



## The Potential of Probiotics in the Treatment of Schizophrenia

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### ABSTRACT

Patients with schizophrenia have a higher prevalence of dysbiosis and metabolic disorders. Some probiotics significantly relieve constipation and improve insulin resistance in patients with schizophrenia, with concomitant improvement in psychiatric symptoms. Schizophrenic patients whose psychiatric symptoms are improved by probiotics have characteristics that begin with the three D's: *Dysbiosis*; *Decreased barrier function* in intestinal tract; and *Dopamine dysfunction* in the prefrontal cortex such as negative symptoms. The effects of probiotics on the central nervous system are nowadays referred to as psychobiotics. However, the underlying mechanism of psychobiotics has not been fully elucidated. In this manuscript, the potential of probiotics in psychiatric practice is discussed based mainly on the author's clinical studies. Modulation of the composition of intestinal microbiota with probiotics may be a new therapeutic target for the treatment of schizophrenia and comorbid insulin resistance.

**Keywords:** *constipation, fecal microbiota, insulin resistance, probiotics, schizophrenia*

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### Introduction

Patients with schizophrenia have a higher risk of premature death from cardiovascular disease (CVD) due to concomitant insulin resistance, which is associated with cognitive decline [1]. The mechanism of comorbid insulin resistance is still unknown, but observational studies have implicated inflammation in both schizophrenia and insulin resistance [2]. Genome-wide association studies support a role for inflammation as a common cause of schizophrenia and insulin resistance, which could partly explain why the traits commonly co-occur in clinical practice [3]. Probiotics can help regulate the immune system and anti-inflammatory response [4]. In schizophrenia, targeting both inflammation and insulin resistance with probiotics may be effective not only in improving metabolic disorders but also in improving psychiatric symptoms. Changes in the

intestinal microbiota with probiotics may improve the symptoms of mental illness, and probiotics that improve psychiatric symptoms have recently gained attention as "psychobiotics". The bidirectional communication between the gastrointestinal tract and central nervous system through psychobiotics is called the microbiota-gut-brain axis [5]. It has been emphasized that abnormalities in the gut microbiota are associated with the onset of certain neuropsychiatric disorders, such as depression, anxiety disorders, autism spectrum disorders, multiple sclerosis, and Parkinson's disease [6]. These diseases are always caused by changes in brain neurons, and the mechanisms are assumed to include direct crosstalk between the gut microbiota and the central nervous system, and the effects of substances produced by the microbiota on the development of neural circuits. Schizophrenia is a chronic neurodevelopmental disorder with complex symptoms, the cause of

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which is unknown. Genetic and epigenetic disorders, abnormalities in the immune system, and environmental influences are involved in schizophrenia, but more recently, abnormalities in the gut microbiota have also been implicated [7]. Even though causality has not yet been established, intestinal dysbiosis has emerged as a hallmark of several neuropsychiatric diseases, including schizophrenia.

### **Probiotics improved both constipation and insulin resistance in schizophrenic patients**

Several studies have shown that probiotics may be effective in treating constipation [8]. In our study, a probiotic mixture, BIO-THREE<sup>®</sup>, including *Streptococcus faecalis*, *Bacillus mesentericus*, and *Clostridium butyricum*, significantly relieved constipation and improved insulin resistance among patients with schizophrenia [9]. After one month of treatment with the probiotic mixture, the triglyceride (TG) / high-density lipoprotein cholesterol (HDL-C) ratio decreased from 3.44 to 2.00, which indicates improvement in insulin resistance [10]. The TG/HDL-C ratio is an atherogenic index that has been proven to be a highly significant independent predictor of myocardial infarction [11]. Patients with schizophrenia are more likely than the general population to develop CVD due to insulin resistance, so lowering the index of insulin resistance with probiotics may contribute to prolong their lives [12]. However, the underlying mechanism by which the probiotic mixture improves constipation and metabolic abnormalities in schizophrenic patients is not fully understood because our study did not include genetic testing of the gut microbiota.

### **Administration of the probiotic mixture improved intestinal inflammation**

Probiotics are live bacteria that can improve the intestinal environment. In contrast, antibiotics can damage the intestinal environment and cause intestinal inflammation. Inflammation activates and increases the expression of several proteins that suppress the insulin-signaling pathways and some probiotics can lower inflammatory signals [13]. *Clostridioides difficile* infection (CDI) is the most common type of antibiotic-induced enteritis [14]. Thus, we compared CDI incidence in hip surgery patients aged over 75 years before and after the introduction of the probiotic mixture. The diagnosis of CDI was confirmed by an enzyme-linked immunosorbent assay for glutamate dehydrogenase and *Clostridioides*

*difficile* toxins A and B using frozen stool specimens for patients with antibiotic-induced diarrhea. The CDI incidence before the introduction of the probiotic mixture was 4.2 cases per 10,000 patient bed-days, which is as many as in EUCLID (the European, multicentre, prospective biannual point prevalence study of *Clostridium difficile* Infection in hospitalized patients with Diarrhoea), that reported as 7.0 cases per 10,000 patient bed-days [15]. Surprisingly, the CDI incidence after the introduction of the probiotic mixture markedly decreased to 0.35 cases per 10,000 patient bed-days, while annual consumption of antibiotics including cefmetazole sodium, the main antibiotic agent for prophylaxis usage in the hospital, and the number of hip surgery patients aged over 75 years did not change compared before and after the initiation of probiotics [16]. The probiotic mixture, BIO-THREE<sup>®</sup>, possessed the possibility of primary prevention of healthcare-associated CDI when administered to patients who receive antibiotics. However, the underlying mechanism of why the probiotic mixture prevents intestinal inflammation has not been fully elucidated because accurate measurements of the intestinal microbiota were not available.

### **Inference of the mechanism of amelioration of intestinal inflammation and insulin resistance from the analysis of intestinal microbiota**

The probiotic mixture, BIO-THREE<sup>®</sup>, clinically improves the intestinal environment; however, no research results to explain how this leads to metabolic improvement. This time, this mystery has been partly solved with elaborate experiments and analysis of human feces. Antibiotics as well as anticancer drugs can induce dysbiosis and cause enteritis. Oxaliplatin, an anticancer drug, induces dysbiosis and causes intestinal inflammation. A study using 16S rRNA high-throughput sequencing to examine changes in the microbial composition of feces from mice and patients with oxaliplatin-induced enteritis showed that BIO-THREE<sup>®</sup> administration altered the bacterial flora and ameliorated enteritis. Oxaliplatin treatment increased the abundance of *Bacteroides* and decreased the abundance of *Prevotella*. After taking this probiotic mixture, the imbalance of these bacterial groups has improved in the feces of both mice and human patients. The probiotic mixture treatment reduced *Bacteroides*, and restored *Prevotella* [17]. Both *Bacteroides* and *Prevotella* can ferment dietary fibers and some of

them produce total short chain fatty acid (SCFA). However, SCFA production is much higher in *Prevotella* than in *Bacteroides* [18]. Essentially, SCFA such as acetic acid, propionic acid, and butyric acid is the main energy source for the intestinal epithelium and has an anti-inflammatory property. In addition, SCFA can stimulate defense barriers by increasing antimicrobial peptide levels. Higher total SCFA production of the *Prevotella* compared to *Bacteroides* enterotype indicates higher fiber utilizing capacity, resulted in improving insulin resistance. However, recent research on intestinal bacterial flora that improves insulin resistance has reported that the abundance of *Prevotella* decreased with the improvement in insulin resistance [19]. *Prevotella* species such as *Prevotella copri* seems to be associated with diabetes, although *Prevotella* enhanced potential for carbohydrate catabolism [20]. The role of intestinal *Prevotella* species in human health is controversial, with both positive and negative associations. Therefore, rather than an increase or decrease in *Prevotella*, a delicate balance between *Prevotella* and *Bacteroides* may improve intestinal inflammation and insulin resistance in relation to diet as well. It has recently been shown that the effects of probiotics on obesity and insulin resistance vary by gut microbial enterotype, with greater responses seen in those with a higher *Prevotella/Bacteroides* ratio [21]. The delicate balance between *Prevotella* and *Bacteroides* that seem to play the same role, such as fermentation, plays an important role in improving insulin resistance and ameliorating enteritis.

By the way, the probiotic mixture, BIO-THREE<sup>®</sup>, contains three bacteria including *Streptococcus faecalis*, *Bacillus mesentericus*, and *Clostridium butyricum*. The results of the animal study by Yuan et al. [17] were obtained using a mixed solution of *Streptococcus faecalis* and *Bacillus mesentericus* in the probiotic mixture, so there is a possibility that *Clostridium butyricum* in BIO-THREE<sup>®</sup> can have a synergistic effect on it. *Clostridium butyricum* produces butyrate (a SCFA) and stimulates regulatory T cell, which can result in the production of important anti-inflammatory molecules such as interleukin-10 [22]. The effect of the probiotic mixture on the improvement of metabolism is presumed to be a synergistic effect of the improvement of the *Prevotella/Bacteroides* ratio and the immunomodulation effect of *Clostridium butyricum*.

So far, the author has presented data from studies

on the probiotic mixture, but there is a wide range of psychobiotic species, and most of the studies have been done with a single species of *Bifidobacterium* or *Lactobacillus*. However, a review of studies comparing single strain probiotics and placebo in a randomized controlled trial unfortunately found no improvement in psychiatric symptoms of schizophrenia [23]. A single strain of probiotics may be sufficient to improve intestinal inflammation, but multiple strains may be necessary to improve psychological symptoms, and fecal microbiota transplantation (FMT), which transplants the entire healthy intestinal microflora as described next, may be effective.

### Psychobiotics in clinical psychopharmacology

Strange as it may seem, in patients with schizophrenia, when probiotics improve inflammation in the digestive tract and restore the barrier function of the intestinal tract, some psychotic symptoms may also improve [24]. Evidence has emerged that probiotics are effective in alleviating some psychotic symptoms of schizophrenia by changing the pattern of fecal microbiota. For example, probiotic diets and FMT are currently the most common treatments, although they are still at the research level [25]. In interventions, the gut microbiota is a complex ecosystem of microorganisms, so introducing all strains as in FMT or a probiotic mixture may be better than a single probiotic regimen [26].

The symptoms of schizophrenia that are improved by psychobiotics are negative symptoms and cognitive functions, and positive symptoms are less effective [27]. Since psychobiotics are not expected to improve the positive symptoms of schizophrenia, the effects of combining antipsychotics and probiotics should be investigated. Schizophrenic patients whose psychiatric symptoms are improved by probiotics have characteristics that begin with the three D's: *Dysbiosis*; *Decreased barrier function* in intestinal tract; and *Dopamine dysfunction* in the prefrontal cortex such as negative symptoms [24]. This suggests that psychobiotics may be conveying instructions to improve the function of dopamine cells in the brain through immune system regulation. Potential mechanisms that may influence the pathophysiology of schizophrenia include microbial regulation of functional pathways related to immune signaling/response and lipid and carbohydrate regulation. Examples include the pathways of trimethylamine-N-oxide reductase and Kdo2-lipid A

biosynthesis [28].

In conclusion, modulation of the composition of intestinal microbiota with probiotics may be a new therapeutic target for the prevention or treatment of schizophrenia and comorbid insulin resistance. However, probiotics alone do not control the symptoms of schizophrenia, and thus these studies need to be conducted within the scope of psychopharmacological treatment. Clinical psychopharmacology combines a clinical focus that directly impacts patient care with scientific advances that can be applied to clinical practice [29]. Psychobiotics will be an important area of research in clinical psychopharmacology in the future. There is a lack of high quality evidence on psychobiotics. Results from large scale placebo-controlled studies are warranted.

### CONFLICT OF INTEREST

The author declares no conflict of interest.

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