The Effect of Gut Probiotic Supplementation on Microglial Activation and Peripheral Blood Inflammation in a Pretangle Tau Animal Model

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INTRODUCTION

Approximately half a million Canadians are living with dementia (1). Alzheimer's Disease (AD) is the most common form of dementia (2).

Inflammation, in both the brain and peripheral blood, has been identified as a key player in the progression of AD (3,4).

Gut microbiota has also been linked to the progression of AD via the Gut-Brain Axis (5,6,7). Gut microbiota can influence the development of AD by increasing the permeability of the blood-brain-barrier (BBB), resulting in increased neuroinflammation (8)

Probiotics have been shown to ameliorate gut health, reduce inflammation, and improve cognitive functioning (8).

Ionized calcium binding adaptor molecule 1 (Iba-1) is a marker that is used to represent the quantity of microglia present in the brain (9,10).

Tumor necrosis factor alpha (TNFa) is a proinflammatory cytokine that can be used to quantify peripheral blood inflammation (4).

OBJECTIVES

To determine the effects of probiotic supplementation on the inflammation present in AD.

To investigate the expression levels of the Iba-1 cells in the locus coeruleus (LC).

To investigate the TNFa expression levels in peripheral blood using an enzyme-linked immunosorbent assay (ELISA).

METHODS

This study used a pretangle tau rat model developed by the Yuan Laboratory which seeds hyperphosphorylated human tau (htauE14) in the rat LC that replicates key pre clinical features (11).

The sample size consisted of 42 tyrosine hydroxylase (TH)-Cre rats which were split into the following groups: (1) GFP + control diet, (2) htauE14 + control diet, (3) GFP +probiotic diet, (4) htauE14 + probiotic diet.

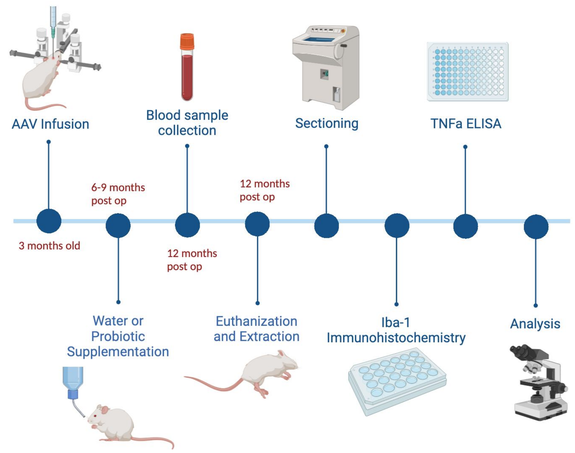
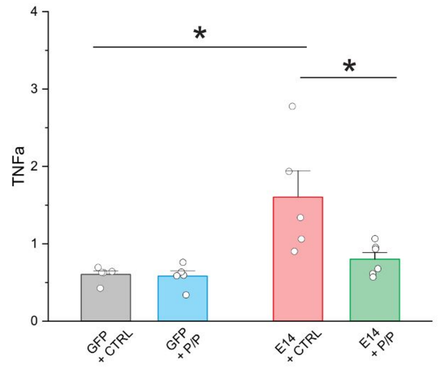


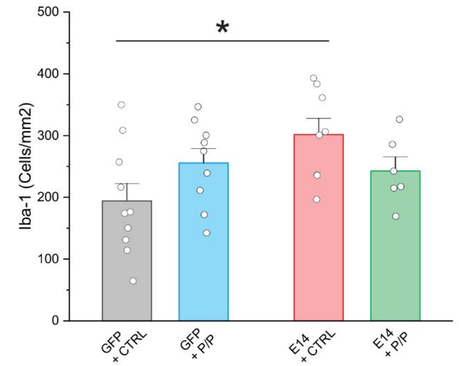
Figure 1: Procedure

RESULTS



TNFa expression was significantly higher in E14 rats on a control diet (N = 5, red bar) than E14 rats on a probiotic diet (N = 6, green bar), GFP rats on a control diet (N = 5, grey bar), and GFP rats on a probiotic diet (N = 5, blue bar) indicated by * $p < 0.05$.

Figure 2: TNFa Levels in Blood Serum Post-Probiotic Feeding



Iba-1 expression was significantly higher in E14 rats on a control diet (N = 8, red bar) than GFP rats on a control diet (N = 10, grey bar) as indicated by * $p < 0.05$. Probiotic supplementation had no significant effect on Iba-1 expression as seen in the GFP rats on a probiotic diet (N = 9, blue bar) and the E14 rats on a probiotic diet (N = 6, green bar).

Figure 3: Microglial quantification through Iba-1 Positive Staining

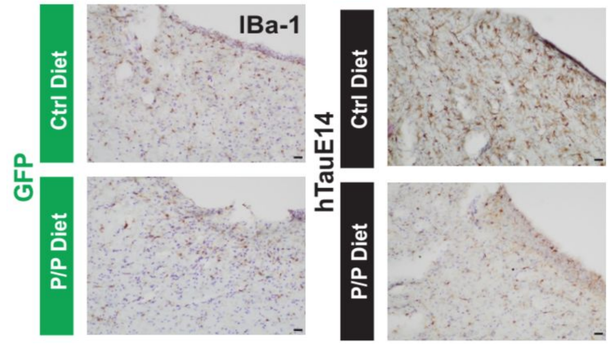


Figure 4: Iba-1 Imaging

CONCLUSION

These results suggest that pretangle tau indeed elevate peripheral and brain inflammation.

Probiotic supplementation reduced inflammation associated with pretangle tau, at least in the blood.

REFERENCES

1. Alzheimer Society of Canada. (2022). *Navigating the path forward for dementia in Canada: The Landmark Study Report #1*. https://alzheimer.ca/en/research/reports-dementia/landmark-study-report-1-path-forward
2. Centers for Disease Control and Prevention. (2019, April 5). *What is dementia?*. Centers for Disease Control and Prevention. https://www.cdc.gov/aging/dementia/index.html#:~:text=Dementia%20is%20not%20a%20specific,a%20part%20of%20normal%20aging.
3. Kinney, J. W., Bemiller, S. M., Murtishaw, A. S., Leisgang, A. M., Salazar, A. M., & Lamb, B. T. (2018). Inflammation as a central mechanism in alzheimer's disease. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *4*(1), 575–590. https://doi.org/10.1016/j.trci.2018.06.014
4. Park, J.-C., Han, S.-H., & Mook-Jung, I. (2020). Peripheral inflammatory biomarkers in alzheimer's disease: A brief review. *BMB Reports*, *53*(1), 10–19. https://doi.org/10.5483/bmbrep.2020.53.1.309
5. Blair, L. J., Frauen, H. D., Zhang, B., Nordhues, B. A., Bijan, S., Lin, Y.-C., Zamudio, F., Hernandez, L. D., Sabbagh, J. J., Selenica, M.-L. B., & Dickey, C. A. (2015). Tau depletion prevents progressive blood-brain barrier damage in a mouse model of tauopathy. *Acta Neuropathologica Communications*, *3*(1). https://doi.org/10.1186/s40478-015-0186-2
6. Zenaro, E., Piacentino, G., & Constantin, G. (2017). The blood-brain barrier in alzheimer's disease. *Neurobiology of Disease*, *107*, 41–56. https://doi.org/10.1016/j.nbd.2016.07.007
7. Carabotti, M., Scirocco, A., Maselli, M. A., & Severi, C. (2015). The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. *Annals of Gastroenterology*, *28*(2), 203–209.
8. Naomi, R., Embong, H., Othman, F., Ghazi, H. F., Maruthey, N., & Bahari, H. (2021). Probiotics for alzheimer's disease: A systematic review. *Nutrients*, *14*(1), 20. https://doi.org/10.3390/nu14010020
9. Hopperton, K. E., Mohammad, D., Trépanier, M. O., Giuliano, V., & Bazinet, R. P. (2017). Markers of microglia in post-mortem brain samples from patients with alzheimer's disease: A systematic review. *Molecular Psychiatry*, *23*(2), 177–198. https://doi.org/10.1038/mp.2017.246
10. Zhang, X., Wang, L.-P., Ziober, A., Zhang, P. J., & Bagg, A. (2021). Ionized calcium binding adaptor molecule 1 (IBA1). *American Journal of Clinical Pathology*, *156*(1), 86–99. https://doi.org/10.1093/ajcp/aqaa209
11. Braak, H., Thal, D. R., Ghebremedhin, E., & Del Tredici, K. (2011). Stages of the pathologic process in alzheimer disease: Age categories from 1 to 100 years. *Journal of Neuropathology & Experimental Neurology*, *70*(11), 960–969. https://doi.org/10.1097/nen.0b013e318232a379