Life Sciences 194 (2018) 111–119

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Targeting gut microbiome: A novel and potential therapy for autism

Yongshou Yang[a,*], Jinhu Tian[b], Bo Yang[a]

[a] Graduate School of Biosphere Science, Hiroshima University, Higashi-Hiroshima 739-8528, Japan
[b] Department of Food Science and Nutrition, Zhejiang University, 866 Yuhangtang Road, Hangzhou, Zhejiang Province 310058, PR China

ARTICLE INFO

Keywords:
Gut microbiome
Probiotics
Gut-brain axis
Autism spectrum disorders
Gastrointestinal problems
Therapy

ABSTRACT

Autism spectrum disorder (ASD) is a severely neurodevelopmental disorder that impairs a child's ability to communicate and interact with others. Children with neurodevelopmental disorder, including ASD, are regularly affected by gastrointestinal problems and dysbiosis of gut microbiota. On the other hand, humans live in a co-evolutionary association with plenty of microorganisms that resident on the exposed and internal surfaces of our bodies. The microbiome, refers to the collection of microbes and their genetic material, confers a variety of physiologic benefits to the host in many key aspects of life as well as being responsible for some diseases. A large body of preclinical literature indicates that gut microbiome plays an important role in the bidirectional gut-brain axis that communicates between the gut and central nervous system. Moreover, accumulating evidences suggest that the gut microbiome is involved in the pathogenesis of ASD. The present review introduces the increasing evidence suggesting the reciprocal interaction network among microbiome, gut and brain. It also discusses the possible mechanisms by which gut microbiome influences the etiology of ASD via altering gut-brain axis. Most importantly, it highlights the new findings of targeting gut microbiome, including probiotic treatment and fecal microbiota transplant, as novel and potential therapeutics for ASD diseases.

1. Introduction

Neurodevelopmental disorders are characterized by disturbances of the growth and development of the brain or central nervous system (CNS). Autism spectrum disorder (ASD) is a severely neurodevelopmental disorder that impairs a child's ability to communicate and interact with others [1]. The core symptoms also include restricted repetitive patterns of behaviors, interests and activities. In addition to the core symptoms of ASD, related conditions and behaviors have been reported recently, including abnormalities in sensory processing (hypo or hypersensitivity), gastrointestinal (GI) symptoms or even self-injurious behaviors [2]. The reported prevalence of ASD has increased dramatically in recent years. Based on the extensive surveys conducted by the Centers for Disease Control and Prevention, the incidence of ASD from 1 in 150 children in 2000 increased to 1 in 68 in 2012 in the United States (https://www.cdc.gov/ncbddd/autism/data.html). In spite of the extensive efforts, the exact mechanisms of ASD have not been clearly elucidated. Recently, emerging works suggested that various environmental factors (including chemical exposures, viral infections, and metabolic imbalances) have been implicated in the etiology and pathogenesis of ASD [3,4]. However, due to the lack of consensus on the causes of ASD, there have been no widely accepted and efficient therapies for such disorder.

A large body of recent studies elucidated the crucial roles of gut microbiome in the functions of CNS, neuroendocrine and neuroimmune systems [5,6]. The altered bidirectional neurohumoral communication system between gut and brain – known as the gut-brain axis – may cause a series of diseases, such as autoimmune and CNS disorders [6]. GI distress, which affects millions of people worldwide, is a most common syndrome among several comorbidities in ASD patients. Morover, a recent multi-case analysis of about 15,000 ASD patients indicated that almost 12% of ASD individuals had comorbidity with bowel disorders [7]. Based on a great many previous studies, dysbiosis of the gut microbiome was implicated in the etiology of several diseases, including inflammatory bowel disease (IBD), obesity, and cardiovascular disorders, in both human and animal models [8,9]. In addition, increasing evidences revealed that the compositions of gut microbiota in ASD patients were largely different compared with the healthy control individuals [10–13]. Taken together, we speculate that gut microbiome, acting singly or in interaction with other factors, may be associated with the pathogenesis of ASD.

This review hopes to provide a better understanding of the gut microbiome as a potential therapy for ASD and its role with respect to neurodevelopmental disorders (e.g., ASD). Then the possible and underlying mechanisms by which the gut microbiome interacts with ASD are fully analyzed. Most importantly, the very recent and compelling

* Corresponding author.
E-mail address: d156196@hiroshima-u.ac.jp (Y. Yang).

https://doi.org/10.1016/j.lfs.2017.12.027
Received 18 August 2017; Received in revised form 12 December 2017; Accepted 21 December 2017
Available online 23 December 2017
0024-3205/

studies that suggested probiotic and fecal microbiota transplant treatments (FMT) can help to improve GI- and ASD-related behavioral symptoms are summarized.

2. Overview of gut microbiome

Human beings, including other mammals, live in a co-evolutionary association with huge numbers of microorganisms that resident on the exposed and internal surfaces of their bodies. The collection of microbes and their genetic material is termed microbiome. The human GI tract contains approximately 10^{14} bacteria belonging to approximately 1000 species [14]. It is estimated that commensal microbiome outnumbers at least 100-folds more than the human somatic genome [15]. The healthy adult GI tract is most dominated by *Bacteroidetes* and *Firmicutes* phyla (both account for up to 70–90% of total bacteria), followed by *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia* [16]. These symbiotic microbiota dwelling in the gut have long been appreciated for the various beneficial effects they offered to the host including providing essential nutrients by metabolizing indigestible dietary compounds, defending against opportunistic pathogen colonization by nutrient competition and antimicrobial substance production, and contributing to intestinal epithelial barrier [17]. Moreover, the studies on the immune defects in germ-free (GF) mice have suggested that gut microbiome was essential to the host immune system [18,19]. A recent review also indicated that gut bacterial colonization could drive maturation and functionality of the host adaptive immune system [17].

The beneficial partnership between gut microbiome and the host immune system contributes greatly to the normal host homeostasis during life. Disruption of a balanced composition of gut microbiome can cause immunological dysregulation that may underlie several inflammatory disorders, such as irritable bowel syndrome (IBS) and IBD or even several kinds of cancer [17]. Moreover, altered gut microbiome also affects microbiota-derived products and metabolites, including pro- and anti-inflammatory materials, which in turn can influence development or composition of the gut microbiome [20]. However, some probiotics, such as *Bifidobacteria* and *Lactobacillus*, may re-establish the composition of the gut microbiome and exert benefits to gut microbial communities, leading to amelioration or prevention of gut inflammation and other intestinal or systemic diseases [21].

3. Communications among microbiome, gut and brain

Ever since the term of gut-brain axis was proposed and the first publication of preclinical studies that revealed the communication among gut microbiome, gut and brain, there are fast-growing studies focusing on this field and further deepening our understanding of those correlations [22]. The gut-brain axis refers to the bidirectional biochemical communications between the GI tract and the nervous system [6]. The reciprocal interaction network consists of CNS, the autonomic nervous system (ANS), the enteric nervous system (ENS), hypothalamic pituitary adrenal (HPA) axis, gut microbiome, as well as the vagus nerve that is the major pathway in the connection between the viscera and CNS [6,23].

In the past several years, many efforts exploring the roles of gut microbiome in modulating brain functions have been performed mainly on animals. Studies conducted on the GF animals demonstrated that bacterial colonization of the gut was vitally significant to the development and maturation of both CNS and ENS [24,25]. Based on the previous publications [6,23,26], we summarized the major categories of mechanisms by which the gut microbiome regulates the brain functions. First, the gut microbiome could influence the production, expression and turnover of neurotransmitters, such as serotonin and gamma-aminobutyric acid (GABA), and brain-derived neurotrophic factor (BDNF), which are an important factor to memory. Second, the gut microbiome contributed to the intestinal barrier and tight junction integrity, and thus attenuated HPA axis and ANS functions. Third, some species of probiotics modulated enteric sensory afferents and ENS activity. Fourth, the gut microbiome could exert effects on the brain through bacteria-derived and/or co-metabolites, including short-chain fatty acids (SCFAs), serotonin and kynurenine productions. Finally, immunological pathways (systemic and mucosal immune) also played a significant role in the regulation of the gut-brain axis by the gut microbiome.

Evidence from animal research have shown that several types of social stressors had an influence on mucus secretion, and the composition as well as total biomass of gut microbiota [27,28]. The fact suggests that brain functions play an important role in the regulation of brain-gut-microbiome signaling. The CNS directly exerts control over the gut microbiota composition via peptides which are sent upon satiation and thus influence nutrient availability. The release of signaling molecules by neurons, immune and enterocromaffin cells under controls of the brain may directly affect the gut microbiome [23]. Moreover, brain can modulate gut functions, including motility, secretion of acid and mucins, and handling of intestinal fluid, all crucial for the maintenance of the mucosal biofilms where bacteria grow in a multiplicity of microenvironment [29]. Furthermore, gut microbiota composition and function may be regulated by the brain via alteration of intestinal permeability, leaving some pathogens across the epithelium and activating the immune response in the mucosa [23]. There is even evidence from rat models that stress in mothers during prenatal development can induce long-term alterations in the gut microbiota, and impact upon other major physiological systems in their offspring [30]. This research implies that a propensity to heightened social stress may also be transmitted biologically via the microbiota through vaginal delivery. Last but not least, HPA regulates cortisol secretion, and cortisol can affect immune function. Cortisol also can influence gut permeability and barrier function, as well as change gut microbiota composition. For instance, a recent study on mice indicated that olfactory bulbectomy induced chronic depression elevated corticotropin-releasing hormone expression and serotonin levels, associated with alteration of motor activity and the microbial profile in the colon likely via activation of the HPA [31].

4. Underlying mechanisms by which gut microbiome is involved in ASD

Despite numerous studies focused on the possible pathogenesis of ASD, the exact causes of this disease have not been clearly stated and the current theory points that ASD should be a result of combinations including several genetic and environmental risk factors. Particularly, accumulating studies underlined the potential roles of environmental risk factors and associated comorbidities in the contribution to core neurobehavioral symptoms of ASD. The microbiome habituating in the body is well known for its functions of interaction between genes and environment. With the increasing knowledge of microbiome, it is believed that ASD-associated alterations of gut microbiome and its metabolites can directly and indirectly modulate corresponding immune and GI disorders, and may play a possible role in the etiology of ASD (see Fig. 1).

4.1. Microbiome-associated maternal risk factors

There are strong evidences from many epidemiological, clinical, and animal studies that showed that maternal infections as primarily influencing the development of ASD symptoms [32–35]. For decades, fetuses were thought to be born germ-free, but recent researches using meconium samples from healthy babies suggested that fetuses were already exposed to maternal bacteria in utero [36,37]. Subsequently, the microbial colonization performed in the infants during vaginal delivery was largely different from that of microbiome acquired in the newborns by cesarean section [38,39]. Therefore, microbial dysbiosis in the maternal microbiome in response to environmental risk exposure or