News Release

Title

Potential for Vitamin B Administration in Parkinson's Disease Treatment: Insights from Gut Microbiota Analysis

Key Points

•A meta-analysis of the gut microbiota of Parkinson's disease patients was conducted using shotgun metagenomic data from five countries: Japan, the United States, Taiwan, China, and Germany.

•In Parkinson's disease patients, bacterial genes related to the synthesis of riboflavin (vitamin B2) and biotin (vitamin B7) are decreased.

•Analysis of fecal metabolites revealed a reduction in intestinal short-chain fatty acids and polyamines in Parkinson's disease patients.

•A positive correlation was found between bacterial genes related to the synthesis of riboflavin and biotin and intestinal short-chain fatty acids and polyamines.

•Supplementation therapy with riboflavin and biotin has shown potential as an effective treatment for Parkinson's disease patients.

Summary

The research group led by Assistant Professor Hiroshi Nishiwaki at the Department of Neurogenetics, Graduate School of Medicine, Nagoya University, and Associate Professor Jun Ueyama at the Department of Pathophysiological Laboratory Sciences, Graduate School of Medicine, Nagoya University, in collaboration with Professor Kinji Ohno from Nagoya University of Arts and Sciences, Professor Masaaki Hirayama from Chubu University, Director Kenichi Kashihara at Okayama Neurology Clinic, Professor Tetsuya Maeda from Iwate Medical University, and Professor Yoshio Tsuboi from Fukuoka University, conducted a meta-analysis of the gut microbiota of Parkinson's disease patients using shotgun metagenomic data from Japan, the United States, Taiwan, China, and Germany. They revealed that genes related to the biosynthesis of vitamin B in gut bacteria are reduced in Parkinson's disease patients. Previous analyses of the gut microbiota from shotgun metagenomes of Parkinson's disease patients have been reported in eight papers. However, it was difficult to identify gut bacteria, bacterial genes, and metabolic pathways associated with Parkinson's disease across different countries, as the composition of the gut microbiota varies significantly among healthy individuals globally. This research team conducted gut microbiota analyses with the cooperation of Parkinson's disease patients and used meta-analysis to

integrate and analyze the gut microbiota data across the aforementioned countries. The meta-analysis showed a reduction in bacterial genes related to the synthesis of riboflavin and biotin in Parkinson's disease patients. Furthermore, the analysis of fecal metabolites revealed a reduction in short-chain fatty acids and polyamines. A positive correlation was also found between the bacterial genes related to riboflavin and biotin synthesis and the levels of intestinal short-chain fatty acids and polyamines. These results suggest that supplementation therapy with riboflavin and biotin could be an effective treatment for Parkinson's disease patients. This study's findings are expected to contribute to the elucidation of the pathogenesis of Parkinson's disease and the development of novel treatments.

Research Background

Parkinson's disease is caused by the abnormal aggregation of a protein called alpha-synuclein in the dopaminergic cells of the substantia nigra in the midbrain, forming Lewy bodies. It is believed that these alpha-synuclein aggregates originate in the enteric nervous system and reach the substantia nigra via the vagus nerve, causing normal alpha-synuclein to also begin aggregating abnormally, which progresses the disease. Known early symptoms of Parkinson's disease include constipation, REM sleep behavior disorder, and depression, which occur before the onset of motor symptoms and may be related to the abnormal propagation of alpha-synuclein. Previous studies have shown that alpha-synuclein aggregates are found in high quantities in the intestines of Parkinson's disease patients. Additionally, an increase in intestinal permeability in Parkinson's disease patients was previously reported by our research team and a group in Germany.

Our team previously used 16S rRNA sequencing in a meta-analysis of data from five countries, revealing an increase in mucin-degrading bacteria *Akkermansia* and a decrease in short-chain fatty acid-producing bacteria *Roseburia* and *Faecalibacterium* across countries in Parkinson's disease. However, 16S rRNA sequencing only identifies bacteria at the genus level and does not allow for analysis at the bacterial gene or metabolic pathway levels. Therefore, we conducted a gene-level analysis of the gut microbiota using shotgun metagenomic analysis to identify metabolic pathways that are either enhanced or diminished in Parkinson's disease. A total of eight reports on the shotgun metagenomic gut microbiota of Parkinson's disease patients were available, but only some of the data from these reports were downloadable for our use. We combined them with shotgun metagenomic data derived from fecal samples collected by our team for meta-analysis.

Research Results

In Parkinson's disease patients, an increase in alpha diversity, an indicator of the diversity of bacteria in the gut, was observed. Similarly to the results from the meta-analysis using 16S rRNA sequencing, there was an increase in *Akkermansia muciniphila* and a decrease in *Roseburia intestinalis* and *Faecalibacterium prausnitzii* in Parkinson's disease patients. Pathway analysis showed a significant reduction in genes involved in the biosynthesis of riboflavin and biotin in these patients. Five out of six categories of carbohydrate-active enzymes were found to be reduced in Parkinson's disease. Fecal metabolite analysis using our team's samples revealed a decrease in intestinal short-chain fatty acids and polyamines. Furthermore, there was a positive correlation between the gene quantities involved in the biosynthesis of riboflavin and biotin and the concentrations of intestinal short-chain fatty acids and polyamines (Figure 1). The bacterial groups that led to the reduction in riboflavin and biotin biosynthesis in Japan, the United States, and Germany were different from those in China and Taiwan.

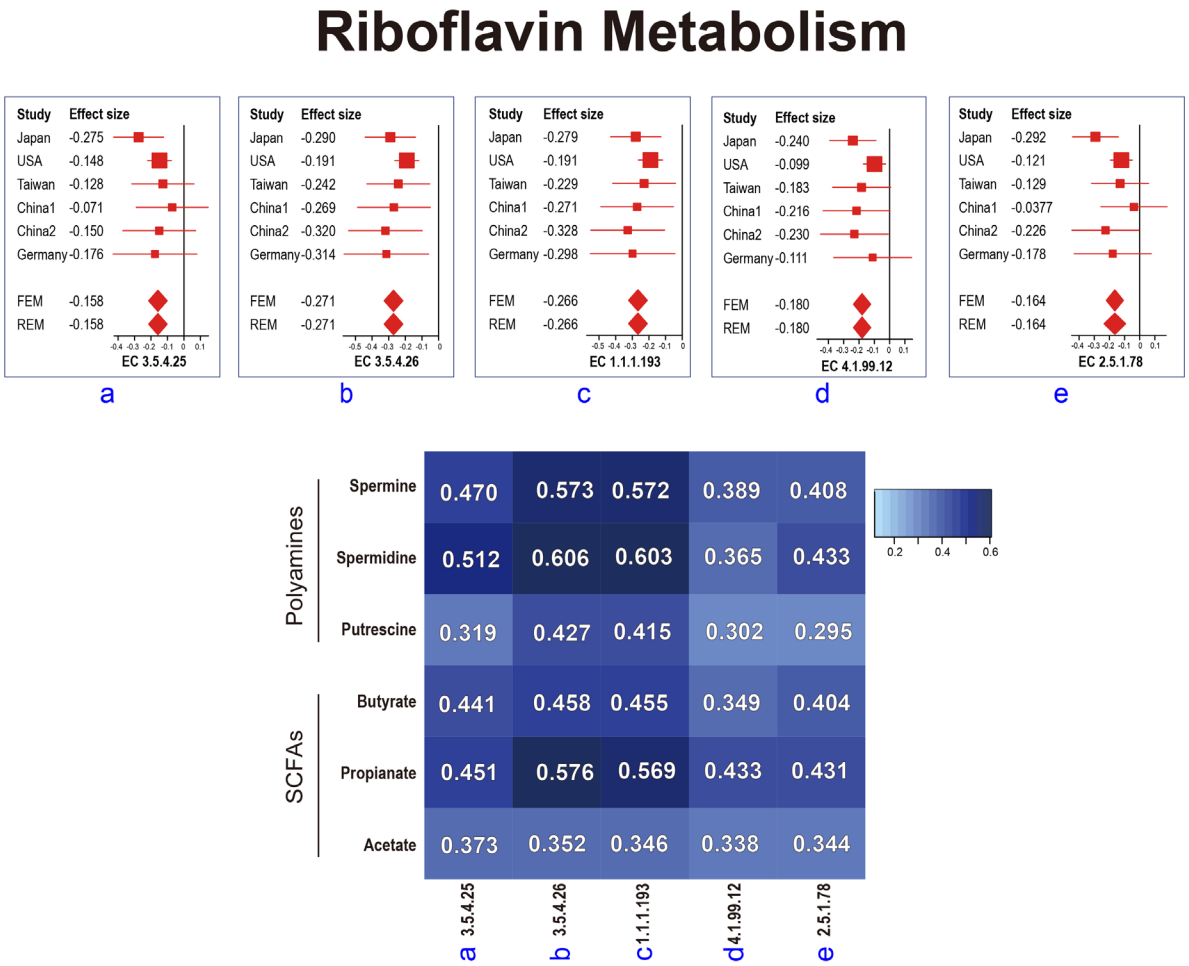

Figure 1: Meta-analysis results of riboflavin metabolism genes and correlation diagrams with fecal short-chain fatty acids and polyamines

Figure 2 illustrates the summary of this study and the speculated pathways. Based on the results of this study and previous research, the following speculation is drawn: The reduction in short-chain fatty acids and polyamines may lead to thinning of the mucosal layer, which in turn increases intestinal permeability. Indeed, intestinal permeability was found to be increased in Parkinson's disease. The increased intestinal permeability may enhance the exposure of the enteric nerve plexus to pesticides, herbicides, and other toxins, potentially triggering abnormal aggregation of alpha-synuclein. Furthermore, short-chain fatty acids and polyamines promote the differentiation of M2 macrophages, relatively reducing M1 macrophages, whose deficiency induces neuroinflammation. Therefore, it is speculated that gut dysbiosis in Parkinson's disease leads to a decrease in the production of intestinal short-chain fatty acids and polyamines, thereby promoting intestinal alpha-synuclein formation and neuroinflammation.

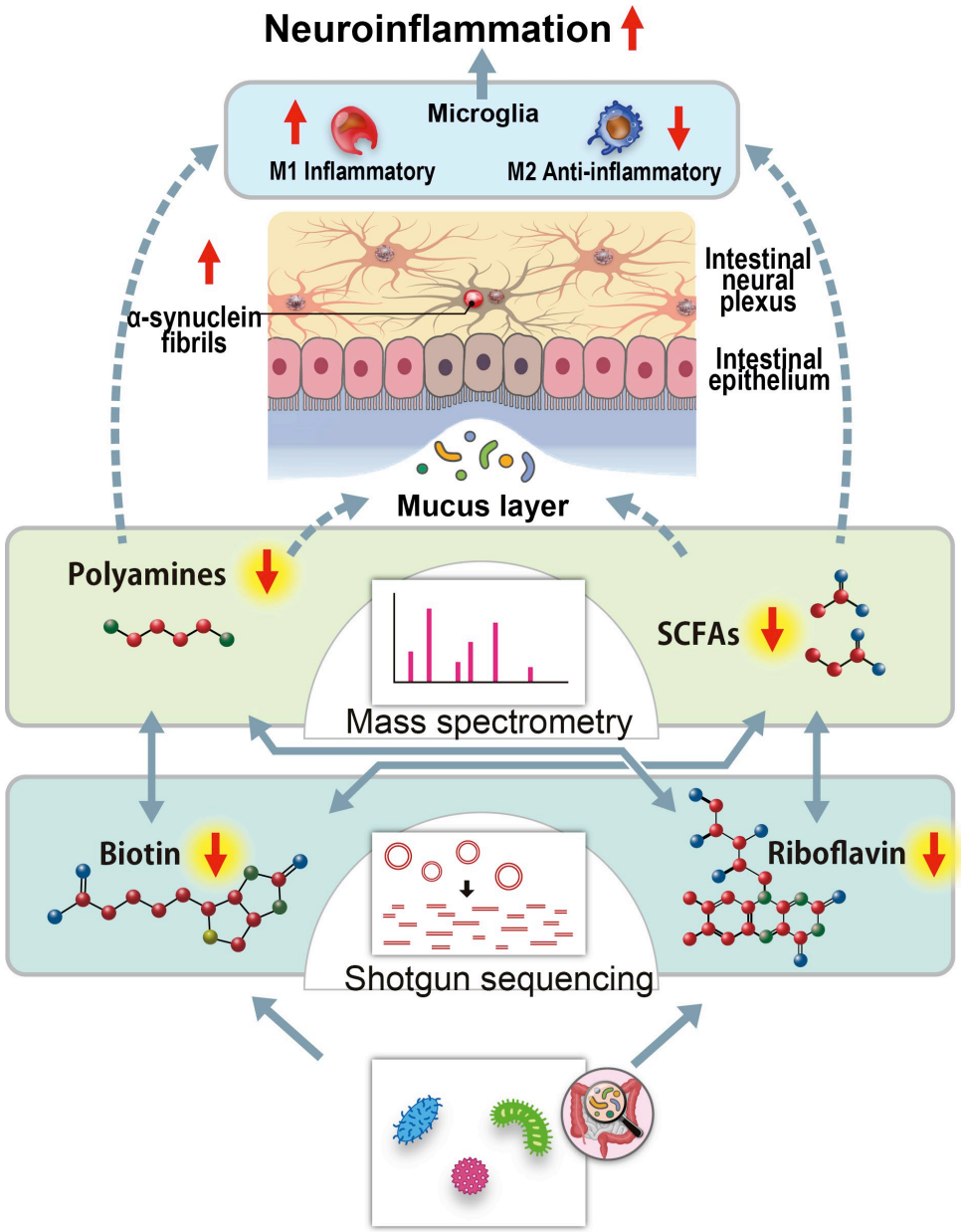

Figure 2: Summary and speculative views of this study. Solid arrows indicate associations observed in this study, while dashed arrows represent speculations based on previous reports.

Research Summary and Future Perspective

Dysbiosis plays a significant role in Parkinson's disease, and supplementation with riboflavin and/or biotin may be beneficial in some patients. Furthermore, it is hoped that this could lead to a better understanding of the pathology of Parkinson's disease and the development of new treatment methods.

Publication

Journal：npj Parkinson’s Disease
Titile：Meta-analysis of shotgun sequencing of gut microbiota in Parkinson’s disease

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DOI: 10.1038/s41531-024-00724-z

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