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Neurotransmitter-producing probiotics for the treatment of CNS inflammatory demyelination

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Abstract

Statement of the Problem:

Multiple sclerosis (MS) is a devastating autoimmune disease characterized by inflammatory demyelination of the central nervous system (CNS). Over 2.8 million patients are affected worldwide. The gut-microbiota-brain axis has emerged as a critical pathway in the regulation of neuroinflammation. The gut microbiome regulates the severity of many experimental models of autoimmune central nervous system (CNS) inflammatory demyelination. Our most recent findings demonstrate that the microbiota of mice from different sources affects the severity of CNS inflammatory demyelination in experimental autoimmune encephalomyelitis (EAE), a mouse model of MS. Neuroinflammation modified the gut microbiota composition. The disease progression resulted in a significant reduction in members of lactic acid bacteria. Among the altered taxa, bacteria producing gamma-aminobutyric acid (GABA) were significantly reduced. We hypothesized that modifying the microbiota with a probiotic while increasing intestinal GABA levels would reduce EAE's severity. Methodology: We genetically engineered a Lactococcus lactis with increased GABA production and used the EAE model induced in C57BL/6 mice from two different commercial vendors to test its protective efficacy. Results: Real-time quantitative PCR data demonstrated an elevated expression of glutamic acid decarboxylase (GAD), while GABA-specific ELISA showed a significant increase in neurotransmitter production when exposed to increasing concentrations of glutamic acid and time. In vivo, five times/week oral gavages with 5 x 108 CFU/mouse of GAD L. lactis but not with empty-plasmid carrier L. lactis protected against EAE compared with sham-treated mice, while preventing weight loss. However, protection was dependent on the initial composition of the microbiome. Conclusion & Significance: Our results show that the increase of GABA at the intestinal level with the oral treatment with a probiotic strain protects against neuroinflammation in the CNS.

Biography:

Javier Ochoa-Repáraz received his Ph.D. in Biological Sciences (Cellular and Molecular Biology Program) from the University of Navarra in Spain. He was trained as a postdoctoral scientist at Montana State University and Dartmouth College, exploring the impact of the gut mucosal immune responses to microbes on CNS inflammatory demyelination. At Dartmouth College, he studied mechanisms of immunomodulation induced by gut symbionts and polysaccharide A (PSA) produced by Bacteroides fragilis in the context of multiple sclerosis (MS) using animal models of the disease. He has industry experience working for a large pharmaceutical company as a scientific member of their MS platform. As a faculty at EWU, he continues working on the reciprocal interaction between the gut microbiome and disease, with a specific focus on immunomodulation mediated by gut microbes and microbiome-modifying treatments in CNS demyelinating inflammation.

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