The Effects of Benfotiamine on Glucose Metabolism in a 6-OHDA mouse model of Parkinson's Disease

Aymane Lachhab, Alfredo Zuniga

Department of Neuroscience, The College of Wooster

Introduction

- Parkinson's Disease is a motor movement disorder characterized by the death of dopaminergic neurons in the basal ganglia.
- Nearly a million Americans are living with Parkinson's Disease.
- It has multiple possible causes: Tau Tangles, Lewy Bodies, Genetic Mutations.
- Studies of Parkinson's patients have provided evidence for altered glucose metabolism.
- The Pentose Phosphate Pathway requires thiamine to breaks down glucose to produce NADPH and 5-carbon sugars.
- In Parkinson's, there is a decline in the activity of the PPP enzymes in the putamen.
- A striking feature of Parkinson's is a profound decrease in the level of mitochondrial complex I activity in the substantia nigra.
- Benfotiamine proved to improve glucose metabolism alterations associated with other neurodegenerative diseases.

Aims

- This study aims to investigate how daily oral 200mg/kg/day of benfotiamine would affect the motor deficit and the glucose metabolism in a 6-OHDA mouse model of Parkinson's disease.

Methods

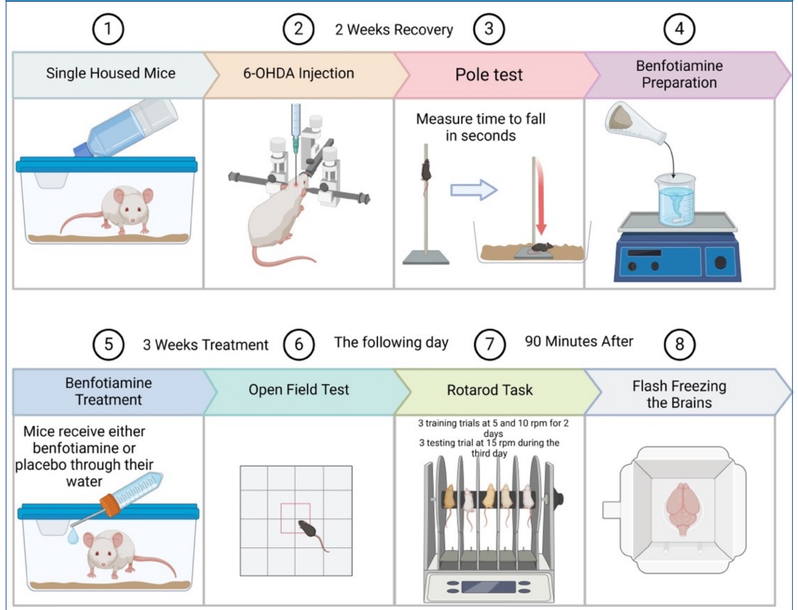

Figure 1. Timeline of the experimental procedure

Results

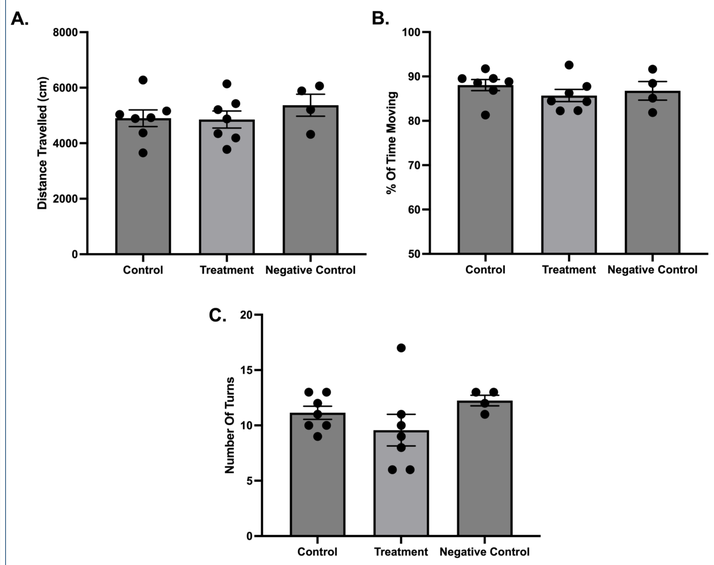

Figure 2. Locomotor activity in the open field maze. A.) Mice that received the benfotiamine treatment did not show any difference in distance traveled compared to mice that did not receive benfotiamine. Neither group showed any significant difference in distance traveled compared to the negative control mice. B.) Mice that received the benfotiamine treatment did not show any difference in the percentage of time moving compared to mice that did not receive benfotiamine. Neither group showed any significant difference in the percentage of time moving compared to the negative control mice. C.) There was no difference between groups in the number of turns. Errors bars depicted the standard error of the mean.

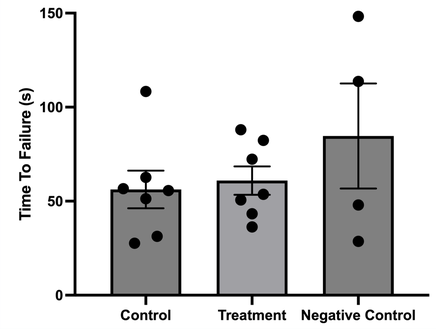

Figure 3. Motor behavior assessment in the rotarod task. Following stereotaxic surgery, mice were treated with benfotiamine for 3 weeks then got exposed to the rotarod task. There was no difference between groups in the rotarod task. Errors bars depicted standard error of the mean.

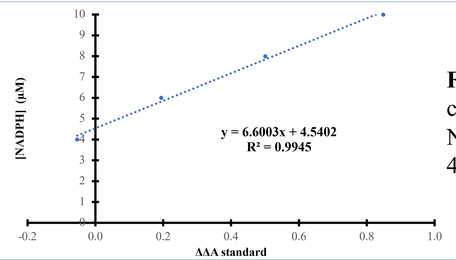

Figure 5. Standard curve of NADPH. Standard calibration curve of NADPH at various known NADPH concentrations against the absorbance at 450nm of these known concentrations.

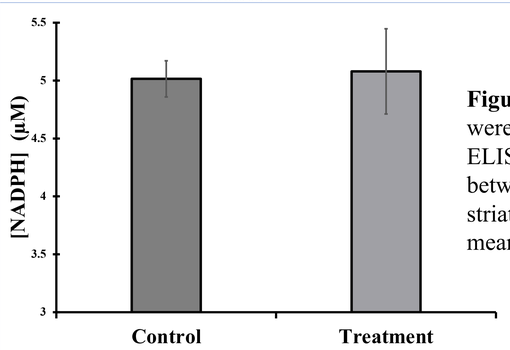

Figure 5. NADPH levels in the striatum. Striatums were isolated from the brain and run through an ELISA for NADPH/NADP$^+$. There was no difference between groups the concentration of NAPDH in the striatum. Errors bars depicted standard error of the mean.

Future Directions

- Future experiments would use immunohistochemistry or tyrosine hydroxylase staining to assess for the loss of dopaminergic neurons in the striatum and the substantia nigra.
- To further improve the experimental design, using a higher sample size, finer motor tasks, a higher concentration of the 6-OHDA injections, or a transgenic Park2 or LRRK2 mouse models of Parkinson's would be needed.

Acknowledgements

Thank you to my advisor Dr. Zuniga, for all the mentorship and guidance offered throughout this process. I would also like to thank my family and friends for their constant support. This project was funded by the College of Wooster Neuroscience Program and the Henry J Copeland Fund.

References

Bloem, B. R., Okun, M. S., & Klein, C. (2021). Parkinson's disease. *Lancet (London, England)*, *397*(10291), 2284–2303. https://doi.org/10.1016/S0140-6736(21)00218-X

DeMaagd, G., & Philip, A. (2015). Parkinson's Disease and Its Management. *Pharmacy and Therapeutics*, *40*(8), 504–532.

Dunn, L., Allen, G. Fg., Mamais, A., Ling, H., Li, A., Duberley, K. E., Hargreaves, I. P., Pope, S., Holton, J. L., Lees, A., Heales, S. J., & Bandopadhyay, R. (2014). Dysregulation of glucose metabolism is an early event in sporadic Parkinson's disease. *Neurobiology of Aging*, *35*(5), 1111–1115. https://doi.org/10.1016/j.neurobiolaging.2013.11.001

Funayama, M., Nishioka, K., Li, Y., & Hattori, N. (2023). Molecular genetics of Parkinson's disease: Contributions and global trends. *Journal of Human Genetics*, *68*(3), Article 3. https://doi.org/10.1038/s10038-022-01058-5

Gibson, G. E., Hirsch, J. A., Cirio, R. T., Jordan, B. D., Fonzetti, P., & Elder, J. (2013). Abnormal Thiamine-Dependent Processes in Alzheimer's Disease. Lessons from Diabetes. *Molecular and Cellular Neurosciences*, *55*, 17–25. https://doi.org/10.1016/j.mcn.2012.09.001

Gibson, G. E., Luchsinger, J. A., Cirio, R., Chen, H., Franchino-Elder, J., Hirsch, J. A., Bettendorff, L., Chen, Z., Flowers, S. A., Gerber, L. M., Grandville, T., Schupf, N., Xu, H., Stern, Y., Habeck, C., Jordan, B., & Fonzetti, P. (2020). Benfotiamine and Cognitive Decline in Alzheimer's Disease: Results of a Randomized Placebo-Controlled Phase IIa Clinical Trial. *Journal of Alzheimer's Disease*, *78*(3), 989–1010. https://doi.org/10.3233/JAD-200896

Lee, J., Sung, K. W., Bae, E.-J., Yoon, D., Kim, D., Lee, J. S., Park, D., Park, D. Y., Mun, S. R., Kwon, S. C., Kim, H. Y., Min, J.-O., Lee, S.-J., Suh, Y. H., & Kwon, Y. T. (2023). Targeted degradation of α-synuclein aggregates in Parkinson's disease using the AUTOTAC technology. *Molecular Neurodegeneration*, *18*, 41. https://doi.org/10.1186/s13024-023-00630-7

Lee, V. M.-Y., Goedert, M., & Trojanowski, J. Q. (2001). Neurodegenerative Tauopathies. *Annual Review of Neuroscience*, *24*(1), 1121–1159. https://doi.org/10.1146/annurev.neuro.24.1.1121

Pedersen, W. A., Culmsee, C., Ziegler, D., Herman, J. P., & Mattson, M. P. (1999). Aberrant stress response associated with severe hypoglycemia in a transgenic mouse model of Alzheimer's disease. *Journal of Molecular Neuroscience: MN*, *13*(1–2), 159–165. https://doi.org/10.1385/JMN:13:1-2:159

Schapira, A. H., Gu, M., Taanman, J. W., Tabrizi, S. J., Seaton, T., Cleeter, M., & Cooper, J. M. (1998). Mitochondria in the etiology and pathogenesis of Parkinson's disease. *Annals of Neurology*, *44*(3 Suppl 1), S89-98. https://doi.org/10.1002/ana.410440714

Wang, X., Becker, K., Levine, N., Zhang, M., Lieberman, A. P., Moore, D. J., & Ma, J. (2019). Pathogenic alpha-synuclein aggregates preferentially bind to mitochondria and affect cellular respiration. *Acta Neuropathologica Communications*, *7*(1), 41. https://doi.org/10.1186/s40478-019-0696-4