

REVIEW

Mind-altering with the gut: Modulation of the gut-brain axis with probiotics

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It is increasingly evident that bidirectional interactions exist among the gastrointestinal tract, the enteric nervous system, and the central nervous system. Recent preclinical and clinical trials have shown that gut microbiota plays an important role in these gut-brain interactions. Furthermore, alterations in gut microbiota composition may be associated with pathogenesis of various neurological disorders, including stress, autism, depression, Parkinson's disease, and Alzheimer's disease. Therefore, the concepts of the microbiota-gut-brain axis is emerging. Here, we review the role of gut microbiota in bidirectional interactions between the gut and the brain, including neural, immune-mediated, and metabolic mechanisms. We highlight recent advances in the understanding of probiotic modulation of neurological and neuropsychiatric disorders via the gut-brain axis.

Keywords: probiotics, gut microbiota, nervous system, gut-brain axis, gut dysbiosis, neurological disorders

Introduction

The human gastrointestinal tract is inhabited by nearly 100 trillion microorganisms that are believed to play important roles in physiology (Gill *et al.*, 2006). These microorganisms, collectively known as gut microbiota, are proposed as an essential “organ” in the maintenance of immune function, carbohydrate metabolism, and metabolic homeostasis (Tremaroli and Backhed, 2012).

Bidirectional communication between the brain and the gut, known as the gut-brain axis, has long been recognized: the brain modulates the gastrointestinal tract by regulating of motility, secretion, absorption, and blood flow; concurrently, the gut can affect brain function and behavior (Grenham *et*

al., 2011). The scaffolding of the gut-brain axis includes the gastrointestinal tract, central nervous system (CNS), autonomic nervous system (ANS), enteric nervous system (ENS), neuroendocrine system, and immune system (Grenham *et al.*, 2011). Recent studies have shown that the gut microbiota is involved in the neurodevelopment and diverse brain functions through regulating the gut-brain axis (Carabotti *et al.*, 2015; Erny *et al.*, 2015). Gastrointestinal symptoms, such as constipation, diarrhea, and abdominal pain, are common comorbidities in many neurological diseases (Westfall *et al.*, 2017). Moreover, recent advances in metagenomic sequencing have revealed that dysregulation in the composition of gut microbiota (gut dysbiosis) is present in a variety of neurological diseases. Consequently, the importance of maintaining a healthy microbiota community (gut symbiosis) in the regulation of the gut-brain axis cannot be overly emphasized. The term microbiota-gut-brain (MGB) axis was introduced to highlight the role of the microbiota in the gut-brain axis.

Probiotics are defined as living microorganisms that, when ingested in adequate quantities, confer a health benefit on the host; these microorganisms have been reported to exert a wide range of effects (Hill *et al.*, 2014). Although their mechanisms in modulating host physiology are not yet fully elucidated, probiotics might be able to modulate host immune system (Bermudez-Brito *et al.*, 2012). For example, *Weissella cibaria* WIKIM28 isolated from kimchi ameliorates atopic dermatitis symptoms by regulating dendritic cell functions and inducing regulatory T cell responses (Lim *et al.*, 2017).

Probiotic bacteria not only modulate host immune responses, but also create a healthy gut environment through balancing of the intestinal microflora. Ingestion of probiotics may restore the composition of the gut microflora to a state more favorable for beneficial microorganisms (Choi *et al.*, 2015; Mountzouris *et al.*, 2007). Probiotics recently have attracted attention in the context of brain function and health because they serve to alter gut microflora toward a beneficial state, which could affect the gut-brain axis (Bravo *et al.*, 2012).

In this review, we will focus on the role of gut microbiota in crosstalk between the gut and brain, as well as how the microbiota affects a variety of neurological disorders. Finally, we will discuss recent findings in probiotic modulation of brain function and neurological diseases.

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Interactions within the gut-brain axis

Gut and brain regulate each other bidirectionally via multiple mechanisms and pathways, including neural, neuroendocrine, and immunological signals. Here, we highlight key communication pathways for a comprehensive understanding of the gut-brain axis.

Neural communication between the gut and brain

Neural communication is mainly conducted within the ENS in the gastrointestinal tract. The ENS is a main division of the ANS and regulates gastrointestinal tract functions such as intestinal motility, mucous secretion, and blood flow (Brown-ing *et al.*, 2017). The ENS interacts with the ANS and CNS via neurotransmitters (adrenaline, noradrenaline, and acetylcholine), as well as sensory and motor neurons, all of which convey signals from the gut to the brain.

The intestinal microbiota regulates electrophysiological thresholds in ENS neurons (Sarkar *et al.*, 2016). For example, a strain of *Lactobacillus reuteri* was shown to activate a calcium-dependent potassium channel in neurons within rat colon myenteric plexus (Kunze *et al.*, 2009). Metabolic compounds by *Bifidobacterium longum* NCC3001 elicited reduction of action potential spikes in myenteric neurons, following electrical stimulation (Bercik *et al.*, 2011b). In germ-free mice, myenteric sensory neurons exhibited decreased excitability, compared with normal mice (McVey Neufeld *et al.*, 2013). Moreover, these neurons in conventionalized germ-free mice (conventionalized with intestinal bacteria from conventionally-raised mice) revealed increased excitability following hyperpolarization (McVey Neufeld *et al.*, 2013). In addition to their actions on myenteric neurons, gut bacteria also play a crucial role in initial colonization and homeostasis of glial cells in the intestinal mucosa (Kabouridis *et al.*, 2015).

Another neuronal pathway in gut-brain communication utilizes the vagus nerve (cranial nerve X that runs from brainstem to gastrointestinal tract) which has both efferent and afferent roles (Cryan and Dinan, 2012). Approximately 80% of vagal fibers are sensory, conveying information regarding the state of the body's organs to the CNS (Thayer and Sternberg, 2009). The vagus nerve regulates several vital functions, including bronchial constriction, heart rate, and gut motility. Many known effects of gut microbiota or probiotics strains are dependent on vagus nerve activity (Goehler *et al.*, 2008; Bercik *et al.*, 2011b; Bravo *et al.*, 2011). For example, chronic treatment with *L. rhamnosus* JB-1 induced increases in γ -Aminobutyric acid (GABA) mRNA expression within specific brain regions, in addition to reducing stress-induced corticosterone and anxiety- and depression-related behavior (Bravo *et al.*, 2011). Moreover, based on experiments in vagotomized mice, the vagus nerve was identified as a major modulator in the gut-brain communication pathway (Bravo *et al.*, 2011). However, vagus nerve-independent mechanisms also exist in gut-brain communication, as antimicrobial treatments failed to show gut-brain dependence on vagus nerve activity (Bercik *et al.*, 2011a).

Immune system mediated interaction

Gut microbiota can directly affect the immune system; this

constitutes a key indirect route for communication between the gut microbiota and the nervous system (Macpherson and Uhr, 2004; Bengmark, 2013). The gut houses the gut-associated lymphoid tissues (GALT) which are the largest collection of lymphoid tissues in the human body; these tissues protect the body from microbial invasion via the gut. A variety of gut and GALT immune cells, such as T cells, macrophages, and dendritic cells (DCs) can cross the blood-brain-barrier (BBB) and affect neurons and glia in the brain (Diamond *et al.*, 2011). In the brain, there are also resident immune cells, such as macrophages and DCs in the choroid plexus, microglia in the parenchymal region of brain, and leukocytes in the cerebrospinal fluid (CSF) (Wang and Kasper, 2014). Therefore, gut microbiota, known to shape the host immune system, can also modulate the activity of these resident immune cells, in addition to their effects on neuronal cells in the CNS (Berer and Krishnamoorthy, 2012). Moreover, a recent study of germ-free mice has revealed that gut microbiota can alter the immune system of the CNS by regulating microglial activation and homeostasis (Erny *et al.*, 2015). Microglia in germ-free mice exhibited global defects in cellular proportions and in maturation, thereby leading to diminished innate immune responses (Erny *et al.*, 2015).

Systemic circulation of immune factors, cytokines, and chemokines influences the brain via the vagus nerve and circumventricular organs (Hosoi *et al.*, 2002). In addition, another pathway consists of direct transport by saturable transport systems along the BBB (Banks, 2005). In the brain, pro-inflammatory cytokines can trigger further neuro-inflammation in the nervous system, thereby causing increased permeability of the BBB (McCusker and Kelley, 2013). Leakage of the BBB leads to immune cell infiltration, exacerbation of inflammatory responses, and reactive gliosis (reactive changes of glial cells in response to damage); causing neurodegeneration eventually (Obermeier *et al.*, 2013). In addition, cytokines alter the concentrations of several neurotransmitters in the brain, including serotonin, dopamine, and glutamate (Miller *et al.*, 2013). Non-inflammatory cytokines also serve as mediators for intestinal microbes to regulate brain function. For example, antibiotic exposure in neonatal mice produced reductions in the level of plasma granulocyte colony stimulating factor (G-CSF) (Deshmukh *et al.*, 2014). G-CSF can stimulate neurogenesis in the brain by crossing the BBB; further, it has a protective role in ischemic injury, as well as in certain models of Parkinson's disease and Alzheimer's disease (Shyu *et al.*, 2004; Meuer *et al.*, 2006; Prakash *et al.*, 2013; Wallner *et al.*, 2015). Thus, by promoting the production of G-CSF, the gut microbiota may provide a potential therapeutic agent for normal neurodevelopment, as well as to combat the progression of neurodegenerative diseases. Additionally, recent findings regarding drainage of the lymphatic system into the brain provide more decisive evidence of direct cytokine entry into the brain, enabling interaction with neural tissues (Louveau *et al.*, 2015; Sun *et al.*, 2017).

Effects of neuroactive compounds and metabolites from gut microbes on the central nervous system

Gut microbiota is capable of producing a spectrum of neurotransmitters, neuroactive compounds, and metabolites. Neurotransmitters and neuroactive compounds that have