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REVIEW ARTICLE

Probiotics as an Adjuvant Therapy in Major Depressive Disorder

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Abstract: ***Background***: Major depressive disorder is a common, debilitating psychiatric disorder, which originates from the interaction of susceptibility genes and noxious environmental events, in particular stressful events. It has been shown that dysregulation of hypothalamus-pituitary-adrenal (HPA) axis, imbalance between anti- and pro-inflammatory cytokines, depletion of neurotransmitters (serotonin, norepinephrine and/or dopamine) in the central nervous system, altered glutamatergic and GABAergic transmission have an important role in the pathogenesis of depression. Due to numerous diverse biological events included in the pathophysiology of depression a large number of antidepressant drugs exerting distinct pharmacological effects have been developed. Nevertheless, clinical needs are still not solved.

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Results: Relatively new research strategies advanced the understanding of psychiatric illness and their connections with disturbances in gastrointestinal tract. The existence of bidirectional communication between the brain and the gut has been proven, and an increasing body of evidence supports the hypothesis that cognitive and emotional processes are influenced through the brain-gut axis. On the other hand, microbiome may influence brain function and even behavior giving to the specific microorganisms a psychobiotic potential.

Conclusions: In this review we discuss the possibilities of classical antidepressant drug treatment being supported with the psychobiotics/probiotic bacteria in patients suffering from major depressive disorder.

Keywords: Antidepressant drug, brain-gut axis, gastrointestinal system, major depressive disorder, microbiota, psychobiotics.

BRAIN GUT AXIS

The bidirectional signaling pathway between the brain and the gastrointestinal system has been recognized and it has been underlined that emotional feeling can influence the function of the gut and vice versa, the condition of gastrointestinal (GI) tract can alter brain functions. One of the first notions in this field was made by surgeon Beaumont [1] who monitored gastric secretions and noted an association between patient's mood and his gut function.

Many studies provided evidence that the brain-gut axis is a bidirectional homeostatic communication pathway which might have pathophysiological consequences when is dysfunctional. One of the first recognized roles of this axis was central regulation of digestive function. Namely, alterations in brain–gut interactions are associated with various GI dysfunctions such as gut inflammation, chronic abdominal pain syndromes, and eating disorders, as well as stress-response and overall behavior (for review see [2]). The existence of the link between the gut and the brain has been underlined due to high co-morbidity between stress-related diseases (anxiety, depression) with gastrointestinal disorders such as irritable bowel syndrome (IBS) and inflammatory bowel disorder (IBD) [3].

Antidepressant medication is widely used to treat depressive symptoms although 30–40% of patients do not respond to current drug strategies [4]. Moreover, studies on depression treatment focused mainly on the genetic, behavioral, and neurological aspects of the disease, while relatively new research strategies involve environmental risk factors and immune dysregulation as important elements. Therefore, the search for appropriate and effective treatment offers new options and among them involvement of probiotic bacteria gives promising results.

MICROBIOME: COMPOSITION AND FUNCTIONS

Bacteria colonization of newborns in mammals appears during early postnatal life whereas commensal/normal microbiota remains throughout the life span notwithstanding being modified. Therefore, microbiota profile could reflect the environmental changes of an individual. In humans lower intestine contains approximately 10^{14}–10^{15} bacteria being more numerous then eukaryotic cells composing human body [5].

The link between the host and microbiota is mainly beneficial, although microbiota can be considered as symbionts (mutual health-promoters) but also as pathobionts

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(opportunistic pathogens) for host [6]. In the recent years our understanding of the diversity and the complexity of bacterial population has been extended due to novel high-throughput molecular and metagenomic methods [7]. Large studies aimed to determine the microbial variation and function across individuals and populations revealed a high inter-individual diversity and stability of microbiota over time, and established the existence of relation between alterations in composition and stability of microbiota and the organism state [8, 9].

In the gut several bacterial phyla are represented with approximately 1000 species [10] and it has been shown, using metagenomic population approach, that, in general, specific bacterial populations are present among groups of individuals [5, 11]. On the other hand, variability in commensally bacterial content among related and unrelated persons has been shown in more detailed analyses [12]. In adults *Bacteroides* and *Firmicutes* phyla predominate while the amount and the diversity of the microbial particles increase from stomach to the small intestine and colon [13].

The colonization of the infant gut starts at birth when exposed to maternal microbiota while infants born by cesarean section develop different microbiota in relation to vaginally delivered babies, thus having abnormal immune responses and an enhanced long term risk for development of immune diseases [14]. At 1 to 3 years age, the specific adult-type microbiome is developed which has been modulated in each person due to different causes, and one of them is diet [5]. The microbiota's composition is influenced also by individual`s genetics, age and sex. *e.g.* the homeostatic balance within the microbiota is diminished in the elderly, with distinct between individuals who age healthy and those having health deteriorated with age [15].

The presence of commensal microorganisms is important for nutrient processing, function of immune system [16], other aspects of host physiology [17], and for brain development and function [3]. In the GI system microbiome has various roles whereas three of them are widely recognized: defense against pathogen colonization throughout the competitive mechanisms and the production of several antimicrobial substances, strengthening of the intestinal epithelial wall and limitation of bacterial penetration into tissue through the stimulation of secretory IgA, and the facilitation of nutrient absorbace through degradation of the indigestible dietary compounds. There is also relatively newly recognized role of microbiome in GI system: the involvement in maturation and functionality of the host immune system. Namely, germ-free (GF) animals have higher susceptibility to infection together with reduced activity of digestive enzymes and thinner muscle wall thickness [18]. It has been shown that GF mice have immune defects at structural (*e.g.* decreased peyer's patches, lamina propria and isolated lymphoid follicles) and cellular (*e.g.* decreased intestinal $CD8^+$ T cells and $CD4^+$ T helper 17 cells and reduced B cell production of secretory IgA) levels [18, 19]. Moreover, gut microbiome gives distinct signals for tuning host immune status toward either regulator or effectors direction and has an important role in peripheral immune response and homeostasis [20].

Microbiome, at a specific niche, is also involved in local as well as systemic effects on host biology. Namely, a disruption of a balanced gut microbiome composition (dysbiosis) may cause chronic low-grade intestinal inflammation, as in the IBS or intense intestinal autoimmunity, as in the IBD. In those patients even a dietary change can bring symptomatic improvement [21].

Although traditionally microorganisms have not been considered important for development and function of the central nervous system or involved in the pathophysiology of brain diseases (especially chronic, *e.g.* disorders of mood and affective disorders, Parkinson's disease, or Alzheimer's disease) new trends in neuroscience demand research based on growing body of evidence of the gut-microbiome-brain interactions in health and disease.

THE INVOLVEMENT OF GUT MICROBIOTA IN BRAIN FUNCTIONS

One of the first diseases that has been suspected to be related to altered gut microbiota is autism spectrum disorder (ASD) [22, 23], a concept that has recently been revisited both in rodent models and in human subjects. Animal studies provided evidence that different types of psychological stress can influence the composition of the gut microbiota (*e.g.* maternal separation, restraint conditions, crowding, heat stress, acoustic stress) [24, 25]. The link between the gut and the brain is bidirectional meaning communication between the microbiome (in the gut), the gut itself, and the brain. Through this pathway endocrine-, neurocrine-, and inflammation-related signals originated from gut microbiota may influence brain functions. And vice versa, the brain produced signals can affect the microbial composition and function throughout endocrine and neural mechanisms.

The most investigated mood disorder and its relation with GI system is anxiety since it has nervous, endocrinal and immunological basis. The gut-brain connection has been underlined in studies were severe but also mild forms of intestinal dysfunctions are associated with stress and anxiety, probably due to neurotransmitter and immune signaling pathways between the gut and the brain [3, 26, 27].

The microbiome can influence the functioning of HPA axis and immune system, it is not surprising when in germ-free (GF) mice with a sterile gastrointestinal tract HPA axis is overactive (one of the traits in depression) in response to stress and thus reversed by introduction of a single microorganism, *Bifidobacterium infantis* (a predominant bacterium in the infant gut) which is commonly used as probiotic organism [28]. Moreover, alterations in the levels of key monoamines (or their receptors) involved in depression (noradrenaline and 5-hydroxytryptamine; serotonin) in corticolimbic regions of the brain have been shown [29, 30], as well as alterations in neurotrophic factors (brain-derived neurotrophic factor, BDNF) in the hippocampus of GF mice [31]. In GF animals reduced anxiety-like behavior has been related to neurochemical changes, such as decreased number of neurotransmitter receptors along with increased tryptophan (serotonin precursor) metabolism [29, 32]. It has been shown that certain bacterial species (mainly *Bifidobacterium* and

Lactobacillus) have anti-anxiety effect, since probiotic treatment with certain strains of *B. longum*, *B. infantis*, *L. helveticus*, or *L. rhamnosus* (one or their combination) normalized behavior of such animals [33-35]. On the other hand, pathogens (opportunistic or obligate) in GI tract can exacerbate anxiety. For example, infection with gram-negative pathogen *Campylobacter jejuni* initiated anxiety-like behavior probably through the activation of visceral sensory nuclei in the brainstem and enhanced expression of c-Fos protein in the hypothalamic paraventricular nucleus [36, 37]. Similar increase in c-Fos expression was also implicated in *Citrobacter rodentium* induced anxiety [38], whereas *Trichuris muris* caused only moderate colonic inflammation and anxiety-like behavior that was associated with immunological (increased TNFα, kynurenine and kynurenine/tryptophan ratio) and neurochemical (decreased hippocampal BDNF mRNA expression) changes [31, 33].

THE CONNECTION BETWEEN MICROBIOTA AND DEPRESSION

It is suggested that microbiota could be involved in the modulation of behavior in stress-related disorders [39], where major depression is a common, recurrent and stress-related. Depression is a complex chronic debilitating mood disorder related to various factors involved in its etiology, such as genetics and environmental. Depression can be described as a mood disorder in which depressed mood and/or loss of interest or pleasure in life situations are present at least 2 weeks or longer, with a minimum of five accompanied symptoms which cause clinically significant impairment in persons everyday functioning (meaning social, work, or other important areas of functioning: unintentional, significant weight loss or gain, sleep disturbances, fatigue, loss of energy, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate, and recurrent thoughts of death) (according to American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5) [40].

Patients with major depressive disorder frequently have alterations in HPA axis (*e.g.* elevated cortisol levels in plasma, elevated corticotrophin releasing factor (CRF) levels in the cerebrospinal fluid). In addition, it has been established that pro-inflammatory cytokines (produced as inflammatory response to microbial pathogens during host infection) induce not only symptoms of sickness, but also symptoms of major depressive disorders in vulnerable individuals with no previous history of mental disorders, thus suggesting that the brain–cytokine system is involved in depression arousal (for review see [41]).

Over the years, relationship between altered gut microbiota and depression has been established in animal models. Three potential mechanisms have been suggested on how microbiota from the gut influences depression. One of them is inflammation since IgA and IgM mediated inflammatory responses to lipopolysaccharide are elevated in depressed individuals. Moreover, lower adaptation capabilities due to abnormalities in circulating cytokines can induce depression as well. HPA is a key element of neuroendocrine stress response system and thus play a critical role in the regulation of mood. The alterations in HPA activity, as already mentioned, are therefore implicated in different mental states (among them anxiety and depression). It has been shown that the treatment with probiotic bacteria *L. farciminis* attenuates HPA stress response through the prevention of intestinal barrier impairment and a decrease of circulating lipopolysaccharide levels [33, 42]. A third potential mechanism is direct interference with neurotransmitter signaling. It has been shown that intestinal bacteria can produce gamma aminobutyric acid (GABA) which is the main inhibitory neurotransmitter and is significantly involved in the regulation of many physiological and psychological processes [43-45]. It is implicated that the changes in the expression of GABAergic receptors are involved in the pathogenesis of anxiety and depression [46-48], whereas Bravo and colleagues [34] showed that chronic treatment with *L. rhamnosus* induces region-dependent alterations in the expression of $GABA_A$ and $GABA_B$ receptor subunit mRNA in the brain. Serotonin plasma levels are higher in GF mice compared to control [49] whereas serotonergic turnover is higher in the striatum of GF animals and has been connected to depression-like behavior [30]. Clarke and colleagues [42] showed in newborn mice elevated levels of serotonin and its precursors upon gut colonization with microbiota.

It is suggested that the gut microbiota affects the brain *via* the humoral and neural mechanisms of the gut–brain axis, with particular attention on the vagus nerve. Bercik and coworkers [50] showed that chronic mild gastrointestinal inflammation induces anxiety-like behavior in mice which in turn affects central nervous system biochemistry. The observed changes could be abolished through inflammation-dependent and -independent pathways, neither of which requires the intact vagus nerve. On the other hand, chronic colitis associated with anxiety-like behavior was not present in vagotomized mice [50].

Neurobiology of depression in a mouse model of depression-like behavior with comorbid anxiety (upon bilateral surgical removal of the olfactory bulb mice exhibit hyperresponsiveness to psychological stressors) has been investigated and the results showed that anxiety and depression influence the microbiota composition in the colon [51]. The authors hypothesized that observed difference in microbial composition was rather due to a shift in the proportion of certain bacterial phyla than the appearance/ disappearance of some of them following bulbectomy and emphasized the importance of redistribution along with abundances of bacterial phyla with a depression- (and anxiety-) related phenotype. Moreover, central CRF infusion, producing similar behavior, reduced intestinal (colon) motility and relative diversity of microbiota suggesting that observed changes are probably due to increased activation of the stress response and alterations in colonic motility [51].

Studies have also shown the impact of dietary and environmental stress on microbial populations in the murine GI tract where stressed animals had lower abundance of lactobacili in comparison to control animals [52]. It has been shown, using the maternal separation model of early-life stress and depression, that adverse early-life events are associated with a weaker stress response and a consecutive

increase in vulnerability to disease in later life thus affecting the brain-gut axis [53]. For example, male rat pups were stressed by maternal separation (removed from mothers for 3 h daily between postnatal days 2–12) while the control animals were left undisturbed. The results showed that early-life stress increases the number of fecal boli and corticosterone levels in animals when they reached adulthood. In stressed animals after an *in vitro* lipopolysaccharide challenge an increase in the systemic immune response was observed, as evidenced by an exaggerated release of pro-inflammatory cytokines. The authors also found a reduction in the diversity of the microbiota in maternally separated relative to the non-separated animals. http://onlinelibrary.wiley.com/doi/10.1111/nmo.12198/full - nmo12198-bib-0024 Increased visceral sensation was also seen along with local morphological changes in the GI tract (mainly in colon) such as increased mucus secretion with an elevation in the number of mucosal goblet cells [26]. Moreover, Pyndt Jørgensen and colleagues [54] found the diet-induced change in the composition of gut microbiota and the association between microbiota and anhedonic-like behavior. Thus, a diet high in saturated fat changes microbiota and contributes to the development of depression-like behavior through the immune system link between the gut and the brain. A high fat diet provokes changes in composition of microbiota and consequent imbalance in local gut immune system (increase in pro-inflammatory cytokines), thereby initiating neuroinflammation and resulting in behavioral changes [54].

Rats treated chronically with probiotic bacteria *Bifidobacteria infantis* had changes in central HPA and monoaminergic (increase in plasma concentrations of tryptophan and kynurenic acid, reduced 5-HIAA concentration in the frontal cortex and a decrease in DOPAC in the amygdaloid cortex) activity, features that have been implicated in the etiology of depression. Namely, the attenuation of pro-inflammatory immune responses (attenuation of IFN-γ, TNF-α and IL-6), and the elevation of the serotoninergic precursor tryptophan by bifidobacteria treatment supported the proposition that this probiotic may possess antidepressant properties [55]. In diabetic rats probiotics (*L. helveticus* and *B. longum*) administration considerably improved impaired spatial memory, recovered declined basic synaptic transmission and further restored disturbed hippocampal long-term potentiation [56]. On the contrary, in humans same probiotics consumption significantly reduced stress-induced GI symptoms (abdominal pain and nausea/vomiting) but did not modify the other physical and psychological symptoms and sleep problems induced by stressful life events [57] although they were beneficial on sleep efficiency in elderly subjects [58].

MICROORGANISMS IN GI TRACT IN HUMANS WITH MOOD DISORDERS

Naseribafrouei and coworkers [60] compared the fecal microbiota of depressed and non-depressed individuals. They specifically examined microbiome alterations in depression in humans and found no significant group differences in microbiota diversity, but reported general overrepresentation of *Bacteroidetes* species while the family *Lachnospiraceae* showed an underrepresentation in individuals diagnosed with depression. The *Oscillibacter* and *Alistipes* type strains, a genus in the phylum of Bacteroidetes, have been more abundant in depressed individuals and thus showed a significant association with depression [60]. Strain *Oscillibacter* has valeric acid as its main metabolic end product (a homolog of inhibitory neurotransmitter GABA), while genus *Alistipes* shows a marked increase following stress in mice [61] and is also more abundant in IBS [62] and in chronic fatigue syndrome [63]. Mentioned taxonomic correlations suggest a possible common feature in several disorders with comorbid anxiety and depression.

USE OF PROBIOTICS

There are only scarce data on the use of probiotics as food and their influence on mood and GI changes. Tillisch and coworkers [59] studied consumption of a fermented milk product with probiotic (*Bifidobacterium animalis*, *Streptococcus thermophiles, Lactobacillus bulgaricus*, and *Lactococcus lactis*) for 4 weeks twice daily by healthy women. Probiotic intake was associated with reduced task-related response of a distributed functional network containing affective, viscerosensory, and somatosensory cortices. The observed differences in activity during the task may be explained by alterations in intrinsic activity of resting brain.

Bangsgaard Bendtsen and coworkers [61] showed that anxiety changes gut microbiota (overrepresented *Alistipes* type strains) through pro-inflammatory cytokines. Moreover, *Alistipes* species are indole-positive and may affect tryptophan availability [64]. Consequently, higher abundance of *Alistipes* type bacteria could disrupt the balance in the intestinal serotoninergic system. Therefore, it is suggested that *Alistipes* type strains abundance is associated with inflammation in depression and may influence behavioral traits. Since the level of *Alistipes* strains levels but also other gut microbiota can be modified through a dietary intervention [65, 66], this may offer alternatives or supportive therapy in depressive disorders. The ingestion of probiotics (*Lactobacillus casei* Shirota strain) induced a significant augmentation in both *Lactobacillus* and *Bifidobacteria* in humans with chronic fatigue syndrome, along with a significant decrease in anxiety symptoms giving further support to the existence of a gut-brain axis and possible adjuvant probiotic-based therapy [67]. The potential anxiolytic effects of probiotics (*L. helveticus* R0052 and *B. longum* R0175) were assessed on human distress, anxiety and depression evaluated with the Hopkins Symptom Checklist (HSCL-90), the Hospital Anxiety and Depression Scale (HADS), the Perceived Stress Scale (PSS) and the coping checklist (CCL). Probiotics intake for prolonged period showed beneficial effects on anxiety and depression related behaviors and thus mitigated psychological distress in humans without displaying any adverse event [68-70]. Jiang and colleagues [71] analyzed fecal samples from patients with major depressive disorder. Despite profound inter-individual variability, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* were overrepresented, whereas *Firmicutes* was significantly underepresented in major depressive

disorder compared to control group. Moreover, several predominant genera (Enterobacteriaceae and *Alistipes*) were more abundant, with negative correlation observed between *Faecalibacterium* levels and the severity of depressive symptoms [70].

It may be hypothesized that the predominance of some potentially harmful bacterial groups and/or a reduction in beneficial bacterial genera influences individuals mood and thus may affect behavior and subsequently lead, along with other predisposing factors, to major depressive disorder. This may be also seen from other point (viewing disorder as a starting point) meaning that the changes induced by alterations in microbiota may be shifted by the introduction of beneficial microorganisms (as a diet or other source) in the GI tract. These microorganisms will serve as a additional pharmacological tool in solving major depressive disorder which affect almost 5 % of human population worldwide. Further studies are warranted to elucidate the temporal and causal relationships between gut microbiota and depression and to evaluate the suitability of the microbiome as a biomarker.

CONCLUSION

The results provide evidence that gut microflora plays a role in stress, anxiety and depression, perhaps *via* the enteric nervous system as well as centrally, thus confirming the existence of brain-gut axis and its bidirectional connection. A demand prior to the introduction of bacteria-based therapy is to define 'healthy' microbiome during and throughout life at the population level and, most important, at individual level. Studies showed that ingestion of probiotic might be associated with changes in midbrain connectivity with subsequent alterations in brain regions which control central procession of emotion and sensation.

Nevertheless, the beneficial effects of probiotics on anxiety and depression may be connected to competitive mechanisms within gut pathogens, decrease in pro-inflammatory cytokines and signals leading to changes in neurotransmitter levels or function in the central nervous system. Thus, probiotics might offer a useful novel therapeutic approach to neuropathological disorders and/or as adjunct therapies in psychiatric disorders, such as major depressive disorder although well-designed clinical trials are needed to make clear conclusions.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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