Review Article

Therapeutic role and importance of gut microbiota in brain and related disorder: A review

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Abstract

Depression is a chronic syndrome with a pathogenesis linked to various genetic, biological, and environmental factors. Several links between gut microbiota and depression have been established in animal models. In humans, however, few correlations have yet been demonstrated. There is a growing emphasis on the relationship between the complexity and diversity of the microorganisms that inhabit gastrointestinal microbiota and health/disease, including brain health and disorders of the central nervous system. It has been demonstrated that changes in the gut environment can lead to a broad spectrum of physiological and behavioral effects including hypothalamic pituitary adrenal axis activation and altered activity of neurotransmitter systems and immune function. Further, it has been demonstrated that microbiota could be an important in normal healthy brain function. Moreover, the relation between stress and microbiota and how alterations in microbiota influence stress related behaviors has been discussed. It has been demonstrated that bacteria including psychobiotics, probiotics and prebiotics in the gastrointestinal tract could activate neural pathways and central nervous system signaling systems. It is possible that probiotic and prebiotic could affect on emotional, cognitive, systemic and neural variables may be relevant to health and disease. In this review, it has been tried to discuss the role of gut microbiota in brain and depression. It can be concluded from the literature review that utilization of gut microbiota data may provide novel approaches for prevention and treatment of mental illness including depression.

***Keywords*:** Depression, gut microbiota, psychobiotics, probiotics, prebiotics

Introduction

Depression is a multi-factorial disease being caused by biological, psychological, and social factors. It is the leading cause of ill health and disability worldwide (Uher, 2010). Despite current and newer drugs being used in depression there is either relapses occur frequently or the treatment does not seem to be very effective. There is a need to develop newer concept or treatment options that are more effective with lesser side effects. In light of this, significant interests have evolved on the gut microbiota in the recent years within the scientific community. Gut microbiota have been associated with a large array of human diseases ranging from luminal diseases such as inflammatory bowel diseases (Ferreira *et al*., 2014) and irritable bowel syndrome (Kennedy *et al*., 2014), metabolic diseases such obesity and diabetes (Karlsson et al., 2013), allergic disease (Bisgaard *et al*., 2011) to neuro-developmental illnesses, though the strength of evidence is not robust with many of them.

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Different roles of gut microbiota

Role of gut microflora in normal function of in the body

Microbiota refers to the entire population of microorganisms that colonizes a particular location and includes not just bacteria, but also other microbes such as fungi, archaea, viruses, and protozoa (Sekirov *et al*., 2010). The large body of evidences reported that gut microbiota bear significant functional role in maintaining the gut in the normal individual and human health as a whole (Jandhyala *et al*., 2015). From an immunological perspective, microorganisms are viewed as pathogens by the host immune system that recognizes and eliminates them. However, majority of the gut bacteria are non-pathogenic and co-habit with the enterocytes in a symbiotic relationship. The gut microorganisms predominantly aid in nutrient metabolism, drug metabolism, prevention of colonization of pathogenic microorganisms and in intestinal barrier function. At the same time, the immune system has co-evolved to live in a

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collaborative relationship with the healthy microbiota, while serving its function to fight off invasive pathogenic microorganisms (Jandhyala *et al*., 2015).

Role of gut microbiota in nutrient metabolism

The gut microbiota largely derives their nutrients from dietary carbohydrates. Fermentation of the carbohydrates that escaped proximal digestion and indigestible oligosaccharides by colonic organisms result in the synthesis of short chain fatty acids (Macfarlane, 2003; Sartor, 2008). Members of the genus *Bacteroides* which are the predominant organisms that participate in carbohydrate metabolism, perform this by expressing enzymes such as glycosyl transferases, glycoside hydrolases and polysaccharide lyases (Jandhyala *et al*., 2015). The gut microbiota has shown to impart a positive impact on lipid metabolism by suppressing the inhibition of lipoprotein lipase activity in adipocytes (Hooper *et al*., 2001). The gut microbiota is also enriched with an efficient protein metabolizing machinery that function *via* the microbial proteinases and peptidases in tandem with human proteinases. Synthesis of vitamin K and several components of vitamin B is another major metabolic function of the gut microbiota (Jandhyala *et al*., 2015). Members of genus *Bacteroides* have been shown to synthesize conjugated linoleic acid that is known to be antidiabetic, antiatherogenic, antiobesogenic, hypolipidemic and have immunomodulatory properties (Badddini *et al*., 2009; Devillard *et al*., 2007; Devillard *et al*., 2009). The gut microbiota, especially *Bacteroides intestinalis* and to a certain extent *Bacteroides fragilis* and *E. coli*, also has the capacity to deconjugate and dehydrate the primary bile acids and convert them into the secondary bile acids deoxycholic and lithocolic acids in the human colon (Fuvika *et al*., 2009).

Role of gut microbiota in Xenobiotic and drug metabolism

A large body of evidences has provided sufficient insights on the role of the gut microbiota on xenobiotic metabolism which could have profound impact on therapy for various diseases in future. It has been reported that a gut microbial metabolite p-cresol can reduce the capacity of the liver to metabolize acetaminophen due to competitive inhibition of hepatic sulfotransferases (Clayton *et al*., 2009). Furthermore, cardiac glycosides like digoxin have been recently shown to up-regulate a cytochrome containing operon in the common organism *eggerthella lenta* from the actinobacteria phyla, which results in inactivation of digoxin (Saha *et al*., 1983). Further, it has been reported that microbiome induced drug metabolism is the microbial β-glucoronidase induced deconjugation of the anticancer drug irinotecan that can contribute to its toxicities such as diarrhea, inflammation and anorexia (Wallace *et al*., 2010).

Role of gut microbiota in antimicrobial protection

The requirement of a healthy gut microbiota for normal homeostasis puts the gut mucosal immune system in a challenging situation in that it needs to be tolerant to the beneficial commensals and yet prevent overgrowth of the resident pathogens. One of the simplest mechanisms of antimicrobial protection is the presence of the two-tiered mucus layer which keeps luminal microbes away from epithelial contact, predominantly in the large intestine. Further, goblet cells also produce factors like trefoil-factor and the resistin-like molecule-β that can stabilize mucin polymers and thereby maintain barrier integrity (Artis *et al*., 2004; Podolsky *et al*., 1993).

Role of gut microbiota in Immunomodulation

The gut microbiota contribute to gut immunomodulation in tandem with both the innate and adaptive immune systems. The components and the cell types from the immune system that participate in the immunomodulatory process includes the gut associated lymphoid tissues, effector and regulatory T cells, IgA producing B cells, group three innate lymphoid cells and resident macrophages and dendritic cells in the lamina propria (Jandhyala *et al*., 2015).

Role of gut microbiota in integrity of the gut barrier and structure of the gastrointestinal tract

Currently, there is a convincing body of evidence that supports the role of the gut microbiota in maintaining the structure and function of the gastrointestinal tract. *Bacteroides* is reported to induce expression of the small proline rich protein 2A, which is required for maintenance of desmosomes at the epithelial villus (Lutgendorff et al., 2008). Another mechanism that maintains the tight junctions is by toll like receptor -2 (TLR2) mediated signaling that is stimulated by the microbial cell wall peptidoglycan (Cario *et al*., 2007). Furthermore, the lactobacillus rhamnosus strain produces two soluble proteins namely p40 and p75 that can prevent cytokine induced apoptosis of the intestinal epithelial cells in an epithelial growth factor receptor and protein kinase C pathway dependent manner (Yan *et al*., 2011). The endocannabinoid system is yet another entity that regulates gut microbiota mediated maintenance of the gut barrier function. e.g., the gram negative bacteria *akkermansia muciniphilia* can increase the levels of endocannabinoids that control gut barrier functions by decreasing metabolic endotoxemia (Cani *et al*., 2009). Other evidence that support role of gut microbiota in maintaining structure and function is obtained from that have a lower intestinal surface area (Gordon, 1961), thin villi (Banasaz *et al*., 2002), increase cell cycle time (Alam *et al*., 1994) and impaired peristalsis (Husebye *et al*., 1994). The gut microbiota can also modulate mucosal glycosylation patterns that are microbial attachment sites both at the cell surface and subcellular levels.

Role of gut microbiota in brain and depression

The development of the mammalian brain is an intricate process that lasts through adolescence and into early adulthood in humans. Further, the process of brain development involves large-scale long-distance migration of cells during fetal development to specific regions or layers, as well as navigation of their processes across even longer distances to build the specific circuits that underlie behavior (Geschwind, 2013; Marin, 2003). As the gut is our largest portal to the molecular universe, various dietary components have been shown to interact directly with the developing brain and to induce functional alterations in the mature brain and there is now mounting evidences for a role by the gut microbiome in directing and facilitating developmental processes in the brain with long term implications to health.

It has been hypothesized that there can be a profound impact of microbiome induced alterations of immmune system. It has been reported that germ-free mice, devoid of all associated microorganisms, exhibit increased risk-taking behaviors and hyperactivity while also displaying learning and memory deficits compared to conventional mice (Geschwind, 2013; Marin, 2003). Further, germ-free mice showed changes in expression of the 5-hydroxytryptamine receptor (5-HT1A), neurotrophic factors such as BDNF and NMDA receptor subunits in the hippocampus (Bercik *et al*., 2011a; Heijtz *et al*., 2011; Sudo *et al*., 2004) while also displaying impaired blood-brain barrier function as well as increased myelination in the prefrontal cortex (Braniste *et al*., 2014; Hoban *et al*., 2016). There is also evidence from animal models for a potential role for the microbiome in neuropsychiatric conditions including depression and anxiety (Foster, 2013), autism spectrum disorder (Krajmalnik-Brown *et al*., 2015), schizophrenia (Severance *et al*., 2014) and even Parkinson's disease and Alzheimer's disease (Keshavarzian *et al*., 2015).

Neurodevelopmental disorders are classically studied from a genetic perspective (De la Torre-Ubieta *et al*., 2016; Parikshak *et al*., 2015). However, gastrointestinal comorbidities and food allergies are common in neurodevelopmental disorders, suggesting a role for the gut microbiome (De Theije *et al*., 2014). Thus, an appreciation for a microbial role in these conditions has been gained through profiling bacterial populations in fecal samples of patients and controls. Recent reports support the notion that the microbiome or its disruption can contribute to the pathology of various neurologic disorders, using mouse models and intervention studies (Sharon *et al*., 2016). Three general mechanisms have been suggested to describe how the gut microbiota influences depression, namely through inflammation or through the hypothalamic-pituitary-adrenal axis (HPA) or interference with neurotransmitter signaling (Foster, 2013).

Role of Microbiodata in neuroinflammation and depression

It has been reported that microbiota could stimulate cytokines and chemokines release which in turn regulates local levels of bacteria in the gut. As well as influencing local immune responses at the epithelium, microbiota can synthesise and release neurotransmitters as well as influence the release of neuropeptides and hormones from enteroendocrine cells of the intestines. Gut peptides such as ghrelin, gastrin, orexin, galanin, cholecystokinin, leptin and neuropeptide Y are thought to influence peripheral neural communication and can also act centrally to influence behaviour. Current hypotheses suggest that these circulating cytokines, chemokines, endocrine messengers and microbial by-products can infiltrate the blood and lymphatic systems or influence neural messages carried by the vagal and spinal afferent neurons to impact on centrally-mediated events including regulation of HPA axis activity and neuroinflammation (Rea *et al*., 2014).

The gastrointestinal microbiota plays a key role in HPA axis activity and immune response. It has been reported that bi-directional microbiome-gut-brain axis in homeostatic conditions and in response to changes in environment likely involve dynamic molecules with multiple effector mechanisms that can traverse different anatomical environments and communicate within their local environment to mediate a complex co-ordinated response on multiple physiological systems. Numerous molecular candidates have been proposed including neurotransmitters, neuropeptides, endocrine hormones and immunomodulators (Rea *et al*., 2014).

It has been reported that there is a likely involvement of the microbiota in mediating or modulating stress and neuroinflammation and their associated behavioural responses. There is a paucity of studies conclusively linking microbiota- mediated changes locally in the gut and periphery with central effects (Rea *et al*., 2014).

***Effect of gut microbiota on HPA axis and its influence in depression*:**

HPA is a neuro-endocrine stress response system, being important in both mood disorders and functional diseases. Alterations of the HPA system have been diagnosed in patients having different mental states including posttraumatic stress disorder (De Kloet *et al*., 2005), schizophrenia (Walker, 1997) social anxiety (Beaton *et al*., 2006) and depression (Holtzheimer, 2006).

Over the past few years, it has become clear that the guts microbiota plays a role in both the programming of the HPA axis early in life and stress reactivity over the lifespan. In a rat model, it has recently been reported that treatment with

probiotic bacteria can interfere with the HPA response to acute physiological stress, suggesting a mechanistic connection between the gut microbiota, HPA and stress (Ait-Belgnaoui *et al*., 2012).

It was reported that gut microbiota alterations in pups can disturb the development of stress-related HPA axis function (Sudo *et al*., 2004). Clinically, depressive episodes are associated with dysregulation of the HPA axis (Barden, 2004) and resolution of depressive systems with normalization of the HPA axis (Heuser *et al*., 1996; Nickel *et al*., 2003). A direct link between microbiota and HPA reactivity was established with the 2004 with report that showed an exaggerated corticosterone and adrenocorticotrophin response to restraint stress in germ-free mice when compared with conventionally house- specific pathogen-free mice (Sudo *et al*., 2004). Germ-free mice have no commensal microbiota and exhibit an undeveloped immune system (Boman, 2000; Macpherson, 2004a; Macpherson, 2004b; Tlaskalova-Hogenova *et al*., 2005). The use of mice raised in a germ free environment allows investigators to assess directly the contribution of the microbiota to the development of brain and body systems. This landmark study, showing increased stress reactivity in germ free mice (Sudo *et al*., 2004) was the catalyst for neuroscientists to consider the importance of microbiota in CNS function.

The stress response system is functionally immature at birth and continues to develop throughout the postnatal period, a developmental period coinciding with intestinal bacterial colonization. Studies using maternal separation in rats showed that neonatal stress leads to long-term changes in the diversity and composition of gut microbiota (García-Ródenas *et al*., 2006; O'Mahony *et al*., 2009), which may contribute to long-term alterations in stress reactivity and stress-related behavior observed in these rats. In support of this, concurrent treatment with probiotics (*Lactobacillus* sp.) during the early stress period has been shown to normalize basal corticosterone levels which are elevated following maternal separation (Gareau *et al*., 2007). An indirect role for microbiota in the stress response was demonstrated in an animal model of stress induced social disruption where it was shown that microbiota are necessary for some of the stress-induced changes in inflammation (Allen et al., 2012). Stress is known to increase intestinal permeability, thus affording bacteria an opportunity to translocate across the intestinal mucosa and directly access both immune cells and neuronal cells of the enteric nervous system (Gareau *et al*., 2008; Teitelbaum *et al*., 2008). This is therefore a potential pathway whereby the microbiota can influence the CNS via the immune system and ENS in the presence of stress. A recent study has shown that pretreating rats with probiotic, *Lactobacillus farciminis* reduced the intestinal permeability that typically results from restraint stress and also prevented associated HPA hyper- reactivity (Ait-Belgnaoui *et al*., 2012).

Gut microbiota and neurotransmitter signaling

Direct interference with neurotransmitter signaling may be involved in depressive disorders. It has been shown that the neurotransmitter GABA can be produced by intestinal bacteria (Barrett *et al*., 2012). Furthermore, probiotic bacteria can modulate depressive behavior through GABA signaling in a mouse model (Bravo *et al*., 2011). The other signaling pathway that has been linked to depression is serotonergic signaling, where it has been shown that the serotonergic turnover is higher in the striatum in germ-free mice compared to conventional animals (Heijtz *et al*., 2011).

The brain neurotransmitter, the monoamine serotonin is an important regulatory factor in the gastrointestinal tract and other organ systems. More than 90% of the body's 5-HT is synthesized in the gut where 5-HT activates as many as fourteen different 5-HT receptor subtypes (Gershon, 2007) located on enterocytes (Hoffman *et al*., 2012) enteric neurons (Mawe, 2013) and immune cells (Baganz, 2013). In addition, circulating platelets sequester 5-HT from the GI tract, releasing it to promote hemostasis and distributing it to various body sites (Amireault, 2013). As such, gut-derived 5-HT regulates diverse functions including enteric motor and secretory reflexes (Gershon, 2007), platelet aggregation (Mercado *et al*., 2013), immune responses (Baganz, 2013), bone development (Chabbi-Achengli *et al*., 2012; Yadav *et al*., 2008) and cardiac function (Coˆ te´ *et al*., 2003). Furthermore, dysregulation of peripheral 5-HT is implicated in the pathogenesis of several diseases including irritable bowel syndrome (Stasi *et al*., 2014), cardiovascular disease (Ramage, 2008) and osteoporosis (Ducy, 2010).

The molecular mechanisms controlling the metabolism of gut 5-HT remain unclear. In the gastro intestinal tract, 5-HT is synthesized by specialized endocrine cells, called enterochromaffin cells (ECs), as well as mucosal mast cells and myenteric neurons (Gershon, 2007), but the functions of these different pools of gut 5-HT are incompletely understood. In addition, two different isoenzymes of tryptophan hydroxylase namely Tph1 and Tph2 mediate non-neuronal versus neuronal 5-HT biosynthesis (Walther *et al*., 2003) but little is known regarding the endogenous signals that regulate Tph expression and activity.

Psychobiotics and depression

Psychobiotics were previously defined as live bacteria (probiotics) which, when ingested, confer mental health benefits through interactions with commensal gut bacteria. Also, prebiotics, which enhance the growth of beneficial gut bacteria, is included in this category.

Probiotics, beneficial bacteria that yield positive health

outcomes, have received particular attention. There was an evaluation for the efforts to manipulate commensal gut bacteria with psychobiotics. These psychobiotics were first defined as probiotics that, when ingested in appropriate quantities, yield positive psychiatric effects in psychopathology (Dinan *et al*., 2013). The bacteria most frequently exploited as probiotics are the gram-positive *Bifidobacterium* and *Lactobacillus* families (Burnet, 2013; Mayer *et al*., 2014). With the presence of such bacteria, the immune system learns to distinguish to between pro- and anti- inflammatory entities and develops appropriate immunogenic responses by identifying pro-inflammatory elements as antigenic (Sansonetti et al., 2009).

Psychophysiological effects of psychobiotics

Much psychobiotic research is based on rodent models which use rodent stress inductions and rodent behavioural tests to assess motivation, anxiety, and depression. Psychobiotics applied to rodent models of illness, infection and neurodegeneration also provide early clinical insight into human diseases.

The psychophysiological effects of psychobiotics fall into the following three categories: (i) Psychological effects on emotional and cognitive processes. (ii) Systemic effects on the HPA axis and the glucocorticoid stress response and inflammation (Dowlati *et al*., 2010). (iii) Neural effects on neurotransmitters and proteins. Relevant neurotransmitters include gamma aminobutyric acid (GABA), glutamate and proteins include brain-derived neurotrophic factor (BDNF) which plays a crucial role in learning and memory processes including spatial learning, extinction of conditioned fear and object recognition (Heldt *et al*., 2007; Lu *et al*., 2008). BDNF is reduced in anxiety and depression, a reduction that is reversible through antidepressant action (Martinowich, 2008).

Psychobiotics and brain signalling

The mechanisms through which psychobiotics exert their effects have yet to be clearly defined and remain poorly understood. Though there are some studies that provide mechanistic insights for humans, the majority of research is based on rodent models. A crucial step in developing knowledge of the mechanisms lies in investigating how the microbiome and the brain communicate with one another (Sarkar *et al*., 2016).

Psychobiotics and enteric nervous system interactions

Gut bacteria could regulate electrophysiological thresholds in enteric nervous system neurons. e.g. myenteric neurons exposed to *Bifidobacterium longum* fermented substances showed reduced generation of action potentials when they were electrically stimulated (Bercik *et al*., 2011b). Similarly, colonic neurons treated with *Lactobacillus rhamnosus* showed increased excitability, an effect that emerged from inhibition of calcium-controlled potassium gates (Kunze *et al*., 2009). Other work showed that neurons from the dorsal root ganglion in the colon did not display hyper-excitability in response to noxious stimulation if they had been treated with *Lactobacillus rhamnosus* (Cryan, 2012; Ma *et al*., 2009). Myenteric neurons are also in close proximity to the gut lumen (Foster, 2013), which would facilitate their contact with the microbiome. In germfree mice, these neurons show lower levels of excitability compared to their normally- colonised counterparts (McVey, 2013). One study found evidence of intestinal neural abnormalities in the jejunum and ileum of germ-free mice in comparison to controls (Collins *et al*., 2014), with germ- free mice showing reduced nerve density, fewer nerves per ganglion and a greater number of myenteric nitrergic neurons. Recent evidence also indicates that the microbiome affects ion transport controlled by cyclic adenosine monophosphate (cAMP) (Lomasney *et al*., 2014).

Overall, these results provide striking evidence of direct, bacteria-induced modulation of the enteric nervous system. Moreover, the influence of the microbiome on the enteric nervous system extends beyond neurons with recent findings demonstrating that gut bacteria also play a crucial role in the development and homeostasis of glial populations in the gut (Kabouridis *et al*., 2015).

It has been found that gut bacteria also produce a range of neurotransmitters through the metabolism of indigestible fibres. These include dopamine and noradrenaline by members of the *Bacillus* family, GABA by the *Bifidobacteria* family, serotonin by the *Enterococcus* and *Streptococcus* families, noradrenaline and serotonin by the *Escherichia* family, and GABA and acetylcholine by the *Lactobacilli* family (Barrett *et al*., 2012; Dinan *et al*., 2015; Lyte, 2011). Though there is no direct evidence as of yet, it is likely that these neurotransmitters modulate synaptic activity in the proximal neurons of the enteric nervous system, and is an important avenue for future research.

Psychobiotics, vagal signalling and depression

Stimulating the vagus nerve exerts anti-inflammatory effects (Borovikova *et al*., 2000) and is used therapeutically for refractory depression. There is also evidence of both antidepressants and anxiolytics exerting vagal effects (Adinoff *et al*., 1992; Salam, 2004; Smith *et al*., 2014), suggesting that vagal modulation may be a common pathway for the effects of antidepressants, anxiolytics, and psychobiotics. Several animal studies have found that the vagus nerve mediates the relationship between psychobiotics and their psychophysiological effects, as severing the vagus nerve abolishes responses to psychobiotic administration (Bercik *et al*., 2011a; Bravo *et al*., 2011; De Lartigue *et al*., 2011). It has been reported that antimicrobials could increase

intrinsic relative abundance of *Lactobacilli* in innately anxious male BALB/c mice, a change that was accompanied by increased exploratory behaviour and BDNF expression.

Although it is unclear to what extent the small fraction of SCFAs crossing into the central nervous system modulates neurotransmission, there is some evidence for their psychotropic properties at pharmacological concentrations. It has been reported that the systemic sodium butyrate injections could produce antidepressant effects in rats by increasing central serotonin neurotransmission and BDNF expression (Sun *et al*., 2016).

The microbiome has also been shown to possess a substantial role in generating metabolites that enter circulation and exert a range of consequences outside the gut (Morris *et al*., 2016). Similarly, gut bacteria crucially affect the metabolism of tryptophan into serotonin in enterochromaffin cells. Though the specific mechanism through which bacteria might control serotonin production in enterochromaffin cells was unknown at that time, a recent study has attributed this role to indigenous spore-forming bacteria in the gut (Yano *et al*., 2015). There were similarly dramatic differences in other tryptophan metabolites, especially those containing indole such as the antioxidant indole-3- propionic acid (IPA) and indoxyl sulphate which were undetected in the germ-free mice and whose production was therefore interpreted as being fully mediated by gut bacteria. It has been assumed that these metabolites are sensitive to psychobiotic action. However, the relationships between the microbiome, bacteria-derived metabolites, and the central nervous system as well as the role of psychobiotics in modulating this network, remain virtually unexplored (Sarkar *et al*., 2016).

Bacteria-immune interactions

Gut microbes can communicate with the enteric nervous system and the innate immune system via interactions between the a microbe-associated molecular pattern (MAMPs) and pattern-recognition receptors embedded along the lumen. The MAMPs of beneficial bacteria by triggering pattern-recognition receptors may precipitate secretion of anti-inflammatory cytokines such as interleukin-10 (Chu, 2013; O'Mahony *et al*., 2005). While rigorous mechanistic descriptions of the relationship between MAMPs, pattern- recognition receptors and reductions in inflammation are lacking. One intriguing hypothesis is that beneficial bacteria might serve as physical barriers that block pathogenic MAMPs from activating host pattern- recognition receptors such as TLR2 and TLR4 by binding to them instead, thereby preventing pro-inflammatory responses (Zhou *et al*., 2015).

Prebiotics may act in a similar capacity, as there is evidence of direct interaction between oligosaccharides and the epithelium, independent of gut bacteria, with substantial reductions in pro-inflammatory cytokines (Bode *et al*., 2004; Eiwegger *et al*., 2010). Prebiotics may prevent pathogenic MAMPs from accessing pattern-recognition receptors, either by acting as physical barriers to reduce the incidence of MAMP binding, or by directly binding to the receptor themselves. Thus, prebiotics need not exert all of their beneficial effects exclusively by growing commensal bacteria.

It has been reported that *Bifidobacterium infantis* 35624 and *Lactobacillus GG* (O'Mahony *et al*., 2005; Pessi *et al*., 2000) have been shown to enhance concentrations of interleukin-10. By reducing the total quantity of pro-inflammatory cytokines, either directly or by increasing anti- inflammatory cytokines, psychobiotics may be reducing the probability of cytokines gaining access to the central nervous system and may also be restoring inflammation- induced permeability of the blood-brain barrier (Banks, 2010; De Vries *et al*., 1996; Ek *et al*., 2001).

A parasitic infection study (Bercik *et al*., 2010) yielded an important mechanistic insight regarding cytokine roles in microbiome-brain signalling. Healthy male mice were infected with the *Trichuris muris* parasite, following which they were treated with *Bifidobacterium longum* NCC3001, *Lactobacillus rhamnosus* NCC4007 or vehicle. Infection increased anxious behaviour and reduced hippocampal BDNF mRNA levels. *Bifidobacterium longum* NCC3001 reduced anxious behaviour and normalised BDNF mRNA concentrations. However, these changes occurred in the absence of prebiotic-induced reductions in any pro-inflammatory cytokines. This may be interpreted as evidence that psychobiotic effects also occur through mechanisms other than cytokine reduction.

The microbiome also controls the development of appropriate immunosuppression in response to dietary antigens through the production of immunosuppressive regulatory T cells (Kim *et al*., 2016). These cells prevent full immunogenic reactions to normal nutritional input whereas germ-free mice do not possess this immunosuppressive activity and show exaggerated immune responses to dietary antigens.

Glucocorticoids and gut barrier

Though stress is not a signalling pathway as such, it nonetheless constitutes an important influence on structural and functional aspects of the microbiome (Bharwani *et al*., 2016). Glucocorticoids dysregulate gut barrier function, reducing the integrity of the epithelium and permitting outward migration of bacteria (Söderholm *et al*., 2001), triggering inflammatory immune responses. Bacterial migration outside the lumen could also directly modulate inflammation by raising the concentrations of pro- inflammatory cell elements such as lipopolysaccharide, (Santos *et al*., 2001; Söderholm *et al*., 2001; Mass *et al*., 2008) a process associated with human

depression (Mass *et al*., 2008; Maes *et al*., 2012). Probiotic supplementation with the *Bifidobacterium* or *Lactobacillus* families is able to restore gut-barrier integrity and reduce stress-induced gut leakiness in mice and rats (Ait-Belgnaoui *et al*., 2012; Zareie *et al*., 2006).

However, both effects on glucocorticoids and cytokines as mechanisms of action for psychobiotic - induced benefits follow ceiling-effect logic. These are reasonable mechanisms for therapeutic benefits in cases of inflammation, stress or poor gut-barrier function at baseline, but cannot explain the benefits observed in healthy groups where these abnormalities are presumably absent (Messaoudi *et al*., 2011;Schmidt *et al*., 2015; Tillisch *et al*., 2013).

Conclusion

It has been concluded from significant progress in recognizing the importance of gut microbiota to brain function that alterations in microbiota could influence behaviour, anxiety and depressive-like behaviours, raising the possibility that innovative approaches in gut microbiota could be useful in treating the neuropsychiatric disorders including depression.

Conflict of interest

The authors declare no conflicts of interest.

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