EDITORIAL

Brain-Gut-Microbiota Axis in Schizophrenia and Parkinson's Disease

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KEY WORDS

schizophrenia, Parkinson's disease, brain-gut-microbiota axis

Dopaminergic cells, which use dopamine as a neurotransmitter, are not as numerous as other brain nerve cells such as serotonergic and GABAergic neurons. However, dopamine neurons project to a variety of important brain regions to control movement, emotion, the reward system, and the secretion of prolactin. Both schizophrenia and Parkinson's disease are disorders of the dopaminergic neurotransmissions, but schizophrenia has excess dopamine in the mesolimbic system, and Parkinson's disease has decreased dopamine in the substantia nigra striatum, with opposite effects in dopaminergic neurotransmission. Recently, it has become clear that the brain-gut-microbiota axis is involved in the pathogenesis of both schizophrenia and Parkinson's disease. This paper describes the similarities and differences in the brain-gut-microbiota axis between schizophrenia and Parkinson's disease.

THE VAGUS NERVE IS INVOLVED IN THE PATHOGENESIS

The disturbance of the dopaminergic neurotransmission in the midbrain may be caused by information from the gastrointestinal tract, not the brain. If the vagal pathways are completely blocked, the frequency of Parkinson's disease is reduced. This is because alpha-synuclein, an abnormal protein that is deposited in dopamine cells in Parkinson's disease, is prevented from being deposited in the brain from the gastrointestinal tract via the vagal pathways[1].

As for dopamine levels, simply put, schizophrenia is the opposite of Parkinson's disease. If the vagus nerve controls the dopaminergic nervous system in the midbrain, and blocking the vagus nerve can prevent Parkinson's disease, can it not induce schizophrenia? Of course, schizophrenia does not involve alpha-synuclein, so this cannot happen. However, science is sometimes an interesting and mysterious fact, and a guess in the direction of a simple intervening factor that omits a mechanism, such as the number of dopamine cells, may turn out to be correct by chance. Rats with severed ascending vagal pathway become schizophrenic. Subdiaphragmatic vagal blockade in rats results in behavioral deficits similar to schizophrenia. Using next generation mRNA sequencing, the amount of dopamine synthesis in the brain was altered to increase. In rats whose vagal afferents were blocked, sensitivity to acute amphetamine administration was increased, and dopamine and its major metabolite, 3, 4-dihydroxyphenylacetic acid, were elevated in the brain, resulting in an excess of dopamine in the brain[2]. When the ventral vagal afferents are completely blocked so that signals from the gastrointestinal tract are not transmitted to the brain, changes in the brain transcriptome, overactivity of the dopaminergic nervous system, and behavioral disturbances as schizophrenia occur. The mRNAs associated with schizophrenia are detected and transcribed by blocking the vagus nerve.

Both Parkinson's disease and schizophrenia can be pathologically altered by blocking the vagus nerve, but the way it is controlled is the exact opposite, with blocking vagal pathways decreasing Parkinson's disease and inducing schizophrenia.

SCHIZOPHRENIA HAS A HIGH PROBABILITY OF LATER DEVELOPING PARKINSON'S DISEASE

Schizophrenia and Parkinson's disease have opposite characteristics, such as changes in the dopamine neurotransmissions in the brain and the role played by the vagal pathways. For this reason, these two diseases cannot coexist. However, in clinical practice, it is not uncommon for schizophrenic patients to develop Parkinson's disease. This linkage has been explained not by disease similarity, but because dopamine blockers are used to treat schizophrenia. Indeed, schizophrenia is treated with antipsychotics, which induce a high rate of drug-induced parkinsonian syndromes. In clinical practice, parkinsonian symptoms are often seen in patients with schizophrenia, that suggests the possibility that schizophrenia and Parkinson's disease are related, not just the effects of antipsychotic medication. According to a case-control study in which parkinsonian syndromes were carefully excluded, the odds ratio of schizophrenic patients developing Parkinson's disease was 4.63 (95% CI 1.76-12.19, $P < 0.01$), which was statistically significantly higher[3].

It is interesting to note that schizophrenia, a condition with excess dopamine in the basal ganglia, is later associated with Parkinson's disease, a condition with decreased dopamine. Signaling through the vagal pathways regulates protein expression in the brain. Analysis of the gut microbiota, which is the source of this regulation, may reveal the mechanism of this mysterious time sequences.

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INTESTINAL MICROBIOTA IS A THERAPEUTIC TARGET FOR BOTH SCHIZOPHRENIA AND PARKINSON'S DISEASE

Recent studies on correlations between gut dysbiosis and psychiatric diseases have noted that both schizophrenia and Parkinson's disease are strongly associated with altered gut microbiota. However, a single phylum or microbial profile is unlikely to cause the disease-specific increase or decrease. As for lines of intervention, probiotic intake (psychobiotics) and fecal microbiota transplantation (FMT) have been used. In our study, a probiotic mixture, BIO-THREE®, including *Streptococcus faecalis*, *Bacillus mesentericus*, and *Clostridium butyricum*, significantly relieved constipation and improved insulin resistance among patients with schizophrenia[4]. And this probiotic mixture can ameliorate the negative symptoms of schizophrenia[5]. Recent studies have speculated that this mechanism is to improve the delicate balance of the fecal microbiota. The probiotic mixture treatment reduced *Bacteroides*, and restored *Prevotella*. Both *Bacteroides* and *Prevotella* can ferment dietary *fibers* and some of them produce total short chain fatty acid (SCFA). SCFA production is much higher in *Prevotella* than in Bacteroides. 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[6].

Thus, the importance of both psychobiotics and FMT has only recently been acknowledged. Only a few preclinical and clinical studies have been carried out in this field. Signals from the gastrointestinal tract shape pathology in the brain through gene expression and protein transport. Parkinson's disease and schizophrenia probably have a high co-morbidity because they share a common mechanism of disruption of the information transfer process from the gastrointestinal tract to the brain.

In other words, even if the brain is the site of onset of the disease, it should be possible to target the gut microbiota that transmits information to the brain for treatment. By targeting the gut microbiota, we can develop therapies that maintain the normal function of the dopaminergic nervous system[7]. These findings allow us to strongly consider the gut microbiota as a potential target for treating neuropsychiatric disorders such as schizophrenia and Parkinson's disease, representing an effective therapeutic option. Neuropsychiatric diseases should not be confined to the brain, but should be studied with the entire body in the open.

REFERENCES

1. Svensson E, Horváth-Puhó E, Thomsen RW, Djurhuus JC, Pedersen L, Borghammer P, Sørensen HT. Vagotomy and subsequent risk of Parkinson's disease. *Ann Neurol* 2015; 78(4): 522-529.
2. Klarer M, Krieger JP, Richetto J, Weber-Stadlbauer U, Günther L, Winter C, Arnold M, Langhans W, Meyer U. Abdominal Vagal Afferents Modulate the Brain Transcriptome and Behaviors Relevant to Schizophrenia. *J Neurosci* 2018; 38(7): 1634-1647.
3. Kuusimäki T, Al-Abdulrasul H, Kurki S, Hietala J, Hartikainen S, Koponen M, Tolppanen AM, Kaasinen V. Increased Risk of Parkinson's Disease in Patients With Schizophrenia Spectrum Disorders. Mov Disord 2021; 36(6): 1353-1361.
4. Nagamine T, Nakamura M. The effect of probiotics on bowel movement and metabolic parameters in schizophrenia patients: a retrospective chart review. *Biosci Microbiota Food Health* 2020; 39(4): 197-198.
5. Nagamine T, Sato N, Seo G. Probiotics Reduce Negative Symptoms of Schizophrenia: A Case Report. *Int Med J* 2012; 19(1): 72-73.
6. Nagamine T. The Potential of Probiotics in the Treatment of Schizophrenia. *Clin Neuropsychopharmacol* Ther 2021; 12: (in press).
7. Nagamine T. Bacterial Translocation in Schizophrenia; Gut Microbiota is a New Target for Treating Schizophrenia. *Int Med J* 2015; 22(5): 444-445.