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Reddy, Bhaskara Lakshmi
Saier, Milton H

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Autism and Our Intestinal Microbiota

Bhaskara Lakshmi Reddy^{a, b} Milton H. Saier^a

^aDepartment of Molecular Biology, Division of Biological Sciences, University of California at San Diego, La Jolla, Calif., and ^bDepartment of Mathematics and Natural Sciences, College of Letters and Sciences, National University, Ontario, Calif., USA

Key Words

Autism · Microbiota · Gastrointestinal disorders

Abstract

Microbial products, released into the bloodstreams of mammals including humans, cross the blood-brain barrier and influence neurodevelopment. They can either promote or alleviate neurological disorders including autism spectrum disorders (ASD). This editorial describes how our microbiota influence our feelings, attitudes and mental states with particular reference to ASD.

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Introduction

The mammalian microbiota is now known to be essential for the maintenance of good health [Ettinger et al., 2014; Schippa and Conte, 2014]. Recently, evidence has been presented suggesting that symbiotic prokaryotes influence brain function and that a balanced microbiota can promote mental health while combating major psychological and physiological disorders [Fond et al., 2014; Tang et al., 2014]. This evidence has led to the use of novel terms such as ‘psychobiotics’ and ‘psychomicrobiotics’

to emphasize the possibility that ‘bad’ intestinal bacteria may negatively influence mental processes [Selhub et al., 2014]. In fact, it has been suggested that microbial imbalance, often referred to as dysbiosis or dysbacteriosis, can give rise to major psychiatric disorders [Dash et al., 2015]. The hope is that probiotics, prebiotics and proper nutrition can help alleviate the symptoms of common neurological disorders. A door to the novel discipline of ‘nutritional psychology’ is opening. In this short review, we focus on one increasingly prevalent disorder, autism, citing evidence that this condition is responsive to the composition of our microbiota.

Autism has been reported to be associated with multiple phenotypic disorders including impairment of verbal and written communication skills, social isolation and repetitive behaviors [Whitehouse and Stanley, 2013]. It is a neurodevelopmental disorder with high variability in its clinical manifestations. Autism spectrum disorders (ASDs) have been reported to be associated with: (1) genetic mutations giving rise to polymorphisms in specific genes [Dachtler et al., 2014; Hevner, 2015]; (2) epigenetic changes in gene expression [Balan et al., 2014]; (3) environmental pollutants [Volk et al., 2014]; (4) maternal infection with pathogenic agents during pregnancy [Zerbo et al., 2013]; (5) sleeping problems [Kotagal and Broomall, 2012]; (6) gastrointestinal metabolic disorders [Kotagal

and Broomall, 2012]; (7) immune dysregulation [Onore et al., 2012]; (8) homeostatic imbalance in gut-to-brain connections [Kotagal and Broomall, 2012]; (9) oxidative stress; (10) mitochondrial dysfunction, and (11) neuroinflammation during development [Zhang et al., 2015]. However, which of these conditions, if any, are causally related to autism remains an open question.

There is increasing evidence that excessive proinflammatory proteins such as interleukin-6 (IL-6), ρ -kinases (ρ -associated, coiled-coil-containing protein kinase 1) and NADPH oxidases (KNOX-2) significantly contribute to neurite outgrowth and retardation. They may contribute to ASDs, Alzheimer's disease and other neurodegenerative diseases [Hernandes et al., 2014; Sorce and Krause, 2009]. NADPH oxidases produce free radicals during the reduction of molecular oxygen and elicit oxidative stress. They are linked to neuroinflammatory diseases and brain injury [El-Ansary and Al-Ayadhi, 2012; Gonzalez et al., 2014; Gotz and Ittner, 2008]. In fact, a correlation between the levels of reactive oxygen species and neurodegenerative diseases has been noted [Ramalingam and Kim, 2012; Tapryal et al., 2009]. Several studies have identified IL-6 as a key cytokine responsible for these abnormalities, possibly because of the altered expression of genes responsible for immunological and neurological development [Meyer and Feldon, 2009; Meyer et al., 2008; Ramalingam and Kim, 2012]. Though several cytokines are released, IL-6 seems to be key, and the inhibition of IL-6 has reversed behavioral abnormalities observed in offspring prenatally exposed to maternal immune activation (MIA) [Smith et al., 2007]. A number of intestinal microbes are known to maintain the integrity of the intestinal barrier and epithelial tight junctions by secreting molecules that inhibit cytokines including IL-6 [Turner, 2009].

Autoantibodies against specific central nervous system proteins and against brain regions such as the cerebellum, thalamus and hypothalamus are known to be present in individuals with autism [Wills et al., 2009]. An altered blood-brain barrier, due to neurological inflammation and increased inflammatory cytokines in the brain, has been reported in ASD children [Noriega and Savelkoul, 2014], along with altered immune properties and cytokine imbalance [Gesundheit et al., 2013; Goines and Ashwood, 2013; Sweeten et al., 2003]. The intestinal mucosa is constantly challenged with antigens from food, microbes, chemicals and allergens. A functional gut mucosa prevents inflammatory diseases while maintaining immune function, mucous production and normal levels of membrane permeability [Pastorelli et al., 2013].

Many children with autism also suffer from gastrointestinal disorders such as diarrhea, vomiting, abdominal pain, chronic constipation and gastroesophageal reflux [Buie et al., 2010]. Abnormalities such as altered gastrointestinal motility and increased intestinal permeability have also been reported in autistic children [D'Eufemia et al., 1996]. A large sample study involving 15,000 individuals also revealed a greater prevalence of inflammatory bowel disease and other gastrointestinal disorders in ASD patients compared to controls [D'Eufemia et al., 1996; Kohane et al., 2012]. Altered gastrointestinal microbial populations were considered to be responsible for the pathogenesis of several of these disorders, including inflammatory bowel disease, obesity and cardiovascular diseases [Casanova et al., 2011; Williams and Gray, 2013]. In fact, disruption of the mucosal microbiota has been extensively reported in ASD children [Finegold et al., 2010, 2012; Kang et al., 2013; Parracho et al., 2005; Williams et al., 2011, 2012]. A reduction in the diversity of microbes in the gastrointestinal tract has been observed in Crohn's disease, a chronic inflammatory disease of the gastrointestinal tract, along with a difference in the composition of fecal bacteria in patients with inflammatory bowel disease compared to healthy controls [Manichanh et al., 2006].

Some studies have suggested a significant risk of autism in children born to mothers with severe infections during pregnancy [Smith et al., 2007]. Moreover, when pregnant female monkeys were exposed to antibodies produced as a result of immune-mediated disorders, the offspring developed pathologies of the central nervous system and exhibited behavioral changes similar to those characteristic of autism [Libbey and Fujinami, 2010]. These were the first studies to report alterations in the intestinal microbiome in offspring born to infected mothers, providing a potential explanation for the gastrointestinal problems suffered by children with autism. Moreover, studies using animal models have suggested that MIA can, in response to pathogens and exposure of the fetus to maternal cytokines, result in neurological, immunological and behavioral abnormalities in the offspring [Smith et al., 2007]. An increased risk of autism in offspring born to pregnant female monkeys infected with pathogens has recently been confirmed [Bauman et al., 2014].

Offspring of MIA mice with behavioral abnormalities exhibit altered gut bacteria and gastrointestinal abnormalities, and similar defects in intestinal integrity have also been reported in human cases of ASD [Hsiao et al., 2013]. Thus, children with ASD have an increased perme-

ability of the gastrointestinal tract, called 'leaky gut', causing microbial products to escape into the bloodstream and possibly reach the brain [de Magistris et al., 2010]. These products alter the immune system, resulting in a progression of the disease [Turner, 2009]. Increased gastrointestinal permeability has even been suggested to be a cause of inflammatory bowel disease, Crohn's disease and autism [Liu et al., 2005]. Differences in the gut microbiota between MIA offspring and controls were observed due primarily to changes in the diversity of Clostridia and Bacteroidia [Hsiao et al., 2013]. The intestines of some ASD patients with intestinal abnormalities are known to bear *Sutterella* and *Clostridium bolteae* [Parracho et al., 2005], organisms lacking in control populations with similar gastrointestinal problems.

The microbiota normally inhabiting the human gut are dominated by 4 major phyla: Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria [Qin et al., 2010]. Children with autism proved to have lower levels of the *Bifidobacterium* species and higher levels of the *Lactobacillus* species, along with other differences in the members of the actinobacterial and proteobacterial phyla [Finegold et al., 2010]. In one study, dietary supplementation with prebiotics significantly increased the populations of *Bifidobacterium breve*, *B. longum* and *Bacteroides distasonis*, while decreasing the populations of *Escherichia coli* and *Clostridium perfringens* [Martin et al., 2008].

Bacteroides fragilis, a common probiotic bacterium, but also an opportunistic pathogen, is part of the normal microbial ecosystem [Cao et al., 2014]. *B. fragilis* treatment has been shown to alleviate symptoms of experimental colitis [Round and Mazmanian, 2010]. It can also decrease inflammation caused by *Helicobacter hepaticus*, another commensal organism in the gastrointestinal tract with a potential for pathogenicity [Mazmanian et al., 2008]. Abnormalities in gastrointestinal tract permeability have been ameliorated by the introduction of *B. fragilis* into the gastrointestinal tracts of 8-week-old offspring of MIA mice [Hsiao et al., 2013]. MIA-induced serum metabolite levels were also corrected by *B. fragilis* treatment, in part by reducing levels of 4-ethylphenylsulfate, a metabolite known to induce behavioral abnormalities in naïve mice [Hsiao et al., 2013]. A depletion of microbes, including *B. fragilis*, was also reported in ASD children with gastrointestinal problems [Kang et al., 2013].

There is a growing interest in fecal microbiota transplantation to treat many diseases caused by an imbalance of gut microbiota [Petrof and Khoruts, 2014]. The first fecal transplants were performed in 1958 at the Uni-

versity of Colorado Medical School in Denver, and since then, there have been more than 500 published cases [Yong, 2013]. Borody's clinic has now performed over 1,500 fecal transplantations with promising results in patients with inflammatory bowel disease, irritable bowel disease and chronic constipation [Borody et al., 2004]. In spite of these successes, many in the scientific community are unconvinced; we are still trying to overcome the 'yuck factor' and our loathing for human waste. Considering the difficulties of physicians to obtain licenses to perform such transplantations, it is not surprising that many patients are opting to do their own transplantations at home, with an enema kit and stools from a healthy relative [Swaminath, 2014].

Through millions of years of evolution, we have acquired a delicate balance of normally beneficial bacteria in our gastrointestinal tracts and elsewhere throughout our bodies. These bacteria coevolved with us and forged essential symbiotic relationships with us, influencing our physiologies and behaviors, especially through the gut-brain axis [Peeters, 2015]. Even the pathogenic bacterium *H. pylori*, which causes gastric ulcer, is known to be useful to us by preventing esophageal cancer through the beneficial effects of the inflammation it causes [Blaser, 2014]. Re-establishing this delicate balance and maintaining the useful gut bacteria are crucial to our health and feeling of well-being.

In summary, numerous studies indicate that gastrointestinal alterations of the microbial ecosystem promote gut permeability, causing the leaky gut syndrome. This condition results in an escape of microbial products and cytokines into the bloodstream, causing neurodevelopmental disorders. Autism is just one of the disorders that may result in part from this condition. The extent to which and mechanisms by which our microbiota influence our feelings, attitudes and mental states represent rich fields for investigation for young microbiologists.

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