

Brief Communication

An adjunct paradigm in the causation and treatment of mental illness: the gut-brain axis and microbial remedies

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Abstract

The link between the gut-brain-axis and the causation of mental illnesses has been studied with an increased interest during the last few decades. There is also emerging evidence that the gut microorganisms prescribed as prebiotics and probiotics have the ability to restore normal microbial balance and hence have a potential role in the prevention and treatment of mental illnesses.

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Introduction

The prevalence of mental illnesses and the burden of disease due to mental illnesses have increased over the last few decades, with depressive and anxiety disorders being some of the most prevalent mental illnesses [1].

Up to now, the accepted theories regarding the causation of mental illnesses include the biological model; where the abnormalities are thought to be localized to the brain and the biopsychosocial model; where one or more biological, psychological and social factors are thought to contribute to the causation of depression. However, in recent years, emphasis has also been placed on a different approach, where communication between the brain and the gut has been held responsible for a range of mental health issues including depression anxiety disorders, autism etc. [2].

Research indicates that trillions of microbes live on and within human beings and that this human microbiota, especially those found in the gut, carry about 150 times more genes than that found in the entire human genome [3]. The human microbiota is called “commensal microbiota” because they have established an interdependent and mutualistic relationship with humans [4]. The interactions between the microbiota and the host are reported to be complex and dynamic, involving a variety of mechanisms that

include immune, hormonal, and neural pathways [3]. This network of communication is called the microbiota–gut–brain axis (GBA) and it is postulated that the symbiotically living microorganisms help to maintain the homeostasis of the central nervous system and influence our behaviour and mood [3].

The existence of a GBA was proposed in a landmark study by Sudo *et al* that discovered an impaired stress response in germ-free mice [5].

Linking mental illness with stress, diet, gut microbiota and the immune response

The hypothalamic-pituitary-adrenal (HPA) axis has been designed to help cope with stressors and is thought to be activated by pro-inflammatory cytokines through secretion of corticotropin-releasing factor (CRF) from the hypothalamus which stimulates adrenocorticotropic hormone (ACTH) secretion from the pituitary gland that, in turn, leads to cortisol release from the adrenal glands [6]. Experimental changes of gut microbiota have been shown to influence stress responsiveness, anxiety-like behaviour and the set point for activation of the HPA stress axis [7].

Studies done in animals have shown the crucial role of the microbiota in regulating stress-related changes. Germ free mice had an exaggerated HPA axis response to stress and this could be reversed by colonization with a specific *Bifidobacteria* species [5]. Liang *et al* showed that chronic stress disturbed the gut microbiota resulting in decreased hippocampus 5-HT content, reduced BDNF mRNA expression, increased plasma stress hormone levels, declined circulatory IL-10 levels resulting in depression [8]. This suggests that there is bacterial translocation from the gut to the systemic circulation during chronic stress, which presumably leads to an inflammatory response that may contribute towards the mood disorder.

Antibiotics and a poor diet are reported to disturb gut microbiota and to change it towards a depressive phenotype, thus increasing the risk of depression [9]. Studies on infants show that those who were exposed to antibiotic treatment during the first year of their lives had a higher risk of developing behavioural problems and depression [9].

Evidence indicates that there is a contribution from microbiome-mediated immune activation to the onset of bipolar disorder and that patients who have been recently treated with systemic antibiotics were approximately twice as likely as other patients to develop bipolar mania [10].

There is also evidence supporting an association between anxiety and the microbiome [11]. Germ free rats have been shown to exhibit more anxiety-like behaviour compared to normally colonized rats [12].

A preliminary study done by Schwarz *et al* among patients with first-episode psychosis has reported differences in the microbiota when compared with healthy age-matched controls [13] and there is evidence indicating differences in the oropharyngeal microbiome of patients diagnosed with schizophrenia [14].

An association between diet and attention deficit hyperactivity disorder (ADHD) has been proposed and patients with ADHD have been shown to have an altered composition in their microbiome [15]. Hsiao reports that there is a strong relationship between autism spectrum disorders (ASD) and gastrointestinal disorders [16].

Probiotics and prebiotics as adjunct psychotropics

Currently available treatment for mental illness includes psychotropics, various psychological therapies and electroconvulsive therapy. The choice of treatment depends on patient preference and the severity of the symptoms.

If the hypothesis of a GBA and the link between mental illness and microbiota is correct, the restoration of microbiota could bring about improvement in the symptoms of mental illness. Studies have shown that this could indeed be the case and that the microbiota could be given as probiotics or prebiotics [17]. Other methods of restoring the gut microbiota are a healthy diet and faecal microbiota transplantation (FMT) [18].

Probiotics are live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. These probiotics are referred to as psychobiotics by some researchers to emphasize their capabilities in producing a health benefit in patients suffering from psychiatric illnesses [19]. Research studies have shown that psychobiotic supplementation alleviates symptoms of mental illness, even achieving similar effects to traditional psychotropics [19]. The psychobiotics that have been utilized to treat mental illnesses in clinical trials mostly consist of special strains of *Lactobacillus casei* and *Bifidobacterium bifidum* [19].

Prebiotics are substrates that are selectively utilized by host microorganisms, conferring a health benefit. Common prebiotics are fructose-oligosaccharide, galacto-oligosaccharide and omega-3 fatty acids [20].

As explained above, patients with mental illnesses are found to have abnormal gut microbiota due to various reasons such as early maternal separation, antibiotic use, stress and a poor diet. Currently, there appears to be a huge interest as well as research regarding the GBA, the relationship between the GBA and mental illnesses and the use of probiotics and prebiotics, either as adjunct treatment modalities or as alternative treatments for patients with depression.

The use of psychobiotics as an alternative or as adjuvant treatment for mental illness would, if proven effective, play a significant role in a country like Sri Lanka where stigma results in reduced help-seeking behaviour in patients with mental illnesses. This is because probiotics are found in normal foods, such as yoghurt and cheese and taking these may be less stigmatizing than taking traditional psychotropics such as antidepressants, antipsychotics or receiving electro convulsive therapy.

Current use and knowledge of psychobiotics in other areas of medicine

Fermented dairy products, such as cheese, yoghurt and acidified milk, contain probiotics in varied amounts and are consumed by people in most countries [21]. Supplementation of probiotics in controlled amounts has been demonstrated to reduce visceral fat mass and body weight [22,23]. Probiotics have been shown to have some effectiveness in preventing antibiotic-associated diarrhoea due to its effect of improving the microbial balance in the gut and by reducing colonisation of the gut by pathogenic bacteria [24]. According to Selma-Royo et al, the method of delivery (vaginal vs Caesarean secession) and place of birth (hospital vs home) may have an effect on the gut microbiota of the neonate and may influence susceptibility to allergic and autoimmune conditions in later life[25].

However, there appears to be significant gaps in research in this area, especially around the type or strain of probiotics, cost related issues, ideal duration of treatment etc, especially with regard to mental illnesses. The authors are aware that some clinicians prescribe probiotics in their regular day to day practice in Sri Lanka. However, to the best of our knowledge, there are no studies regarding the GBA and psychiatric disorders in Sri Lanka or in other South Asian countries. Therefore, studies are needed, especially in the Sri Lankan context, to determine the relationship between the GBA and mental illnesses as well as the efficacy of psychobiotics in treating patients with mental illnesses.

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