Impact of Probiotics and Gut Microbiota on Host Behavior

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Abstract Probiotic bacteria are living organisms that inhabit the gut and contribute towards the health of the host. The idea that implanting the intestines with probiotic bacteria may improve quality of life and mental health is not a new one. Accumulating clinical evidences suggest that probiotics can modulate the stress response and improve mood and anxiety symptoms in patients with chronic fatigue and irritable bowel syndrome. One such organism is *Lactobacillus rhamnosus* (JB-1), which has shown antidepressant and anxiolytic-like properties in mice as observed recently. Probiotic supplementation can also lead to significant improvement in motor coordination and spontaneous locomotor activity, in addition to reduction in anxiety and cognitive behavior in rats. There are increasing, but largely indirect, evidences to point out the effect of commensal gut microbiota on the central nervous system. Microbes in gastrointestinal (GI) tract which constitute normal gut microbiota are represented by a wide variety of bacterial species. Emerging studies have shown that probiotic bacteria can directly communicate with the central nervous system by way of the vagal sensory nerve fibers and the peripheral immune system. Indeed, experimental studies have shown that even minute doses of these bacteria within the gastrointestinal tract are capable of influencing neurotransmission. Probiotic bacteria and gut microbiota can exert numerous effects on the intestinal neuroimmune system and influence a variety of host functions such as metabolic activity, immune response, and physiological functions. Thus, the emerging concept of probiotics on "microbiota–gut–brain axis" provides a novel insight for improved understanding of their potential role in psychological disorders.

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1 Introduction

In the last few years, evidences from studies in rodents have demonstrated that the gut microbiota can influence neural development, brain chemistry, and a wide range of behavioral phenomena, including emotional behavior, pain perception, and response to stress system. Researchers have found a balance between beneficial and disease-causing bacteria in an animal's gut which can alter its brain chemistry to make it either bolder or more anxious. The brain can also exert a powerful influence on gut bacteria; as many studies have shown, even mild stress can tip the microbial balance in the gut, making the host more vulnerable to infectious diseases and triggering a cascade of molecular reactions that provide feedback to the central nervous system.

Such findings offer the possibility of using beneficial or probiotic bacteria to treat mood and anxiety disorders, either by administering beneficial microbes themselves or by developing drugs that mimic their metabolic functions. The new research also hints at new ways of managing chronic gastrointestinal (GI) disorders that are commonly accompanied by anxiety and depression and that also appear to involve abnormal gut microbiota. Microbes in the gastrointestinal (GI) tract are represented by a wide variety of bacterial species. They can exert numerous effects on the intestinal neuroimmune system and influence a variety of host functions such as metabolic activity, immune response, and physiological functions (O'Hara and Shanahan 2007). The gut microbiota (whose genes represent the intestinal microbiome) composition and activity is influenced by host physiology, immunology, diet, antibiotic usage, and enteric infections. Microbial dysbiosis is associated with gastrointestinal and metabolic disorders. A growing body of evidences suggests that the host–microbial interaction may result in deregulated neuroimmune functions, thus impacting behavior (Bercik et al. 2012; Grenham et al. 2011). Probiotic bacteria are "live microorganisms which when administered in adequate amounts confer a health benefit on the host." Dietary prebiotics, "selectively fermented dietary ingredients that result in specific changes on consumption and/or alter activity of the gastrointestinal microbiota, thus conferring benefit (s) upon host health," have been used in animal studies and human clinical trials to improve peripheral (gastrointestinal) and central (psychological) symptoms.

2 Probiotics

Probiotics are defined as live microorganisms which beneficially affect the host by improving its intestinal microbial balance (Fuller 1989). The probiotics recommended for human applications are primarily two classes of lactic acid producing microorganisms: the bifidobacteria and lactic acid bacteria (LAB) including species of *Enterococcus*, *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Pediococcus*, *Vagococcus*, *Aerococcus*, *Carnobacterium*, *Tetragenococcus*,

Streptococcus, and *Weisella* (Felis and Dellaglio 2007; Weiss et al. 2011). Some yeast strains such as *Saccharomyces cerevisiae* and *Saccharomyces boulardii* have also emerged as probiotics due to their influence on the human health (Bao et al. 2010; Sourabh et al. 2011). Most LAB are Generally Regarded As Safe (GRAS) for human consumption due to their ubiquitous appearance in food and their contribution to the healthy microflora of human mucosal surfaces (Donohue et al. 1993; Sanders 1993; Marteau and Rambaud 1993). They have been of scientific and commercial interest due to a range of health-promoting attributes, including suppression of growth of pathogens, control of serum cholesterol level, modulation of the immune system, improvement of lactose digestion, synthesis of vitamins, ability to adhere to gut tissue, increase in bioavailability of minerals, antigenotoxicity, and possible anticarcinogenic activity (Kailasapathy and Chin 2000; Kullisaar et al. 2002; Chan and Zhang 2005; Wagar et al. 2009; Foligné et al. 2010; Todorov et al. 2012; Walia et al. 2014).

Probiotics have multiple mechanisms of action, including prevention of pathogenic bacterial growth, prevention of penetration of pathogens to mucosal surfaces, stimulation of mucosal barrier function, production of antimicrobial agents or altering immunoregulation, decreasing proinflammatory, and promoting protective molecules (Novak and Katz 2006; Sartor 2006). The intake of probiotics in humans has also been shown to enhance cytokine production in vivo and by peripheral blood mononuclear cells in vitro. Probiotic intake has been reported to be effective in restoring the age-related decline in phagocyte function (Gill 2003). Some of the clinical evidences suggest that probiotics can modulate the stress response and improve mood and anxiety symptoms in patients with chronic fatigue and irritable bowel syndrome (Rao et al. 2009; Silk et al. 2009). LAB such as *L. rhamnosus* (JB-1) can also modulate depression and anxiety-like behavior in healthy mice (Bravo et al. 2011). Moreover, there are some clinical evidences to support a role of probiotic intervention in reducing anxiety, decreasing stress, and improving mood in individuals with irritable bowel syndrome and with chronic fatigue (Logan and Katzman 2005; Rao et al. 2009).

In a recent study, ingestion of *Lactobacillus rhamnosus* (JB-1) has decreased anxiety and despair-like behavior and has reduced the stress-induced increase of plasma corticosterone levels in mice (Bravo et al. 2011). Moreover, this potential probiotic has also altered the mRNA expression of both GABAA and GABAB receptors in several brain regions (with a complex pattern of region- and receptor-specific increases and decreases). Alterations in these receptors have been associated with anxious and depression-like behaviors in animal models. Interestingly, these effects are vagus dependent as vagotomy prevented the anxiolytic and antidepressant effects.

3 The Gut Microbiota

The gut microbiota consists of a complex of microorganisms that live in the digestive tracts of animals and is the largest reservoir of microorganisms commensal to humans. The gut microbiota is a population of estimated 100 trillions of microbes that reside within the GI tract. This population of microbes harbors 100-fold more genes than are found in the human genome. The human gastrointestinal tract is inhabited by 10^{13}–10^{14} microorganisms—more than 10 times that of human cells in our bodies and containing 150 times more genes as our own genome (Gill et al. 2006; Qin et al. 2010; O'Hara and Shanahan 2006). Bacteria make up most of the flora in the colon and up to 60 % of the dry mass of feces. The estimated number of species in the gut microbiota varies greatly, but it is generally accepted that the adult microbiota consists of more than 1000 species (Qin et al. 2010) and more than 7000 strains (Ley et al. 2006). Most bacteria that make up the gut microbiota belong to the genera *Bacteroides*, *Clostridium*, *Fusobacterium*, *Eubacterium*, *Ruminococcus*, *Peptococcus*, *Peptostreptococcus*, and *Bifidobacterium*. Other genera, such as *Escherichia* and *Lactobacillus*, are present to a lesser extent. Species from the genus *Bacteroides* alone constitute about 30 % of all bacteria in the gut, suggesting that this genus is especially important in the functioning of the host (Eckburg et al. 2005). The currently known genera of fungi which harbor gut flora include *Candida*, *Saccharomyces*, *Aspergillus*, and *Penicillium*. Archaea constitute another large class of gut flora which are important in the metabolism of the bacterial products of fermentation (Guarner and Malagelada 2003).

It is becoming clear that the microbiota normally has a balanced compositional signature that confers health benefits and that a disruption of this balance confers disease susceptibility (Cryan and O'Mahony 2011). Diet is one of the key factors that can substantially affect microbiota composition. The composition of the microbiota plays an important role in the maintenance of intestinal homeostasis and host health. Other factors, including infection, disease, and antibiotics, may transiently alter the stability of the natural composition of the gut microbiota and thereby have a deleterious effect on the well-being of the host (Forsythe et al. 2010). Given the overarching influence of gut bacteria on health, it is perhaps not surprising that a growing body of literature focuses on the impact of enteric microbiota on brain and behavior. A brief account of effect of microbiota and probiotics on brain and behavior is given in Table 1.

Microbiota provides the significant protection against incoming bacterial pathogens. It has been shown that microbiota helps and protects the host against the viruses. There is a growing appreciation of the critical role played by the commensally microbiota, both in our general well-being and in the specific functioning of the brain–gut axis. Interestingly, bacteria may respond directly to stress-related host signals because of interplay between stress and gut microbiota.

Table 1 Summary of animal studies evaluating the effect of the gut microbiota and probiotics on host behavior

Animal model	Gut microbiota/probiotics	Effect(s)	References
Balb/c male mice	GF vs. SPF vs. gnotobiotic mice (with *Bifidobacterium infantis*; with enteropathogenic *Escherichia coli* with/without intimin receptor gene)	GF male mice had a decrease in brain-derived neurotrophic factor (BDNF)—a key neurotrophin involved in neuronal growth and survival—compared with SPF mice. Effect was reversed in gnotobiotic animals colonized with *B. infantis*, but not with *E. coli*	Sudo et al. (2004)
Urethane anaesthetized rats	*Lactobacillus johnsonii* La1	Intraduodenal injection of *Lactobacillus johnsonii* La1 reduced renal sympathetic nerve activity (RSNA) and BP and enhanced gastric vagal nerve activity (GVNA)	Tanida et al. (2005)
Sprague dawley rats	*Lactobacillus reuteri* ATCC 23272	Live, killed probiotic bacteria, or conditioned medium inhibited the constitutive cardioautonomic response to colorectal distension in rats through effects on enteric nerves	Kamiya et al. (2006)
Male Balb/c mice or AKH mice infected with *Trichuris muris*	*Lactobacillus rhamnosus* NCC4007 and *Bifidobacterium longum* NCC3001	Infection with *Trichuris muris* induced mild to moderate colonic inflammation and anxiety like behavior. However, treatment with *B. longum* reversed the effect and normalized brain-derived neurotrophic factor level	Bercik et al. (2010)
Rat maternal separation model	*Bifidobacterium infantis*	Probiotic treatment resulted in normalization of the immune response, reversal of behavioral deficits, and restoration of basal noradrenalin concentrations in the brainstem	Desbonnet et al. (2010)
Balb/c mice	*Lactobacillus rhamnosus* (JBI)	*L. rhamnosus* (*JB-1*) reduced stress-induced corticosterone and anxiety- and depression-related behavior and also increased $GABA_{A\alpha 2}$ expression	Bravo et al. (2011)

(continued)

Table 1 (continued)

Animal model	Gut microbiota/probiotics	Effect(s)	References
Balb/c mice and NIH mice	SPF + antibiotic vs. GF mice	Administration of oral antimicrobials to SPF mice transiently altered the composition of the microbiota and increased behavior and hippocampal expression of brain-derived neurotrophic factor. Interspecies gut microbiota transplantation changed species specific associated phenotype	Bercik et al. (2011)
Swiss Webster female mice	GF vs. SPF mice	GF mice have a more pronounced anxiolytic behavior and increased expression of BDNF mRNA in the hippocampus compared with SPF mice. They have reduced serotonin 1A receptor mRNA expression in the hippocampus	Neufeld et al. (2011)
NMRI mice	GF vs. SPF	GF mice have increased motor activity and reduced anxiety compared with SPF with a normal microbiota. GF mice exposed to gut microbiota early in life display similar characteristics as SPF mice	Diaz Heijtz et al. (2011)

GF germ-free, *SPF* specific pathogen free

4 Mechanisms by Which Microbiota Affect CNS Function

4.1 Activation of Vagus Nerve

The vagus nerve plays a major role in communicating changes in the gastrointestinal tract to the CNS. Information from the heart, lungs, pancreas, liver, stomach, and intestine is delivered to the brain via sensory fibers in the vagus nerve (Browning and Mendelowitz 2003). Moreover, activation of the vagus nerve has been shown to have a marked anti-inflammatory capacity (Wang et al. 2003). Many of the effects of the gut microbiota or potential probiotics on brain function have shown to be dependent on vagal activation (Goehler et al. 2008; Bravo et al. 2011; de Lartigue et al. 2011). There is now strong evidence from animal studies that gut microorganisms can activate the vagus nerve and that such activation plays a critical role in mediating effects on the brain and, subsequently, behavior. However, the mechanisms through which gut microbiota activate the vagus nerve are

currently unclear. Therefore, considerable investigations are needed to be conducted to understand the molecular mechanisms at a microbiome level underlying the effects observed.

4.2 Alteration of Microbial Composition

Probiotics may restore the composition of the gut microbiome and introduce beneficial functions to gut microbial communities, resulting in amelioration of gut inflammation and other intestinal or systemic diseases. Exogenously administered potential probiotic bacteria or infectious agents can affect the composition of the gut microbiota in multiple ways (O'Toole and Cooney 2008). Mechanisms whereby probiotics impact on the intestinal microbiota include competition for substrates, direct antagonism by inhibitory substances, competitive exclusion, and potentially host-mediated effects such as improved barrier function and altered immune response, thereby altering intestinal properties for colonization and persistence (O'Toole and Cooney 2008). All of these can have marked effects on gut–brain signaling.

4.3 Immune Activation

Microbiota and probiotic agents can have direct effects on the immune system (Forsythe and Bienenstock 2010; Duerkop et al. 2009). It has been observed that decreased intestinal microflora increases antigen transport across gastrointestinal mucosa, which is the primary interface between the external environment and the immune system. This suggests that the normal gut microflora is important in maintaining gut defenses. The beneficial probiotic bacteria have been found to interact with gut epithelial cells, the M cells in the Peyer's patches, and allied immune cells to initiate immune responses. In addition to regulating immunoglobulin production, these bacteria are also involved in increasing the profiles of some cytokines (TNF-alpha, IFN-gamma, IL-10) which are known to regulate the immune responses and maintain intestinal homeostasis. Indeed, the innate and adaptive immune systems collaborate to maintain homeostasis at the luminal surface of the intestinal host–microbial interface, which is crucial for maintaining health (Duerkop et al. 2009). The immune system also exerts a bidirectional communication with the CNS (Sternberg 2006; Dantzer et al. 2008), making it a prime target for transducing the effects of bacteria on the CNS. The cytokine production and other immune changes can modulate the peripheral and central nervous system and are associated with altered mood and behavior (Dantzer et al. 2000; Vitkovic et al. 2000). In addition, indirect effects of the gut microbiota and probiotics on the innate immune system can result in alterations in the circulating levels of pro-inflammatory and anti-inflammatory cytokines that directly affect brain function.

4.4 Production of Microbial Metabolites

Gut bacteria modulate various host metabolic reactions, resulting in the production of metabolites such as bile acids, choline, and short-chain fatty acids that are essential for host health. Through the cooperative action of different functional microbial groups, the gut microbiota synthesizes essential amino acids and vitamins. In addition, by deploying an array of glycoside hydrolases and polysaccharide lysases, the microbiota facilitates utilization of otherwise indigestible food compounds. Short-chain fatty acids (SCFAs) are organic fatty acids with 1–6 carbon atoms and are the principal anions which arise from bacterial fermentation of polysaccharides, oligosaccharides, proteins, peptides, and glycoprotein precursors in the colon. Increase in SCFAs results in the decrease of pH which indirectly influences the composition of colonic microflora, decreases solubility of bile acids, increases absorption of minerals, and reduces ammonia absorption by protonic dissociation of ammonia and other amines. It has been suggested that short-chain fatty acid delivery through probiotic ingestion may be an exciting treatment option for neurodegenerative diseases. Microbial metabolites are indispensable for majority of the biological effects of gut microbiota. Under physiological conditions, soluble dietary fibers and resistant starch can be actively fermented by commensal microbiota in the large intestine. The fermentation products such as SCFAs have been appreciated for their beneficial effects on intestinal epithelium and the gut immune system and are also known to have neuroactive properties (Thomas et al. 2012; MacFabe et al. 2011).

4.5 Production of Neurometabolites

Probiotics may act via their ability to produce various biologically active compounds, such as peptides and mediators normally associated with mammalian neurotransmission. Several molecules with neuroactive functions such as gamma-aminobutyric acid (GABA), serotonin, catecholamines, and acetylcholine have been reported to be microbially derived, many of which have been isolated from bacteria within the human gut. It has been postulated that *Lactobacillus* spp. and *Bifidobacterium* spp. produce GABA; *Escherichia* spp., *Bacillus* spp., and *Saccharomyces* spp. produce noradrenalin; *Candida* spp., *Streptococcus* spp., *Escherichia* spp., and *Enterococcus* spp. produce serotonin; *Bacillus* spp. produce dopamine; and *Lactobacillus* spp. produce acetylcholine (Lyte 2011; Matur and Eraslan 2012; Barrett et al. 2012). Secreted neurotransmitters from bacteria in the intestinal lumen may induce epithelial cells to release molecules that in turn modulate neural signaling within the enteric nervous system and consequently signal brain function and behavior of the host. Consequently, neurochemical containing/producing probiotic bacteria may be viewed as delivery vehicles for neuroactive compounds, and as such, probiotic bacteria may possibly have the potential as a therapeutic strategy

in the prevention and/or treatment of certain neurological and neurophysiological conditions.

4.6 Cell Wall Polysaccharides

The health-promoting effects of probiotics are largely due to their outer exocellular polysaccharide coating of probiotic bacteria. The exocellular polysaccharide of the probiotic bacteria protects the bacteria from acid and bile in the gut and shields from the host immune response (Fanning et al. 2012). Such studies suggest possibility of nonviable bacterial components as microbial-based therapeutic alternatives to probiotics. Like neuroactive metabolites, cell wall components of microorganisms in the intestine are believed to induce epithelial cells to release molecules which modulate neural signaling (Forsythe and Kunze 2012).

Multiple potential direct and indirect pathways exist through which the gut microbiota can modulate the gut–brain axis. They include endocrine (cortisol), immune (cytokines), and neural (vagus and enteric nervous system) pathways (Fig. 1). The brain recruits these same mechanisms to influence the composition of the gut microbiota. The hypothalamus–pituitary–adrenal axis regulates cortisol secretion, and cortisol can affect immune cells (including cytokine secretion) both

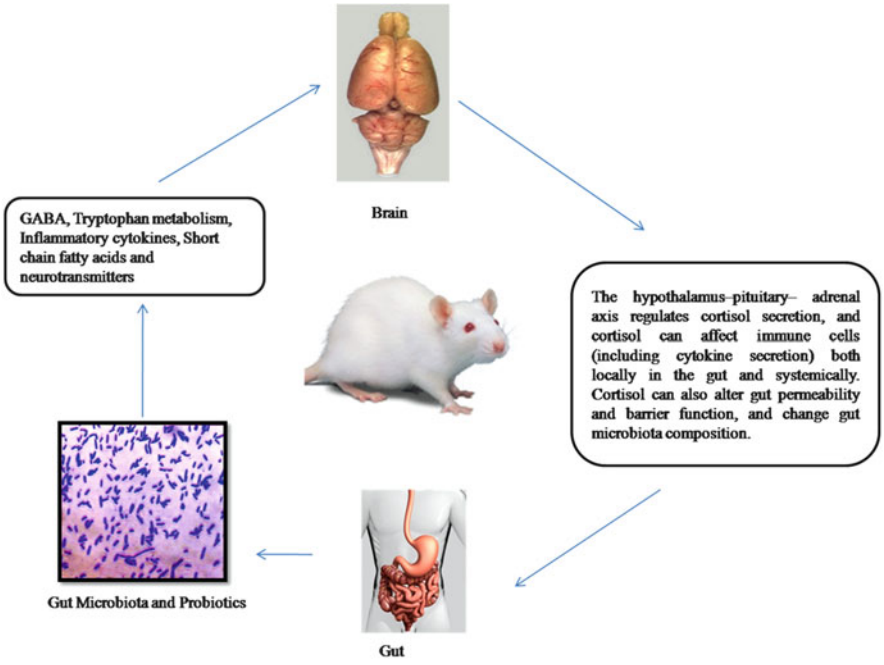

Fig. 1 Bidirectional communication between gut and brain

locally in the gut and systemically. Cortisol can also alter gut permeability and barrier function and change gut microbiota composition. Conversely, the gut microbiota and probiotic agents can alter the levels of circulating cytokines, and this can have a marked effect on brain function.

5 Conclusions

It is now established that there is a symbiotic interaction between gut microbiota and mental well-being and the integrity of both is essential to maintain the homeostasis. There is a growing body of experimental data and clinical observations which support the existence of the microbiota–gut–brain axis and suggest that it controls brain and behavior in health and disease. The knowledge gained in recent years about the ability of gut microbes to influence and contribute to host health and well-being opens new opportunity for nutritional and pharmacological tools to improve host–microbe symbiosis by using probiotics and prebiotics. It is essential that researchers should manipulate the microbial impact on gut–brain axis to elucidate the mechanisms by which microbiota communicate with the gut–brain axis which seems to be crucially important for the development of any microbiota-based and microbiota-specific therapeutic strategies for CNS diseases.

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