

High *Prevotella*-to-*Bacteroides* Ratio Predicts Antidepressant Effect of 4G-beta-D-Galactosylsucrose

Yumiko Ido¹⁾, Megumu Yano²⁾, Seiichiro Tarutani³⁾, Takahiko Nagamine⁴⁾

KEY WORDS

Prevotella-to-*Bacteroides* ratio, 4G-beta-D-Galactosylsucrose, depression

The gut microbiota is closely associated with the pathogenesis of psychiatric disorders, including depression. Intervention with the gut microbiota of depressed patients by probiotics and prebiotics may improve depressive symptoms. However, our randomized, double-blind, placebo-controlled trial of 4G-β-D-galactosylsucrose (LS) at 3.2 g/day for 24 weeks showed no efficacy in improving depression versus placebo¹⁾. Double-blind, placebo-controlled trials of depression are difficult to detect actual drug effects because of the relatively large placebo effect²⁾. In fact, in our study, about half of the patients treated with LS showed improvement in depressive symptoms, although not significantly different from placebo. Since we did not change psychiatric medications during the study period, we believe that LS may be effective for some depressed patients. Therefore, we divided LS-treated patients into two groups: the depression-improved group with a decreased MADRS (Montgomery-Asberg Depression Rating Scale) score and the non-improved group with a flat or increased MADRS score after 24 weeks, and compared 16S rRNA analysis of fecal microflora in the two groups. All participants gave their written consent. The depression-improved group consisted of five patients, all female, with a mean age of 48.8 years, and the average improvement in MADRS scores went from 16.6 to 7.6. The non-improved group consisted of four patients, three female and one male, with a mean age of 57.0 years, and their MADRS scores worsened from 17.3 to 25.8. Since MADRS scores before LS administration did not differ between the two groups, psychiatric symptoms before LS intervention were judged to be equivalent in both groups. Similar to our previous report on LS administration to psychiatric patients³⁾, *Bifidobacterium* were increased with LS in both groups, but *Prevotella* was the only significant difference in the fecal flora of the two groups both before and after LS administration. In other words, the *Prevotella*-to-*Bacteroides* ratio (P/B ratio) was clearly different between the two groups. In the depression-improved group, the P/B ratio was high (33.54%) even before LS administration, and it was further increased (+6.05%) after LS ingestion. In contrast, the non-improved group originally had a very small P/B ratio (0.19%), and LS intake resulted in a slight increase in the P/B ratio (+ 2.91%) (Figure 1). Patients with higher levels of *Prevotella* prior to treatment and further increase with LS tended to have more improvement in their depressive symptoms.

LS is selectively assimilated by *Bifidobacterium* as a prebiotic and increases beneficial bacteria, but the mechanism by which depression is improved is unknown. Patients whose depressive symptoms improved with LS had a higher P/B ratio, which was further increased with LS,

suggesting that *Prevotella* interacts with LS. *Prevotella*, along with *Bacteroides*, is classified in the phylum *Bacteroidetes*. Members of the phylum *Bacteroidetes* are known to be efficient degraders of dietary fiber. The main action of *Prevotella* and *Bacteroides* is to ferment dietary fiber to produce short-chain fatty acids (SCFAs) such as acetic, propionic, and butyric acids from dietary fiber, which are the main source of energy for the intestinal epithelium⁴⁾. However, in vitro the *Prevotella*-driven and *Bacteroides*-driven microbiota have been shown to produce different amounts and profiles of SCFAs from the same carbohydrate substrates. Higher P/B ratios are more favorable for degradation of oligosaccharides and more efficient production of SCFAs⁵⁾. Although the relationship between psychiatric disorders and SCFAs is still being elucidated, efficient production of SCFAs may be effective in improving psychiatric symptoms, since impaired intestinal epithelial barrier function has been postulated in psychiatric disorders⁶⁾.

In conclusion, patients who respond to LS have characteristics of their gut microbiota, one of which may be the P/B ratio. The time may come when treatment strategies will be based on each pattern of gut

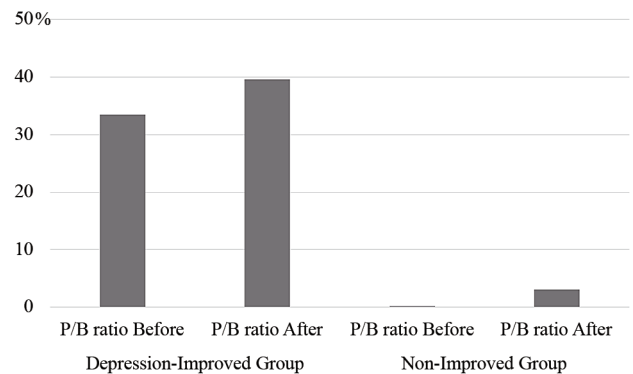


Figure 1: *Prevotella*-to-*Bacteroides* ratio (P/B ratio) before and after 4G-beta-D-Galactosylsucrose (LS) administration in the depression-improved and non-improved groups, respectively.

Received on October 14, 2022 and accepted on October 29, 2022

1) Department of Food and Nutrition, Faculty of Home Economics, Kyoto Women's University, Kyoto, Japan

2) Department of Pathophysiology, Osaka Metropolitan University, Graduate School of Medicine

3) Osaka, Japan

4) Shin-Abuyama Hospital, Osaka Institute of Clinical Psychiatry, Department of Psychiatry, Osaka, Japan

5) Sunlight Brain Research Center, Yamaguchi, Japan

Correspondence to: Yumiko Ido (e-mail: idoy@kyoto-wu.ac.jp)

ORCID ID:

Yumiko Ido: 0000-0002-5768-9094

Takahiko Nagamine: 0000-0002-0690-6271

microbiota, so research in this area needs to be pursued.

DISCLOSURE STATEMENT

The authors have no conflicts of interest relevant to the content of the article.

REFERENCES

1. Tarutani S, Omori M, Ido Y, Yano M, Komatsu T, Okamura T. 2022. Effects of 4G-beta-D-Galactosylsucrose in patients with depression: A randomized, double-blinded, placebo-controlled, parallel-group comparative study. *J Psychiatr Res.* 148: 110-120.
2. Enck P, Klosterhalfen S. 2013. The placebo response in clinical trials-the current state of play. *Complement Ther Med.* 21(2): 98-101.
3. Nagamine T, Ido Y, Nakamura M, Okamura T. 2018. 4^c-β-D-galactosylsucrose as a prebiotic may improve underweight in inpatients with schizophrenia. *Biosci Microbiota Food Health.* 37(2): 45-47.
4. Hjorth MF, Blädel T, Bendtsen LQ, Lorenzen JK, Holm JB, Kiilerich P, Roager HM, Kristiansen K, Larsen LH, Astrup A. 2019. *Prevotella*-to-*Bacteroides* ratio predicts body weight and fat loss success on 24-week diets varying in macronutrient composition and dietary fiber: results from a post-hoc analysis. *Int J Obes (Lond).* 43(1): 149-157.
5. Chen T, Long W, Zhang C, Liu S, Zhao L, Hamaker BR. 2017. Fiber-utilizing capacity varies in *Prevotella*- versus *Bacteroides*-dominated gut microbiota. *Sci Rep.* 7(1): 2594.
6. Caputi V, Popov J, Giron MC, O Apos Mahony S. 2021. Gut Microbiota as a Mediator of Host Neuro-Immune Interactions: Implications in Neuroinflammatory Disorders. *Mod Trends Psychiatry.* 32: 40-57.