microbiota.[125] Thus, it can be proposed that the intestinal inflammatory response in children with ASD, which is exacerbated by the gut microbiota, can lead to a further increase in 5′-HT levels and, ultimately, to upstream behavioral effects on the brain.

Short-chain fatty acids

Another potential mechanism linking the gut microbiota to behavior in ASD is via SCFAs, most notably propionate. Because SCFAs can cross the blood–brain barrier and modulate neurotransmission and behavior, they have been proposed to be neurotoxic.[126,127] Elevated levels of propionate in the brain were correlated with decreased concentrations of linoleic acid, linolenic acid, arachidonic acid, and docosahexaenoic acid.[128] Altered brain phospholipids and acylcarnitine profiles were observed in rodents infused intracranially with propionate.[129] Individuals with impaired propionate metabolism also displayed neurodevelopmental abnormalities similar to symptoms of ASD.[130,131] The precise mechanisms of how SCFAs alter behavior in ASD are unknown, but effects on mitochondrial function (eg, Krebs cycle) or epigenetic alterations may be involved.[132] In addition to direct effects on the brain, propionate has been shown to modulate 5′-HT secretion in the gut and deplete 5′-HT and dopamine levels in the brain, which could potentially contribute to the hyperserotonemia observed in children with ASD.[129,132,133]

HPA axis

The HPA axis, a major integrative system for stress adaptation, was found to be another key pathway in the microbiota–brain communication. In a landmark study, Sudo et al.[99] identified the crucial role of the microbiota in the normal development of the HPA axis during the early postnatal period. Since then, studies have shown that commensal bacteria are capable of regulating HPA axis activity.[27,100,134] Whether the gut microbiota is involved in regulating the HPA axis in the ASD population remains to be determined, but increased activity of the HPA axis in this population has been observed.[135] Likewise, cortisol, the end product of HPA axis activation, was significantly higher in a subgroup of children with ASD compared with controls.[136]

NUTRITION, MICROBIOTA, AND ASD – WHAT IS THE CONNECTION?

Diet is a major environmental factor regulating the establishment, maturation, and maintenance of gut microbiota diversity and abundance.[56,137–139] Although nutrition plays a key role in shaping the gut microbiota and nutrition interventions are commonly used to treat some symptoms of ASD, the available published studies lack a systematic investigation of the effect of dietary habits of children with ASD on the composition of the gut microbiota (Table 2). Only Son et al.[140] collected

Table 2 **Dietary information provided in human studies investigating the microbiota composition in children with autism spectrum disorder**

Publication	Dietary information provided
Horvath et al. (1999)[58]	GF/CF diet
Finegold et al. (2002)[141]	Many patients on a GF/CF diet
Parracho et al. (2005)[17]	Varied or restricted (GF/CF) diet
Wang et al. (2011)[38]	GF/CF diet, probiotics, antibiotics
Adams et al. (2011)[46]	Probiotic use, seafood and fish oil consumption
Kang et al. (2013)[35]	Information on special diets (eg, GF/CF, nutritional supplements, probiotics, seafood)
Son et al. (2015)[140]	Dietary information collected for 7 d prior to collection of stool samples; total kilocalories, protein, carbohydrate, fat, fiber, and sugar analyzed

Abbreviations: GF/CF, gluten-free, casein-free.

dietary information and analyzed the macronutrient content of the diet. However, short- as well as long-term dietary changes can alter the microbial community substantially, and children with ASD are often picky eaters, which can have a fundamental effect on the gut microbiota.[139,141,142] Thus, it is important to understand how diet modulates the microbiota in the ASD population.

An interrelationship between dietary intake, neurodevelopment, and cognitive function has been demonstrated in healthy children, and most results are attributed to the direct effect of dietary components on the central nervous system.[143,144] In ASD, it has been suggested that the gut–brain axis plays a substantial role in symptomatology.[145] The effect of microbial changes through dietary modification on cognitive processes is not well described. In malnourished individuals, it has been hypothesized that the microbiota is causally related to neurological abnormalities.[146] A few animal models have shown that diet-induced changes in gut microbiota could contribute to observed behavioral changes.[147,148] Thereby, the interaction between diet and behavior could be due to altered metabolism of dietary components and changes in metabolic products as well as direct interaction of the gut microbiota with enteric neurons.[149,150] In ASD, the gut microbiota might provide a potential link between diet and the symptoms of ASD. First, dietary interventions and probiotic supplementation alleviated some ASD symptoms and normalized some systemic bacterial metabolites in an animal model of ASD. Second, SCFAs that are altered in children with ASD and can elicit ASD-like behavior in animal models are a major product of bacterial carbohydrate fermentation. Fiber (eg, inulin, pectin) present in fruits and vegetables, which is usually low in the diet of children with ASD, decreased propionate production in vitro.[151] Thus, the substrate available could drive microbial activity in ASD. Lastly, the gut microbiota is capable of both producing 5′-HT from the amino acid tryptophan and regulating the availability of dietary tryptophan. The potential relationship between dietary intake, microbiota composition, and ASD symptomatology is summarized in Figure 1.

Including diet history and detailed diet diaries to clarify the relationship between dietary patterns and gut microbiota is important when investigating the correlation between nutrient intake and changes in the microbiota. Because the diet of children with ASD is often characterized by a lack of variety, an inadequate amount of fiber-containing foods, and an increased amount of sugar-containing foods, investigating a relationship between diet and microbial dysbiosis could lead to new potential pre- or probiotic interventions to alleviate symptoms.

The mechanisms underlying the microbiota–gut–brain communication in ASD are complex and are likely to involve more than one mechanism. An interaction between neural, hormonal, and metabolic pathways seems probable. Future research delineating the contribution of each pathway will provide a better understanding of the microbiota–gut–brain communication and may identify new therapeutic interventions for neurological diseases such as ASD. Thereby, the use of germ-free and gnotobiotic animal models will be of fundamental importance. The use of gnotobiotic rodent models has led to significant processes in defining how the gut microbiota regulates body processes, including gut-to-brain communication. However, rodent models are limited by several important physiological and metabolic differences from humans. Therefore, the piglet is the preferred model for studying human-related host–microbe interactions, owing to its similarity to humans in anatomy and physiology.[153,154]

EVIDENCE FOR INVOLVEMENT OF THE GUT MICROBIOTA IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by persistent patterns of inattention and/or hyperactivity-impulsivity. Several genetic and environmental risk

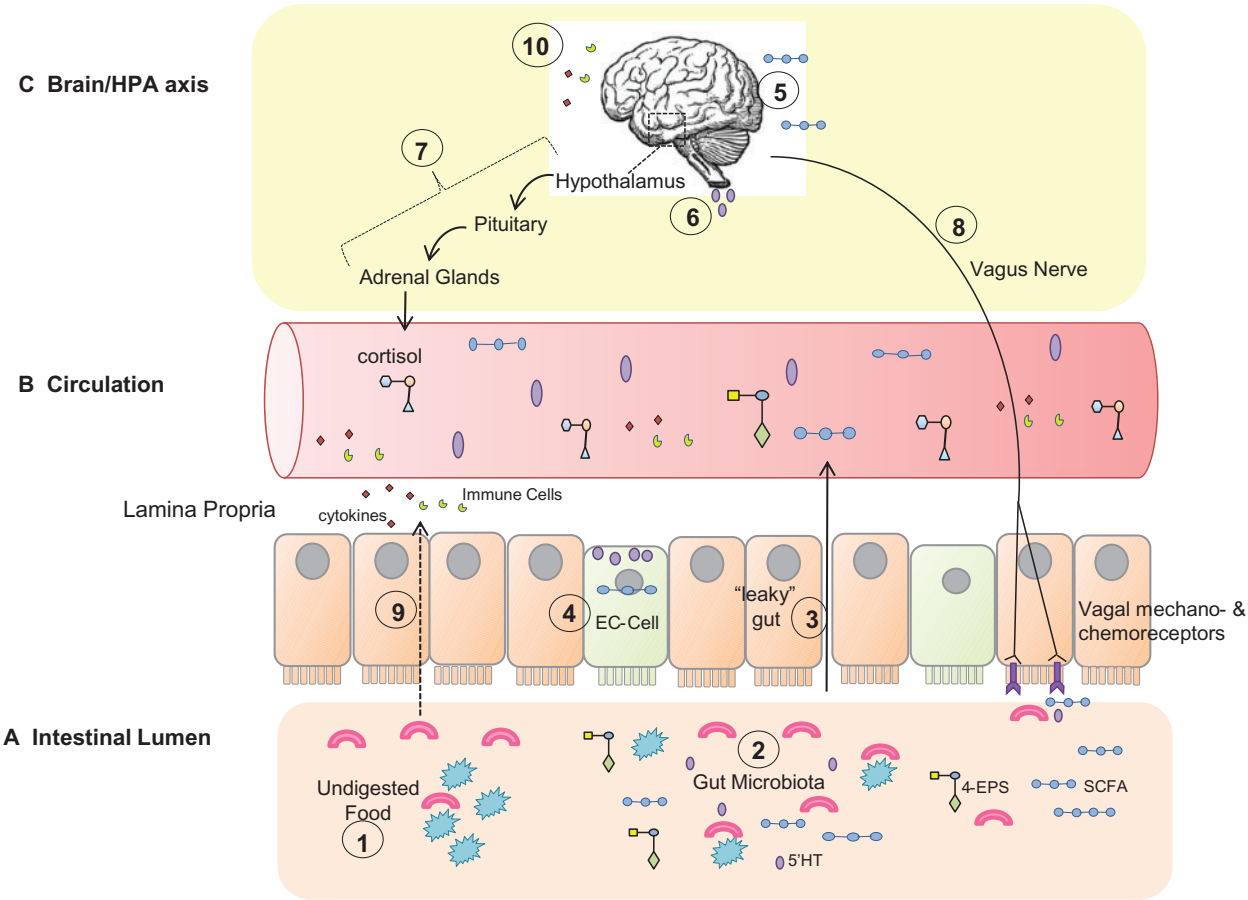

Figure 1 **Nutrition and the microbiota–gut–brain axis in the etiology of autism spectrum disorder (ASD).** Several possible pathways of the microbiota–brain interaction in ASD can be proposed. (1) Food that escapes digestion by the host can be used by the gut microbiota as energy sources. In turn, bacterial metabolites (eg, SCFAs, 5′-HT) that can be used for physiological functions by the host are produced. (2) Bacterial metabolites with relevance to ASD symptomatology include 5′-HT and SCFAs. 5′-HT is produced by certain *Lactobacillus*, *Streptococcus*, and *Lactococcus* species.[152] Microbial genera that occur more frequently in children with ASD include propionate producers, such as Clostridia, Bacteroidetes, and *Desulfovibrio* species.[16,17] Increased 5′-HT production by the microbiota could lead to tryptophan depletion and contribute to hyperserotonemia observed in ASD. (3) Bacterial metabolites can be translocated into the systemic or lymphatic system, transported to the brain, and cause behavioral and chemical changes. In addition, abnormal intestinal permeability in children with ASD could allow passive diffusion of metabolites.[120] (4) Although 5′-HT is produced predominantly from EC cells in enterocytes, its secretion can be stimulated by SCFAs, which could increase the amount 5′-HT is released into the circulation.[132] (5) Upon reaching the brain, SCFAs can have neurotoxic effects, and propionate could elicit ASD-like behavior in animal models.[126,130] (6) The microbiota itself can have direct effects on the brain by modulating the blood–brain barrier[95] and causing changes in the metabolism of 5′-HT in the brainstem (eg, *Bifidobacterium infantis*).[117] (7) Certain species of the gut microbiota have been shown to influence the activity of the HPA axis.[27,99,134] In children with ASD, increased activity of the HPA axis[135] as well as increased levels of cortisol in the circulation were observed.[136] (8) The vagal-mediated signaling from the gut microbiota to the brain can be transmitted through vagal chemoreceptors on mucosal villi that are activated by bacterial metabolites (eg, 5′-HT, SCFAs) or by vagal mechanoreceptors that sense motility changes induced by some bacterial species.[103] (9) The microbiota can influence the development of the immune system through various microbial signals.[20,93,137] For example, pattern recognition receptors can recognize microbial cell components and metabolites and can adjust the immune response accordingly.[137] In addition, disturbance of the gastrointestinal tract can lead to increased permeability of the intestinal barrier, allowing immune cells (eg, lymphocytes) and cytokines to translocate to the circulation. (10) In the brain, these immune cells can elicit an immune response by increasing the permeability of blood–brain barrier or binding to epithelial cells.[62] *Abbreviations*: 4-EPS, ethylphenylsulfate; 5′-HT, serotonin; EC cells, enterochromaffin cells; HPA, hypothalamic–pituitary–adrenal; SCFAs, short-chain fatty acids.

factors that could contribute to the development of ADHD have been identified. Although ADHD has not been linked to an abnormal gut microbiota, several arguments can be made supporting a dysbiosis as a potential contributing factor. First, factors associated with an increased risk of developing ADHD, such as duration of breastfeeding, early-life antibiotic exposure, gestational age, and birth weight influence the

development of the gut microbiota.[155–161] Second, mechanisms proposed to play a role in the etiology of ADHD are also involved in a bidirectional connection with the gut microbiota. For example, certain bacterial species are capable of regulating HPA axis activity, which is dysfunctional in children with ADHD.[27,162] 5′HT, a by-product of *Lactobacillus*, *Streptococcus,* and *Lactococcus* species, modulates attention performance and aggressive behavior.[163,164] Third, ASD and ADHD show a high comorbidity, and children with ASD are often treated for ADHD symptoms such as inattentiveness and hyperactivity. Fourth, similar to symptoms in children with ASD, GI problems such as constipation, fetal incontinence, and celiac disease are often reported in children with ADHD.[165,166] Lastly, early dietary patterns were linked to the development of ADHD.[167] A lower risk for having ADHD was associated with a diet low in fat but high in carbohydrates, fatty acids, and minerals.[167] On the other side, snack pattern diets (vs meal pattern diets), a diet high in sugar and refined grains, or a diet high in processed and commercially produced food was associated with increased risk of ADHD.[167] Likewise, the Western diet, which is characterized by high levels of n-6 fatty acids, sodium, and sugar intake, has been suggested to promote the development of ADHD.[168] Whether these early dietary patterns cause changes in the microbiota and ultimately lead to development of ADHD symptoms is unknown. However, clinical studies have shown an improvement in inattention and hyperactivity behaviors in children who were supplemented with the probiotics *Lactobacillus acidophilus* and *Lactobacillus bifidus*, suggesting that mechanisms elicited by the gut microbiota could contribute to the symptoms of ADHD.[169]

CONCLUSION

Accumulating evidence demonstrates strong associations between the gut microbiota and ASD symptoms. Differences in microbiota composition are presented in the literature, but no clear trend is emerging yet, which may be attributable to differences in methodology, study population, and confounding factors, especially diet. Likewise, whether microbial dysbiosis contributes to the development of ASD symptoms or is caused by diet and medication remains unknown. To better understand the role of the microbiota and understand the interplay between nutrition and the microbiota in ASD, future studies should systematically investigate the role of nutrition in the microbial composition of children with ASD and stress the importance of analyzing the microbiota in the context of diet and medication. Identifying the influence of nutrition, dietary supplements, and medications on the short-term gut microbial profile and its effect on longitudinal changes in bacterial species would contribute to greater understanding of the etiology of ASD and provide an early intervention strategy to decrease the severity of the disease in genetically at-risk children. New therapeutic measures will be of key focus in the upcoming years to decrease the financial burden on the economy as well as to address parents' concerns about the safety of medications. There is no specific, effective drug therapy for the treatment of children with ASD, making the development of new treatments that can ameliorate symptoms of the disease an urgent need.

Genetic predisposition in conjunction with environmental factors might explain the increase in new ASD diagnoses over the past 10 years. Whether the gut microbiota contributes as an environmental factor is still unknown. Carefully designed longitudinal studies are needed to elucidate the changes in the microbiota in the period leading up to ASD diagnosis in order to establish a role of the microbiota in the development of symptoms. In addition, more research showing a specific correlation between bacterial species and ASD symptoms could provide support for determining which bacterial strain needs to be targeted by probiotic supplementation.

The data to date provide some evidence linking the microbiota–gut–brain axis to ASD and, potentially, to ADHD. Future longitudinal studies can provide new insight into the cause-and-effect relationship between the microbiota and ASD development. Animal studies have shown that early-life perturbations of the microbiota can impact the development of the central nervous system and have lasting effects on cognitive function later in life. Germ-free and gnotobiotic animal models will provide new information on the underlying molecular mechanisms of the microbiota–gut–brain axis in ASD. Research on the trajectory of the microbiota composition in the development of children at risk for ASD will be fundamental to establish potential causative relationships and to develop potential therapies targeting the gut microbiota.

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