The relationship between gut microbiota and schizophrenia: Recent research and treatment application

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Abstract. Schizophrenia (SZC) is a common, chronic, and severe mental illness. Recent years have witnessed increased study into the link between gut microbiome and psychotic disorders, particularly schizophrenia. Focusing on inflammatory, tryptophan compounds, and BDNF concentrations, we examine the data that currently exists linking intestinal microbiota to schizophrenia and explain how the presumptive dysregulation could fit into accepted theories of the disease's pathophysiology. We looked at recent research and assessed the therapeutic possibility of modifying the intestinal microbiota with prebiotics as adjuvant therapy for schizophrenia. Overall, although the available information on microbiome changes in schizophrenia is extremely erratic and inadequate to draw any firm conclusions. There were successful attempts that decreased the risk of SCZ by interfering with the intestinal microbiota. The gut microbiota is a possible approach to the treatment of schizophrenia.

Keywords: Gut Microbiota, Schizophrenia, Fecal Transplantation.

1. Introduction

Schizophrenia is a common, enduring, and debilitating mental condition. It is marked by problems in perceiving, thought, emotion, and behavior, as well as the incoordination of mental processes. It often manifests as auditory hallucinations, paranoia, peculiar delusions, or language and thinking disorders, accompanied by apparent social or occupational dysfunction. Mostly onset between the ages of 15 and 55. Schizophrenia is divided into positive symptoms and negative symptoms. Schizophrenia's unclear origin and pathophysiology, which could be related to genetic factors, are currently not well understood, brain structure, neurotransmitters, and other factors. Some schizophrenia patients have a favorable prognosis after receiving aggressive treatment; however, some patients may cause significant social impairment. The combined effect of genetic variation and environmental factors may be an important cause of the disease. The relationship between gut microbes and mental illness has also attracted the attention of many scholars in recent years. This article examines the connection between intestinal microbiota and schizophrenia in different aspects is reviewed based on recent research and the implication on the treatment of schizophrenia will be discussed.

2. The connection between schizophrenia and the microbiota of the gut

There is a significant link between schizophrenia and altered gut microbiota [1]. Multiple retrospective studies addressing the association between the gut microbiota and schizophrenia demonstrate that the gut microbiota plays an essential role in early life development and brain maturation, including the immune and endocrine systems [2]. Patients with schizophrenia are frequently impacted by these physiological and behavioral mechanisms. Prenatal microbial infections, for example, have been linked to a 10- to 20-fold increased risk of schizophrenia [3]. In addition, it has been discovered that early life stress can lead to long-term alterations in the gut microbiota that result in the development of neuronal and endocrine function as well as behavioral changes, which may play a key part in the etiology of mental disorders [4]. According to a recent study, both untreated and treated SCZ patients had a lower microbiome alpha diversity index than healthy controls. In

addition, germ-free animals who received the schizophrenia microbiome exhibited altered glutamate/glutamine and GABA levels in HPC, exhibiting the same characteristics as earlier murine models of schizophrenia, such as pyroglutamate [5].

Microbiome acts as a mediator to transmit environmental impact as immune signals to the brain [6]. A previous study transplant schizophrenia patients' gut microbiota to healthy mice induced schizophrenic symptoms in mice [7]. The gut microbiota of individuals with schizophrenia differs significantly from that of healthy individuals and those with metabolic syndrome, according to a study. Different species of bacteria exhibit varying degrees of affluence. It was discovered that Flavonifractor plautii, Collinsella aerofaciens, Bilophila wadsworthia, and Sellimonas intestinalis were significantly enriched, while Faecalibacterium significant because it provides, Micrococcus lactaris, Ruminococcus bicirculans, and Veillonella rogosa were significantly depleted[8]. The same decrease in Ruminococcaceae were also found in another research, accompanied with reduction of Oscillibacter, Enterorhabdus, Bautia, Lachnospiraceae[9]. Moreover, patients with antipsychotic-induced constipation has increased diversity of gut microbiome with hypomotility of gastrointestinal [10]. This research also found that patients with SCZ has less Bacteroidetes and more Firmicutes and Synergistetes [10], which is inconsistent with Tigchellaar and Vandepputte's finding [11].

There were successful attempts that decreased the risk of SCZ by interfering with the gut microbiome. Dietary intake of sulforaphane glucosinolate during pregnancy and breastfeeding may have prolonged positive benefits on offspring by modifying the gut microbiota, which increases offspring's resistance to psychiatric disorders including schizophrenia and autism spectrum disorder[9]. The connection between the intestinal bacteria, symptoms of schizophrenia, and the immune system is complex. The psychiatric disorders will induce systematic inflammation and changes in the gut microbiome, inflammation response will also cause gut microbiome's alternation and that change in gut microbiome enhanced inflammation response in return [12].

3. Kynurenine Pathway

As its relationship to inflammation, the immune system, and neurological diseases became clearer, the kynurenine pathway attracted more and more interest. It serves as the main pathway for the liver's breakdown of tryptophan and the beginning of mammals' nicotinamide adenine dinucleotide production. The kynurenine route involves tryptophan, kynurenine, kynurenic acid, and quinolinic acid as metabolites. [13]. The pathway is considered as a signal connection between peripheral immune activation and central neurotransmitter [8]. The tryptophan metabolism from kynurenine is increased in SCZ [5], [13]. Quinolinic acid is neurotoxic and is found enriched in SCZ [8], however, this trend is not shown in Marx's research [13].

4. Changes in gut microbiota caused by parasites

Based on the hypothesis that the inflammation response to an infection may play a role in blood-gut and blood-brain communication, which leads to mental disease, the purpose of this study was to examine the relationship between inflammation and mental illness. It has been shown that T. gondii (a neurotrophic factor plasmodium parasite) and NMDAR immunoglobulin seroprevalence in schizophrenia are associated with mental illness. The level of cognitive impairment as indicated by the delayed recall test was elevated [14]. Another human investigation assessed the immune-inflammatory response of people with schizophrenia-related cognitive impairment (SCZ) to five distinct Gram-negative bacteria, similar to the cognitive tests widely used to detect cognitive problems in schizophrenia. There was a substantial correlation [15] between negative performance and adverse outcomes. Decreased gut immune responses are associated with reduced gut microbiota organization. They are resulting in mental disorders.

5. Probiotic intake and fecal transplantation

The current definition of probiotics is a living microorganism that, while ingested in suitable quantities, provides health benefits. Certain Lactobacillus and Bifidobacterium strains produce GABA, a neurotransmitter that affects a variety of psychophysiological functions [16]. This observation has led to the concept that probiotics can serve as functional carriers of neuroactive medicines and, by extension, potential psychoactive drugs. [17]. Thus, Dinan and Cryan [18] define a "spiritual organism" as a living entity that promotes the health of people with mental disease. Through vagal afferents, this bacterium can create and transfer neurotransmitters such as acetylcholine and serotonin. In one investigation, Rats fed Lactobacillus rhamnosus exhibited decreased anxiety as measured by a variety of behavioral parameters and altered appearance of GABAa and GABA receptors within the central nervous system. To investigate the mechanism of action, vagotomy or sham surgery was performed on animals. Vagotomy hindered the onset of the anxiolytic effects of probiotics and expression alterations of GABA receptors [19]. A diabetic rat model traversing the Morris water maze to document excitatory postsynaptic potentials (EPSPs) from the CA1 glutamatergic region was also given lactobacillus. The bifidobacteria mixture enhanced memory formation in this model, according to the results [16]. Using the association between probiotic diets and GABA-central activity in neurophysiological studies of psychiatric disorders such as SCZ, these results only hint at what could be achieved. Dinan and Cryan's concept of "psychobiology" reveals fertile ground in which new seeds can be sown in significant fields of neuroscience research, linking the neurophysiology of psychiatric disorders and the classical fields of nutrigenomics.

6. Microbiome and neurotrophic factor in the brain

BDNF is an essential neuroprotective element involved in neural development, particularly memory and learning functions, and neurodevelopmental models of schizophrenia frequently incorporate changes in BDNF, highlighting its role in cognitive impairment in the disease [20]. Postmortem hippocampus samples [21] and plasma from patients with schizophrenia who did not receive medication showed decreased BDNF levels, Nonetheless, low BDNF levels at baseline were associated with a worse response to antipsychotic therapy [21]. Throughout experiments with mice, it was discovered that broad-spectrum bacteriocins significantly suppress the interpretation of BDNF and TrkB in the mouse cerebral cortex. [22], whereas a study employing a similar methodology demonstrated a substantial increase in BDNF levels in the hippocampus. In contrast, the populations of Lactobacillus and Actinomycetes grew, whilst those of -Proteobacteria and Bacteroides decreased [23]. These inconsistent results are problematic since it is uncertain whether the microbiome and antibiotics mediate BDNF changes. In two separate investigations [24], It was discovered that GF mice express less BDNF in the hippocampus. GF NIH Swiss mice with a BALB/c microbiome displayed lower BDNF expression in the cerebral cortex one week after compared to those who did to GF NIH Swiss mice with an NIH Swiss microflora, whose BDNF levels turned down at 3 weeks [25]. Again, none of these studies are specifically correlated to the microbiome in schizophrenia, and studies examining the impact of FMT on BDNF expression in people with schizophrenia provide stronger evidence. Intriguingly, proinflammatory cytokines were also associated with decreased hippocampal BDNF expression, suggesting a supplemental link among both BDNF levels and modifications in gut microbiota [26].

7. Epigenetic modulations

Epigenetics includes a number of modulations including chromatin restructuring, RNA- guided heritable changes, DNA methylation, and histone acetylation[27]. Recent research points to the complex interaction between genetic and epigenetic regulation of neurodevelopmental pathways, suggesting that certain loci associated with schizophrenia risk might affect random variance in gene

regulation. Epigenetic changes in schizophrenia and other diseases may be significantly influenced by environmental variables and may appear as molecular 'scars'. Lifetime impact on brain functioning may be caused by these scars and the impact can be passed down through generations via epigenetic germline inheritance. Epigenetic changes are probable biological causes of phenotypical variation and present an objective for therapies, whether they are brought on via either genetic or environmental factors [28].

In schizophrenia and other related psychoses, immunological and inflammatory mechanisms are dysregulated, and patients with higher levels of peripheral and neuroinflammation perform less well on cognitive tests and have aberrant brain structures. [29]. Serum amino acids level is found to have relationship with symptoms of schizophrenia. Arginine, leucine, methionine, and glutamine levels differ significantly between SCZ individuals and healthy controls, making these amino acids potential SCZ indicators[29]. The intelligence quotient of SCZ patients is correlated with the ability of gut bacteria to produce tyrosine, a precursor for dopamine, indicating that intestinal microbiota could be a potential target for attempt to mitigate cognitive decline in SCZ[8]. In addition, the gut microbiota is a vital part of the immune system, and it has been reported that anti-inflammatory drugs, such as cannabinoids, are effective in reducing the symptoms of the condition of SCZ[30].

8. The significance of prebiotics for schizophrenia

Prebiotics are essential to the use of microorganisms by the host, creating optimal conditions for "beneficial" microorganisms [31].They typically include indigestible fructooligosaccharides (FOS) and galactooligosaccharides (GOS) that are preferentially broken down by bifidobacteria. Two components of schizophrenia have indeed been researched in animals: perceptual decrease and antipsychotic-mediated excess weight, formed the basis for a recent study demonstrating the possibility of prebiotics as an adjuvant treatment for schizophrenia.

Substantial evidence demonstrates that the both schizophrenia and its treatments are linked to cognitive decline. Subjects with schizophrenia performed 1.5–2.0 standard deviations worse even than control subjects on a variety of neurocognitive tasks, with recognition memory, attention, issue, processor speed, and executive function exhibiting the greatest deficits [32]. Despite therapeutic benefits, risperidone reduces working memory for space [32], but lower doses of antipsychotics or olanzapine were not associated with cognitive impairment. Improved RBANS and DIEPSS scores significantly [33]. These alterations might have substantial functional consequences, such as decreased job performance, thus treating them is crucial for effective treatment.

Rats using a B-GOS® prebiotic formulation shown a considerable improvement in cognitive flexibility [34]. Although schizophrenia isn't the only condition associated with reduced fluid intelligence, B-GOS® supplementation improved overall comprehension as evaluated by the Brief Evaluation of Schizophrenia Learning and memory [31] compared to placebo cognitive ability [35]. To fully comprehend the possible treatment value of prebiotics in schizophrenia, however, larger studies that evaluate positive and undesirable symptoms and signs must be conducted.

Although the mechanism of the cognitive-enhancing effects of B-GOS® in schizophrenia is unclear, sourdough supplementation in rats was reported to improve the responsiveness of PFC pyramidal neurons to NMDA application as well as the GluN2B and GluN2A subunits of cortical-expressed NMDA receptors [34]. Moreover, higher hippocampus BNDF concentrations have been documented [36]. It is hypothesized that NDMA hypofunction and lower BDNF levels contribute to the pathophysiology of schizophrenia and its affiliated memory deficits [37].

9. Conclusion

The importance of gut bacteria for neural transmission has been shown. Strong connections between the gut and brain are made possible by their mutual interaction, which is mediated by multiple signaling pathways. The etiology of SCZ, the kynurenine metabolic pathway, is connected

to gut dysbiosis. SGS consumption during pregnancy can affect the gut microbiome of the offspring and reduce the risk of SCZ. Prebiotic supplementations increase NMDA application, which reduced BDNF levels and is closely related to cognitive impairment in SCZ patients. Even though many researchers have indicated the interaction effect between SCZ and gut microbiota, the mechanism and the trend of microbiota alternation are still unclarified. Future research on the clarification of the mechanism which can give insights into the novel therapeutics of SCZ is expected.

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