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Psychobiotics: The Potential Therapeutic Promise of Microbes in Psychiatry

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INTRODUCTION

The recognition of the importance of human microbiome for health and disease is a relatively recent issue. Studies suggest that the microbiome may contribute to the regulation of multiple neurochemical pathways that interconnect the gastrointestinal tract and other organs with the central nervous system.

The microorganisms play a vital role in the immunological development of the host. Therefore, a selection between beneficial and harmful microbes is needed, and this vital role is guided by the immune system of the host[1]. Probiotic therapy is the application of potentially beneficial microorganisms to support the balance of beneficial and harmful microbiota in our body system[2]. The probiotic microorganisms not only compete with the pathogens of the host but also improve the immunological state of the host. As they colonize in the human intestine, they intricately involve with different systems of the body[3]. Organisms used as probiotics are bacteria that exist naturally in the gut and are most frequently of the Lactobacillus, Bifidobacterium, Enterococcus, and Pediococcus species.

The concept of modulating the microbiome is a novel and promising idea in various areas of medicine. "Vaginal seeding" is one of the most popular issues in the press, related to modulation of the microbiome. The term "vaginal seeding" describes the use of a gauze swab to transfer maternal vaginal fluid, and hence vaginal microbiota, on to an infant born by caesarean section[4]. The composition of the early microbiota of infants is heavily influenced by mode of delivery[5]. In infants born by caesarean section, the microbiota resembles that of maternal skin, while in vaginally born infants it is similar to that of the maternal vagina. These early differences in the microbiota have been suggested to determine susceptibility to some common diseases[6]. In theory, vaginal seeding might rebuild the microbiota of infants born by caesarean section to a more "natural" state and decrease the risk of disease.

Strong evidence supports a therapeutic role for probiotics in the treatment of inflammatory bowel disease, irritable bowel syndrome, atopic dermatitis, and arthritis[7]. Probiotics have immunomodulatory, hypocholesterolemic, antihypertensive, and anti-allergic properties. They are proclaimed to lighten postmenopausal symptoms and have an effect of protection toward lung emphysema[8,9]. While probiotics have been suggested as an adjuvant therapy for depression, our knowledge is limited about the potency of probiotic treatments to modulate CNS function[10].

DEFINITIONS

Probiotics

The definition of probiotics has undergone some revisions over the time. The definition has recently been refined by World Health Organization and is now accepted to be 'live microorganisms, which confer a health benefit on the host, when administered in adequate amounts'. This definition requires that the term 'probiotic' only be

used for the live microbes having a beneficial effect, although preparations of cell components may also exert some health-promoting physiological effects[11].

Prebiotics

The original definition for a prebiotic was limited to a benefit to the gastrointestinal tract, and therefore, it was formerly defined as 'a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host's health. A more recently adapted definition is 'a selectively fermented ingredient that results in specific changes in the composition and/ or activity of the gastrointestinal microbiota, thus improving host health[2].

Postbiotics

Postbiotics have been defined as non-viable bacterial products or metabolic by-products from probiotic microorganisms that have biological activity in the host[12]. For some physiological benefit, it is evident that the cells need to be active. However, for other benefits, e.g., lactose intolerance, it is hypothesized that lysis of the cells within the gastrointestinal tract is required to enhance digestion of lactose in lactose-intolerant individuals[12].

Psychobiotics

A psychobiotic can be defined as a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness. As a class of probiotic, these bacteria are capable of producing and delivering neuroactive substances such as gamma-aminobutyric acid and serotonin, which act on the brain-gut axis. Evidence support the notion that pro-inflammatory cytokines such as INFα or TNFα alone might evoke symptoms of depression, and because their circulating levels might be decreased by gut bacteria, the therapeutic application of psychobiotics in mood disorders would seem a reasonable suggestion[13].

Fecal Microbiota Transplantation

Fecal microbiota transplantation or the application of a mixture of selected beneficial bacteria strains could be another treatment alternative that merits further investigation. The use of feces for the treatment of gastrointestinal diseases was described in the 4th-century Chinese remedy for the treatment of diarrhea. More recently there has been reawakened interest in this alternative biological therapy, particularly for the treatment of recurrent Clostridium difficile infection[14,15]. Fecal microbiota transplantation involves the introduction of enteric bacteria from the feces of healthy donors to restore a healthy balance of bacteria in the gut. The efficacy of fecal microbiota transplantation for C. difficile infection has already been demonstrated[14]. The use of fecal microbiota transplantation for different diseases, such as inflammatory bowel disease, irritable bowel syndrome, insulin resistance, and metabolic syndrome, is now being evaluated.

BRAIN-GUT-MICROBIOTA AXIS

The brain and the gut are involved in continuous communication. This bidirectional interaction becomes apparent when the information about to the alterations in gastrointestinal function are transmitted to the brain, inducing the perception of visceral events such as nausea or pain. In turn, stressful experiences lead to a change in gastrointestinal secretions and motility[16]. This communication system involves neural, immune, and endocrine mechanisms. The gastrointestinal tract is the site of interaction between microorganisms, the body's largest concentration of immune cells, and a vast network of over 100 million neurons[17].

Evidence from human and animal studies shows that stress can affect the gut microbiota[18]. Lactobacillus and Bifidobacterium seem especially

susceptible to signals from the CNS. Reduced levels of lactobacilli have been associated with the display of stress-indicative behaviors in animals. Studies with primates have determined that maternal stress during pregnancy can result in a reduction of both lactobacilli and bifidobacteria in offsprings[19].

These alterations in the gastrointestinal microbiota may be a consequence of changes in gut motility or gastrointestinal acidity and/ or the direct effects of neurochemicals such as norepinephrine. For example, in Escherichia coli, the QseC sensor kinase is a bacterial receptor for the host epinephrine/ norepinephrine[20]. Bacteria respond to the host's neuroendocrine changes, on the other side they are can influence the neuroendocrine environment by the production of various biologically active peptides and neurotransmitters such as nitric oxide (NO), melatonin, gamma-aminobutyric acid, and serotonin. For example, lactobacilli convert nitrate to NO, which is a potent modulator in the CNS[21].

The Immune System and Mood Disorders

Results of studies have suggested that subjects with depression have activated inflammatory pathways, as indicated by increased pro-inflammatory cytokines and acute-phase proteins. The most frequent observations are increased plasma concentrations of IL-6, C-reactive protein, IL-1, and tumor necrosis factor[22]. Positive correlations between levels of inflammatory mediators and severity of depression have also been reported[23].

All the main classes of antidepressants can increase the release of anti-inflammatory cytokines while suppressing pro-inflammatory cytokine production, adding to the efficacy of these psychotropic agents[24]. A study by O'Brien et al. demonstrated that pro-inflammatory cytokine levels are not suppressed in depressed patients who are resistant to SSRI treatment, suggesting that inflammation may be an important component of pathophysiology[25]. Electroconvulsive therapy and psychotherapy also reported decreasing inflammatory activity in depressive patients[26,27].

In a study, the infusion of small dose Salmonella endotoxins increased anxiety and depressive mood in healthy participants, possibly as a result of increased cytokine release[28]. The relationship between inflammatory cytokines and decreased mood is supported by the fact that depression is a common side effect of chronic hepatitis treatment with INF-α[29]. Endotoxin and IL-1 administration to animals result in so-called sickness behaviors such as hypomotility, hypophagia, hyperalgesia, and a diminished interest in exploring the environment. These cytokine-induced behavioral changes are associated with alterations in brain chemistry consistent with the pathophysiology of depression[30].

An essential component of the interaction between the brain and the gut is the hypothalamic-pituitary- adrenal axis (HPA axis). Stress activates the HPA axis, which causes the release of the corticotrophin-releasing hormone (CRH). CRH increases intestinal permeability via mast cell activation[31]. The enhanced intestinal permeability can result in immune activation and lipopolysaccharide translocation into the blood (endotoxemia), as it was established in rats exposed to acute stress[32].

It is a continuing dispute whether inflammatory activity causes depression or it is a consequence of depression. It is likely that chronic stress leads to overactivation of the HPA axis, resulting in increased intestinal permeability to bacteria and/ or lipopolysaccharides. This could result in a vicious cycle of increased immune activation and inflammatory activity and further translocation of bacteria as several cytokines are known to damage the intestinal barrier.

When the immunomodulatory actions of probiotics and the role of cytokines in mood disorders were taken together; it is possible that probiotic-induced immunomodulation has a potential to treat mood disorders.

Mechanism of Action of Psychobiotics

The gut microbiota can influence CNS function through several mechanisms, including direct

effect via microbe–host interaction or indirect effect mediated by microbial metabolites. Some bacteria can activate the vagus nerve directly[33]. Infusion of a Lactobacillus species into the jejunum of mice led to activation of vagal afferents, confirmed by an increase in their firing frequency. In vagotomized mice, probiotics were not present any the neuronal effects[34].

Psychobiotics probably also have beneficial effects via protection against oxidative stress or anti-apoptotic effects. It has been suggested that bacteria not necessarily require being intact, but that also bacterial DNA and metabolites can be effective[35].

It is unclear what molecular effect determines whether one strain is active while another is not[36]. Probiotic effects are strain dependent and not every strain is beneficial for every disorder. For probiotics and psychobiotics the proper dose for efficacy is also not known. Nevertheless, some recent studies have determined that there is an optimal dose[37].

PSYCHOBIOTICS IN NEUROPSYCHIATRIC DISEASE

There is growing evidence that certain aspects of brain function are affected by gut function, which in turn is influenced by its microbial composition. This bidirectional relationship between gut and brain function is established by findings of altered gut microbial composition in major depression, autism spectrum disorder, and several other neuropsychiatric disorders.

Chronic Fatigue Syndrome and Fibromyalgia

Chronic fatigue syndrome and fibromyalgia are frequently associated with depressive symptoms. Many patients with chronic fatigue syndrome also present gastrointestinal disturbances. Indeed, patients with chronic fatigue syndrome are more likely to encounter irritable bowel syndrome-related symptoms.

While chronic fatigue syndrome is neither a gastrointestinal nor psychiatric disorder per se, however, 50% of patients with chronic fatigue syndrome meet the diagnostic criteria for irritable bowel syndrome, and anxiety itself is often a hallmark symptom in those with irritable bowel syndrome[38]. High rates of associated psychiatric disorders have been reported in patients with functional gastrointestinal disorders. In the case of irritable bowel syndrome, 50 to 90% of individuals seeking treatment have comorbid psychiatric disorders, especially depressive and anxiety disorders[39]. Irritable bowel syndrome patients have decreased Lactobacillus and Bifidobacterium counts and a reduction of anaerobe-to-aerobe ratios[40].

Although the mechanisms behind this frequent overlap with irritable bowel syndrome, mood disorders, and chronic fatigue syndrome are far from understood, researchers have documented lower levels of Bifidobacterium and higher levels of Enterococcus in these patients. The Enterococcus count in chronic fatigue syndrome and fibromyalgia patients found to be correlated with neurological and cognitive deficits[41]. In a study, 39 chronic fatigue syndrome patients were randomized to receive either 24 billion colony forming units of Lactobacillus casei strain Shirota (LcS) or a placebo daily for two months. The researchers reported a significant increase in both Lactobacillus and Bifidobacteria in those taking the LcS, and there was also a significant decrease in anxiety symptoms among those taking the probiotic vs. placebo ($p= 0.01$)[42]. These studies support the vital link between gut and brain function and the search for alternative treatment modalities, principally addressed the intestine with the aim of treating brain disorders.

Autism Spectrum Disorder

There is a consensus that children with autism spectrum disorder (ASD) frequently encounter gastrointestinal problems. Several restricted diet options (such as gluten-free or casein-free diets) have been associated with reduced gastrointestinal disorders and improved behavior in patients with ASD. Although the pathophysiology is unclear,

food intolerance is speculated to have a role in ASD[43]. ASD patients and their first-degree relatives were reported to have an increased intestinal permeability[44]. Several studies have analyzed the gut microbiota in children with ASD. An altered composition has been found both in fecal samples as well as the intestinal mucosa[45]. A study investigating the effect of vancomycin supports the role of the gut microbiota in ASD. Treatment with vancomycin for eight weeks improved autistic behavior in 8 out of 10 treated children. Unfortunately, this effect did not persist after ending the treatment[46].

The fecal flora of ASD patients contained a higher number of Clostridium histolyticum group of bacteria than that of healthy children[47]. Clostridium histolyticum group bacteria are known as toxin-producers and their metabolic products also exert systemic effects. Strategies to reduce clostridial population levels in ASD patients or to improve their gut microflora profile through dietary modulation may help to relieve gut disorders. Based on such data, it has been suggested that modulation of the gut microbiota of ASD patients by reducing the numbers of certain clostridia while stimulating beneficial gut bacteria may help alleviate some of the neurological symptoms. Administration of probiotics might be a promising therapeutic option. However, no clinical intervention trials have been published yet.

Parkinson's Disease

It is well-known that Parkinson's disease (PD) patients frequently suffer from gastrointestinal discomfort. It was shown that nearly half of all PD patients report long-term constipation before the onset of signs of motor impairment, inferring a link between initial gastrointestinal problems and succeeding onset of Parkinson's disease[48].

The pathological hallmark of PD is neuronal inclusions of alpha-synuclein protein. The finding of these Lewy bodies in the intestinal enteric nerves led to the hypothesis that the intestine might be a site of PD in response to an environmental toxin or pathogen. Forsyth et al. hypothesized that subjects with PD might display increased intestinal permeability to pro-inflammatory bacterial products[49]. To test their hypothesis they evaluated intestinal permeability in subjects newly diagnosed with PD and compared their values to healthy subjects. Their results suggest that PD subjects exhibit significantly greater intestinal permeability (gut leakiness) than controls. Also, this intestinal hyperpermeability significantly correlated with increased intestinal mucosa staining for E. coli bacteria, nitrotyrosine, and alpha-synuclein. These data represent not only the abnormal intestinal permeability in PD subjects but also the correlation of increased intestinal permeability in PD with intestinal alpha-synuclein, as well as staining for gram-negative bacteria and tissue oxidative stress. Pro- and/ or postbiotics that strengthen the epithelial barrier function might be beneficial to these patients and should perhaps be considered in the clinic.

Alzheimer's Disease

Amyloid protein precursor (APP) is a key protein in the formation of the plaque-inducing amyloid-β protein, which causes neuronal degeneration in the brain of Alzheimer's disease patients. Its expression was increased by the cytokines IL-1β and TNF-α in vitro[50].

Zhang et al. identified significantly increased plasma levels of lipopolysaccharides in Alzheimer's disease patients and they suggest that Alzheimer's disease patients suffer from elevated intestinal permeability deteriorating neuroinflammation[51].

The NMDA targeting, glutathione-depleting and oxidative-stress-inducing neurotoxin β-N-methylamino-L-alanine, found elevated in the brains of subjects with amyotrophic lateral sclerosis (ALS), PD and Alzheimer's Disease. It has been hypothesized to be generated by cyanobacteria of the intestinal microbiome and stress, gastrointestinal tract disease or malnutrition may further induce β-N-methylamino-L-alanine excess to contribute to

neurological dysfunction[52]. Other cyanobacteria-generated neurotoxins such as saxitoxin and anatoxin-α may further contribute to human neurological disease, especially during aging when the intestinal epithelial barrier of the gastrointestinal tract becomes more permeable[53].

Psychobiotics with anti-inflammatory effect or by reducing bacterial and/or lipopolysaccharide translocation might be beneficial for neuronal degeneration in patients with Alzheimer's disease. This should be addressed in preclinical studies and clinical trials.

Depressive Disorder

Although in its early stages, the emerging field of human microbiome research has indicated that gut microbiota may also play a major role in the pathophysiology of depressive disorder.

The relationship between stress, microbiota, and mood is an important area of research. A recent study in which mice were subjected to stress over an extended period, the genus Alistipes was one of the bacterial groups that showed the highest increase[54]. Alistipes has been found to be elevated in chronic fatigue syndrome and irritable bowel syndrome too[55]. It has been suggested that Alistipes is associated with inflammation, and therefore potentially linked to depression through inflammatory pathways[56]. It has previously been shown that Alistipes levels can be modified through dietary intervention. A diet high in easily fermentable oligo- or mono-saccharides with a low healthy food diversity index promoted the level of Alistipes[57].

A reduced level of Oscillibacter in the gut is also found to be related to depression[58]. Oscillibacter has valeric acid as its primary metabolic end product[59]. Valeric acid structurally resembles GABA and has been shown to bind the GABAa receptor. Therefore, it is possible that bacteria involved in the valeric acid production and/ or metabolism could also be associated with depression[60].

Lactose malabsorption is a very common condition characterized by lactase deficiency, an enzyme occurring in the brush border membrane of the intestinal mucosa that hydrolyzes lactose to its components. Lactose malabsorption has been associated with early signs of major depressive disorder in women[61]. It has been suggested that high intestinal lactose concentrations may interfere with L-tryptophan metabolism and thus alter serotonin bioavailability. Probiotics and yogurt have been shown to improve lactose digestion[62].

Depression could also be intensified by micronutrient deficiencies since lactose and fructose malabsorption is often associated with decreased intestinal transit time, resulting in the vitamin deficiencies. Interestingly, an increased frequency of depression was found in subjects with fructose malabsorption[63]. Patients with depression have low levels of folic acid, vitamin B12, and vitamin B6. Accumulating evidence suggests that elevated homocysteine levels are associated with depression. Also, data indicate that probiotic treatment can reduce homocysteine levels in humans[64].

In a recent double-blind, placebo-controlled, randomized, parallel group study, volunteers received either the probiotic combination L. helveticus and B. longum or placebo for 30 days[65]. Daily administration of probiotic combination significantly reduced psychological distress in volunteers, as measured by clinical depression and anxiety scales. Urinary free cortisol levels were found to be reduced significantly by the utilization of probiotics, providing a potential mechanism for the improvement in psychiatric symptoms.

Another study by Benton et al. reported that the consumption of a probiotic-containing yogurt improved mood[66]. Desbonnet et al. observed a reduction in depressive-like behaviors in adult rats after feeding them with Bifidobacterium infantis. This decrease was comparable to the effects of administering the antidepressant citalopram[67].

Steenbergen et al. investigated the role of the human microbiota in cognitive and affective functioning with a hypothesis that probiotic supplementation may act as a strategy to ameliorate or prevent depression. In a triple-blind, placebo-controlled, randomized, pre- and post-

intervention assessment design, 20 healthy participants without current mood disorder received a 4-week probiotic food supplement intervention with the multispecies probiotics, while 20 control participants received an inert placebo for the same period. Compared to the placebo group, the probiotics group showed a significantly reduced rumination and aggressive thoughts[68].

Results of studies suggest that psychobiotics may be beneficial in reducing depressive and anxiety symptoms; however, more studies evaluating their therapeutic potential in neuropsychological disorders are needed.

Traditional "Kefir" as a Source of Probiotics

A traditional Turkish fermented dairy product, kefir, have been rediscovered and reborn as probiotic food[1]. Kefir is a thin yogurt-like fermented compound that was made with grains of kefir as a yeast and bacterial fermentation starter. Kefir grains are a mixture of lactic acid bacteria and yeasts in a matrix of proteins, lipids, and sugars. Lactobacilli in kefir may subsist in concentrations in a range of 1 million-1 billion colony-forming units per milliliter[69]. The kefir beverage was a traditional product highly consumed in Ottoman cuisine. Traditional kefir was prepared in skin bags that were hung to a doorway to help keep the milk and kefir grains well mixed; so the bag would move with every hit of people passing through the entrance.

Historically, the traditional healers used kefir for the treatment of several diseases such as gastrointestinal problems, hypertension, and allergies[70]. Kefir has become the subject of scientific research as a renewed interest in probiotics has arisen, given its high probiotic properties. Rattay et al. reported that kefir consumption may change the intestinal microbiota composition by direct inhibition of pathogens by acid and competitive pathogen elimination in the intestinal mucosa[71]. Healing and anti-inflammatory activities of kefir were observed in mice after a seven-day treatment with kefir gel[72]. Researchers reported that kefir can further act as an antioxidant[73]. Medrano et al. noted that kefir was able to modify the balance of the immune cells in the intestinal mucosa[74]. The current scientific studies confirm the health benefits reported empirically by traditional kefir consumption.

More knowledge of the probiotic effect of kefir could lead to improved diet in many areas of the developing world. Recognizing its probiotic properties, it would be worthwhile to encourage further study of traditional kefir as an adjunctive in clinical conditions. Human health, in general, would benefit from a reconsideration of this traditional dairy product as it represents a cheap and easy to obtain source of probiotics.

CONCLUSION

There is growing evidence for bidirectional interaction along the gut–brain axis, which promises novel treatment modalities for disorders such as autism spectrum disorders, Alzheimer's disease, Parkinson's disease, and depressive disorder. Alterations in the gut microbiota may contribute psychiatric disorders and psychobiotics are targeting altered intestinal ecosystem. They are capable of producing and delivering neuroactive substances such as gamma-aminobutyric acid and serotonin, which act on the brain-gut axis. Overall, the utilization of psychobiotics in the treatment of several psychiatric disorders warrants further investigation.

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