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Perspective on the relationship between microbiota dysbiosis and neuroinflammation: probiotics as a treatment option

Chiao W. Ng, Zahoor A. Shah*

Introduction: In the 1680s, Antonie van Leewenhoek was the first to observe the differences in the human gut microbiome *versus* the oral cavity diversity, and it led to the birth of a new term, "microbiota". Later, the link between the brain and the gut was observed to be facilitated by the vagus nerve, allowing for neurotransmitters secreted in the gastrointestinal tract to travel to the brain, directing signals that influence brain function. The gut microbiome is linked to various diseases ranging from autism spectrum disorder to Parkinson's disease (PD) and is projected to be the new "disease-causing mechanism," calling for interventions that can modulate gut microbiota and mitigate brain disorders. Gut dysbiosis is observed before and after the onset of various neurodegenerative diseases and often manifests itself into gut-related diseases such as; gut inflammation, chronic constipation, and colitis. Dysbiosis of the gut can be the outcome of neuroinflammatory signaling, and the phenomenon could possibly become a marker for neurodegenerative diseases. Based on the microbiota and its role in disease conditions, new and emerging therapeutic alternatives such as probiotics (**Figure 1**) and prebiotics are recommended, including the fiber and the gut bacterial products such as short-chain fatty acids.

Probiotics for reducing neuroinflammation: Common probiotic bacteria widely researched and marketed to be in dairy products are *Bifidobacterium spp.*, *Lactobacillus acidophilus*, and *L. casei* (Yerlikaya, 2014). *Lactobacillus spp*. are commonly found in the gastrointestinal tract and the urogenital tract (Hill et al., 2018). These species reduce intestinal infections, decrease allergies, lessen atopic eczema, and alleviate inflammatory bowel disease (Farid E and Nancy C, 2019). *Lactobacilli spp*. modulate the regulation of genes that encode adheren junction proteins and those that affect the epithelial barrier function. A few of these species can increase human mucin, which has a protective effect on the gastrointestinal tract. Specifically, *Lactobacillus acidophilus* A4 cell extract was enough to increase mucin 2 expression in HT29 cells (Bermudez-Brito et al., 2012). The protection of junctions in the gastrointestinal tract led to a decreased risk of leaky gut syndrome.

Bifidobacterium longum has been incorporated into many food items due to its health benefits. They are also the first to colonize the gastrointestinal tract. Human and rodent studies on stressed subjects showed *Bifidobacterium longum's* ability to improve cognition and reduce stress-dependent behaviors (Hadizadeh et al., 2019; Wang et al., 2019). In a study using 5XFAD mice, it was observed that *Bifidobacterium longum* has a beneficial role as it suppresses the gut microbiome's production of lipopolysaccharide (LPS), a bacterial endotoxin and pathogen-associated molecular pattern. It is recognized by toll-like receptors and reportedly causes intestinal inflammation by inducing nuclear factor kappa beta (NF-kB) activation and tumor necrosis factor-alpha synthesis (Kawasaki and Kawai, 2014). In BV-2 cells, *Bifidobacterium longum* suppress LPS induced NF-kB activation (Lee et al., 2019), as NF-kB promotes the transcriptional activity of proinflammatory cytokines and chemokines involved in inflammation (Kawasaki and Kawai, 2014). *Bifidobacterium longum* also decreased the blood LPS and tumor necrosis factor-alpha levels during acute inflammation, a signaling pattern responsible for causing apoptosis or necrosis. While assessing cognitive functions, it was found that 6-month-old 5XFAD mice given *Bifidobacterium longum* for 8 weeks experienced a reduction in cognitive decline and suppressed accumulation of amyloid-beta plaques. Amyloid-beta accumulation causes the activation of glial cells to stimulate proinflammatory cytokines leading to the damage and loss of neurons. Tests performed on aged mice demonstrated that *Bifidobacterium longum* had a similar effect on LPS production as seen in 6-month-old 5XFAD mice and had a significant reduction of age-related cognitive decline (Lee et al., 2019).

Using a combination of probiotic strains in the transgenic MitoPark PD mouse model resulted in improved motor functions (rotarod, gait pattern, and beam balance tests) than the sham treatment group (Hsieh et al., 2020). The possible mechanism is that probiotics are known to decrease intestinal inflammation through the downregulation of toll-like receptor expression (Bermudez-Brito et al., 2012), which is responsible for recognizing pathogen-associated molecular patterns and inducing innate immune responses by activating NF-kB transcription factor (Kawasaki and Kawai, 2014). This prolonged probiotic therapy slowed PD progression and showed neuroprotective effects (Hsieh et al., 2020). In LPS injected rats, probiotics consisting of a mixture of *Lactobacillus helveticus*, and *Bifidobacterium longum* reduced apoptosis in the hippocampus through the gut-brain axis (Mohammadi et al., 2019). Another probiotic combination, ProBiotic-4, given to SAMP8 mice, to study the effects on the gut-brain axis and cognitive functions, improved

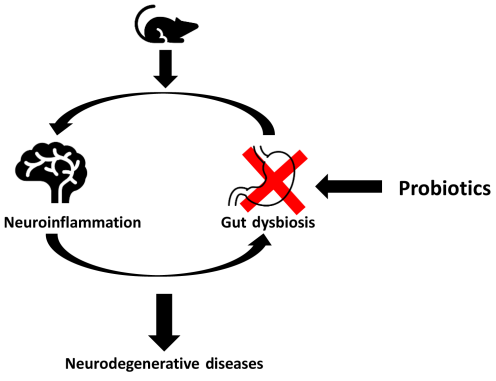

Figure 1 | **Effects of probiotics on the gut-brain axis.**
In various mouse studies, mice with gut dysbiosis showed signs of neuroinflammation, which often can lead to neurodegenerative disease. However, when probiotics were administered, the gut dysbiosis was resolved. The probiotics help increase short-chain fatty acids, and beneficial bacterial strains in the gut. These beneficial bacterial strains then help reduce apoptosis and increase tight junction proteins to reduce the gut's permeability.

not only memory but also inhibited glial activation, oxidative DNA damage, and neuronal injury (Yang et al., 2020).

Conclusion and future perspectives: Neuroinflammation is a common factor in neurodegenerative diseases, such as stroke, PD, and AD. Over the past few years, the gut microbiome has become the prime focus for researchers, mainly looking at the correlation between the gut and the brain, connections via the vagus nerve. However, due to the limitations of extrapolating data from mice models to humans, the difficulty of maintaining the same gut microbiome throughout and its replicability is challenging. As humans and mice have differences in the distribution of bacterial genera, it is expected to have different probiotic bacterial strains secreting different concentrations of beneficial metabolites (Nagpal et al., 2018). Further studies into the symbiotic relationships of bacterial and fungal strains when administering probiotic strains are needed as there is no complete understanding of the interconnection between species and its effects. Studies have been performed on common strains that are typically already found in commercially available food products. Although various studies have shown promising results on reducing neuroinflammation, further intensive studies are required to see if long-term usage of probiotics is needed to maintain the therapeutic effects. With the resolution of these questions, probiotics pose to become the treatment of choice, in conjunction with other medications or as a standalone therapy to treat a plethora of diseases and, in particular, neurodegenerative diseases.

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Chiao W. Ng, Zahoor A. Shah*
Department of Medicinal and Biological Chemistry, College of Pharmacy and Pharmaceutical Sciences, University of Toledo, Toledo, OH, USA
***Correspondence to:** Zahoor A. Shah, PhD, zahoor.shah@utoledo.edu.
https://orcid.org/0000-0001-8977-1618 (Zahoor A. Shah)
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