# Investigating the Role of Glymphatic Clearance of Amyloid Beta Through Exercise in C57BL/6J Mice

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## Abstract

Alzheimer's disease (AD) is a very prevalent neurodegenerative disorder characterized by widely distributed amyloid plaques and neurofibrillary tangles. AD is clinically associated with a progressive decline in memory and other cognitive functions. Several pieces of evidence have indicated that amyloid beta accumulates to form oligomeric states in the AD brain and cause the cognitive dysfunction commonly seen in patients. Our lab's previous investigations found voluntary running to decreased amyloid beta burden in C57/BL6 mice. The present experiment seeks to further explore the mechanism through which exercise induced amyloid beta clearance occurs. Previous studies have pointed to the function of the glymphatic system in the clearance of amyloid beta. The level and distribution of aquaporin 4 (AQP4) is crucial to the normal function of the glymphatic system. We hypothesize that mice receiving intraperitoneal TGN injections, a selective AQP4 antagonist, thus blocking the function of AQP4, will experience decreased glymphatic clearance of amyloid beta. To test this hypothesis mice were given intraperitoneal injections of saline or LPS every morning for one week. The following two weeks, doses of either TGN or saline injections were given twice daily morning and night. During this period, mice were moved into individual cages with running wheels at 6:00 PM daily and returned to group housing cages the following morning at 7:00 AM. 24 hours following treatment mice were trained and tested in hippocampus dependent contextual fear conditioning (CFC) to explore possible cognitive differences between treatment groups.

## Introduction

- Alzheimer's disease (AD) is a very prevalent neurodegenerative disorder and is the 6th leading cause of death in the United States. (1)
- Typical hallmark's of AD is AB deposition in the hippocampus, decrease in cognitive function and motor abilities. (2)
- Our lab's previous investigations found voluntary running to decreased amyloid beta burden in C57/BL6 mice.
- Previous studies have pointed to the glymphatic system, specifically AQP4, in the clearance of amyloid beta (3)
- We hypothesize mice who receive intraperitoneal injections of TGN, a selective AQP4 antagonist, will experience decreased glymphatic clearance of amyloid beta.

## References

1. Alzheimer's Disease International. World Alzheimer Report 2009. London: Alzheimer's Disease International, 2009.
2. Bushman, A. S., et al., (2012). *Neurolongy, 78*: p. 1323-1329
3. Lan, Y.L., et al. (2016). *Mol Neurobiol*, 53: p. 5300-5309

## Results

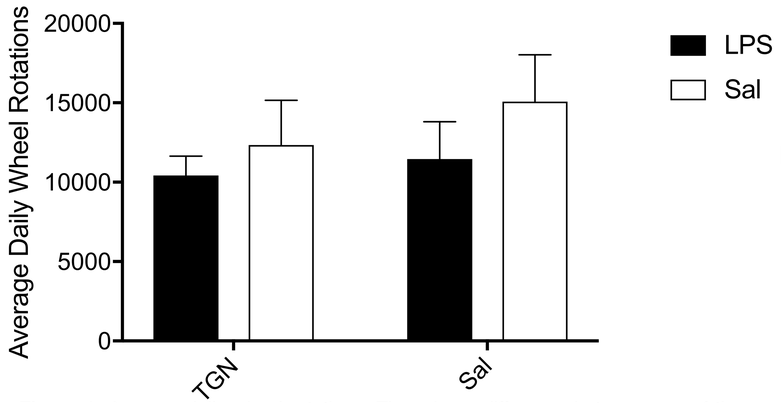


**Figure 1.** Average daily wheel rotations. There is no difference between any of the groups in their average activity.

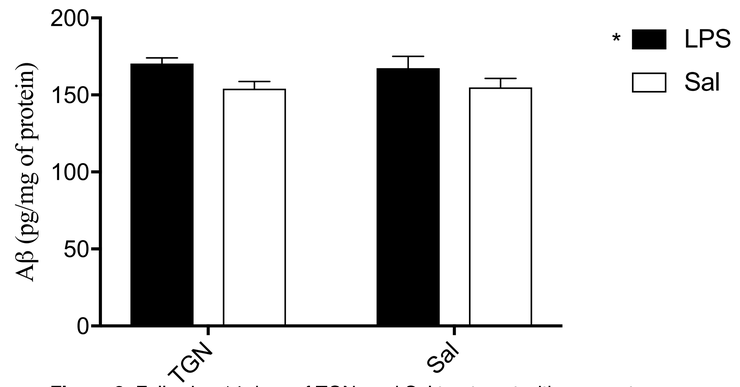


**Figure 3.** Following 14 days of TGN and Sal treatment with access to exercise, there was no significant increase in Aβ. There is an affect of treatment where LPS animals have more amyloid beta than saline animals however no affect of condition of TGN.

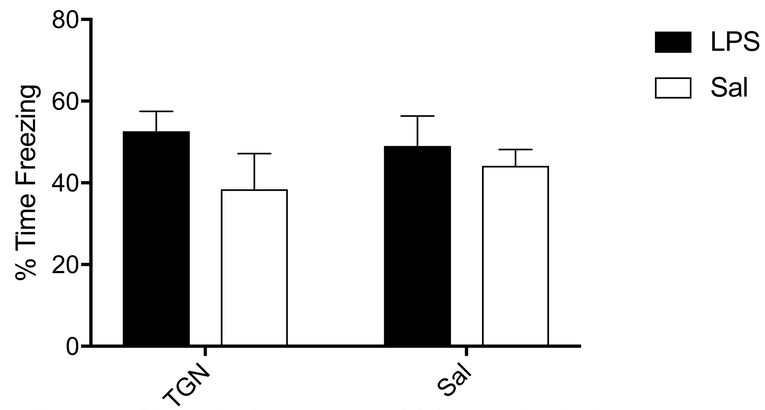


**Figure 3.** CFC Results. There were no statistical significant differences between any groups.

## Methods

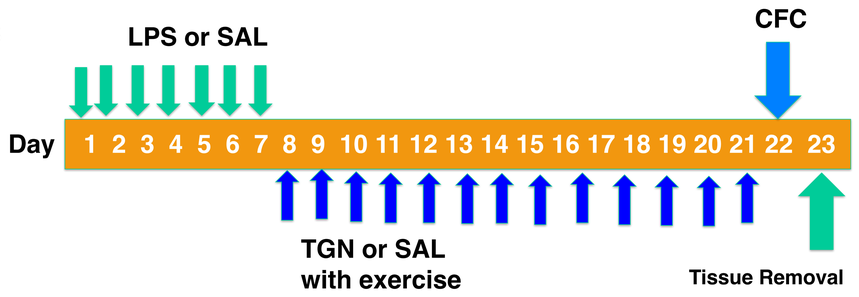


Figure 4: Experimental timeline of treatment groups.

**Figure 2.** Voluntary running using a Med Associates running wheel.

## Conclusions

- Our lab's previous research found voluntary running to decreased amyloid beta burden in C57/BL6 mice.
- We were interested to further explore the mechanism through which exercise induced amyloid beta clearance occurs, specifically involving the glymphatic system via AQP4.
- Following 14 days of treatment with TGN, a selective AQP4 antagonist, and CFC, no significant differences in cognitive deficits or amyloid beta clearance were noted.
- Possible explanations involve the concentration of TGN not being strong enough to fully inactivate AQP4.
- Likewise, the TGN may be too quickly metabolized in the body to adequately affect AQP4.

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