Neuroscience 324 (2016) 131–139

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.

http://dx.doi.org/10.1016/j.neuroscience.2016.03.013
0306-4522/

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