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Effects of Probiotics on Inflammatory Responses in Neuronal Tissue

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Introduction

Alzheimer's Disease Inflammatory Hypothesis

- Alzheimer's disease (AD) is a neurodegenerative disease characterized by neuronal loss, intraneuronal neurofibrillary tangles, and extracellular beta-amyloid plaques.[1] One suggested pathogenesis of AD implicates the deleterious effects of inflammation: the inflammatory hypothesis suggests that neuronal damage is caused not by the disease itself, but by the body's inflammatory response to the disease. Microglial cells become hyperactive in the presence of beta-amyloid plaque accumulations, producing a pro-inflammatory response.[2]

Blood Brain Barrier (BBB)

- The blood brain barrier is a highly regulated diffusion barrier around the brain. This barrier allows only small, lipid soluble molecules to freely diffuse, while others must be transported in.

Gut- Brain Axis (GBA)

- The gut-brain axis facilitates the bidirectional communication between the intestines and the brain. It plays a roles in managing gut functions and communicating the resulting signals to the brain. This includes activation of the immune system and other signalling pathways.

- Based on these concepts, it can be proposed that probiotics may prove to be a suitable candidate for treating the damaging inflammation of neuronal tissue involved in AD, as they incorporate the use of the GBA and may produce anti-inflammatory products.

Results

The addition of single probiotic molecules to a model of the BBB has no effect on either pro- or anti-inflammatory molecules produced by microglia. Also, the FA & H combination produced an increase of the pro-inflammatory molecule TNFα.

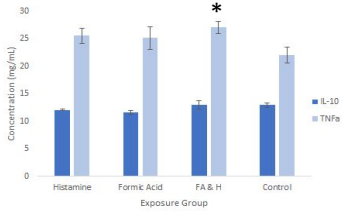

Figure 1: Concentrations of IL-10 and TNFα in transwell cultures. Concentrations of TNFα were only significantly different ($p = 0.00006$) from the control in the FA + Histamine treatment group. IL-10 concentrations in the treatment groups were not different. Accumulations of IL-10 and TNFα were largely undetected.

Methods and Materials

-Cell cultures within a transwell system of astrocytes, endothelial cells, and microglia were completed as shown in Figure 2.

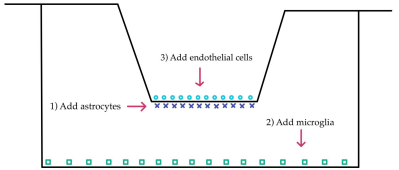

Figure 2: Configuration of transwell system used including culture location.

-Once cultured, human peripheral blood T cells were added into the top well of the transwell.

-Samples of formic acid, histamine, and formic acid plus histamine were mixed with media resulting in concentrations of 0.2 mM formic acid and 6.5 nM histamine, and then added directly into the top well of the transwell system.

-Media samples in the bottom well were collected at intermittent time intervals.

-Protein analysis was run on the samples.

-ELISA analyses of TNFα and IL-10 were run on the samples.

Hypothesis

-If neuronal cell cultures are exposed to the products of *E. coli* (formic acid) and *L. reuteri* (histamine) via a transwell system, then the cultures exposed to formic acid will show increased inflammatory cytokine production (tumor necrosis factor α, TNFα) and decreased anti-inflammatory cytokine production (interleukin-10, IL-10), those exposed to histamine would show reduced TNFα and increased IL-10, and those exposed to a combination of histamine and formic acid will show reduced TNFα and increased IL-10.

Discussion and Future Directions

-There are many factors that could have caused the end result of accepting the null hypothesis:

- -The BBB is impermeable to the molecules. Measuring to see if the molecules actually crossed the barrier in future experiments is advised.
- -This model may not be completely representative of the BBB with the lack of neurons and other cells that could have played a roll in this process.
- -The stimulatory molecules chosen (formic acid and histamine) may not be the most effective, or higher concentrations were needed to observe alterations.
- -The exposure duration may need to be lengthened.
- -Perhaps a specific combination of probiotic products are needed to observe a cellular physiological effect.
- -Lastly, more collection points from the transwells is advised for future experiments.

References

1. Mosser DM and Zhang X. Interleukin-10: New perspectives on an old cytokine. *Immunol Rev*. 2009; 226(1):205-218.
2. Su F, Bai F, and Zhang Z. Inflammatory cytokines and Alzheimer's disease: a review from the perspective of genetic polymorphisms. *Neurosci. Bull*. 2016;32(5):469–480.

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