Prior exposure to repeated LPS injections prevents further accumulation of hippocampal-beta-amyloid

Calcagno, A.[1,3], Crain, P.[1,3], White, J.[1,3], Peterman, J.[1,3], Hardy, A.[1,2], Eimerbrink, M.[1,3], Paulhus, K.[1,2], Thompson, M.[1,2], Boehm, G.[1,3], & Chumley, M.[1,2]

[1]Neurobiology of Aging Collaborative [2]Department of Biology and [3]Department of Psychology at Texas Christian University Fort Worth, TX 76129

Alzheimer's Disease is a neurodegenerative disease characterized by decline of cognitive function. This correlates with accumulation of neurofibrillary tangles and Aβ protein fragment plaques, which can initiate an inflammatory response. Injections of LPS can lead to an inflammatory response that stimulates production of Aβ. This project explored whether another series of LPS injections could exacerbate this effect. The animals were given 7 days of LPS or saline injections, a two-week break, and another 7 days of LPS or saline. Contrary to our prediction, Aβ levels were not exacerbated. This was related to a decreased inflammatory response shown by a decrease in IL-1β mRNA in animals given two rounds of LPS. Our lab is now evaluating what mechanism leads to this result.

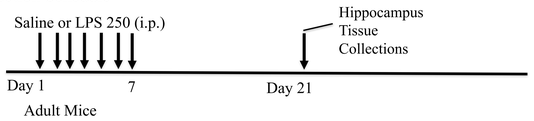
Introduction

- Alzheimer's disease (AD) is a neurodegenerative disease affecting nearly 5.5 million Americans, and there is currently no cure (1).
- AD is characterized by Aβ plaques of Aβ protein fragments and neurofibrillary tangles of hyperphosphorylated tau protein (pTau) in the brain, predominantly in the hippocampus (2).
- The presence of Aβ plaques has shown to correspond to stimulation of an inflammatory response, predominantly with the release of cytokines (3).
- Our lab has shown that 7 consecutive days of lipopolysaccharide (LPS) injections result in an increase in hippocampal expression of Aβ1-42 peptides along with deficits in learning and memory (4).
- We hypothesize that the effect of LPS injections will be exacerbated through a second injection series of LPS after a fourteen-day recovery interval, thus modeling multiple, independent, bacterial infections, like that seen in humans.

Methods

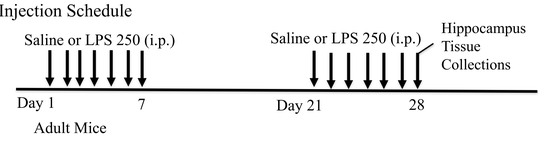
Experiment 1

LPS Injection Schedule



Experiment 2

LPS Injection Schedule



Conclusion

- 14 days after the last injection, animals administered LPS still have significantly higher levels of Aβ in the hippocampus compared to saline-treated animals. This pattern is not replicated in levels of phosphorylated tau within the hippocampus.
- Contrary to our hypothesis, Aβ levels were not increased after the second round of LPS injections.
- Additionally, the lack of increase of Aβ levels corresponded to a decreased inflammatory response upon secondary administration of LPS, as IL-1β mRNA was significantly lower in the group administered two rounds of LPS.

References

1 Fact and figures
2 Mattson MP. Pathways towards and away from Alzheimer's disease. Nature. 2004 Aug 5;430(7000):631-9. Review.
3 Meraz-Rios M.A., Toral-Rios D., Franco-Bocanegra D., Villeda-Hernandez J., Campos-Peña V. Inflammatory process in Alzheimer's Disease. Frontiers in Integrative Neuroscience 2013; 7:59
4 Kahn M, Kranjac D, Alonzo C, Haase J, Cedillos R, McLinden K, et al. Prolonged elevation in hippocampal Aβ and cognitive deficits following repeated endotoxin exposure in the mouse. Behavioural brain research 2012; 229: 176– 84.

Results

Experiment 1

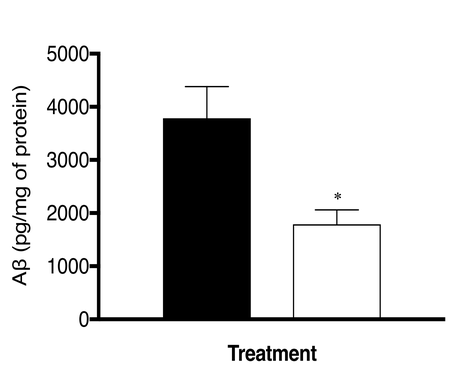


Figure 1. Hippocampal Aβ Levels 14 days after the last LPS Injection. LPS-treated animals had significantly more Aβ than SAL-treated controls. Mean ± SE

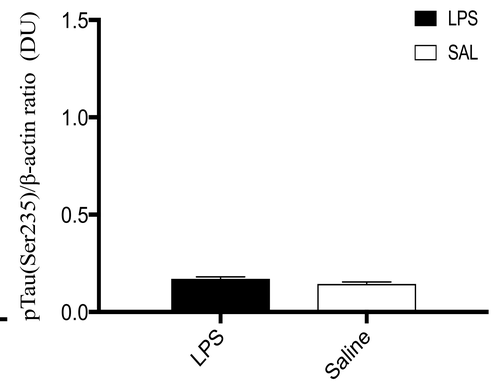


Figure 2. Hippocampal pTau Levels 14 days after the last LPS Injection. LPS-treated animals had significantly more pTau than SAL-treated controls. Mean ± SE

Experiment 2

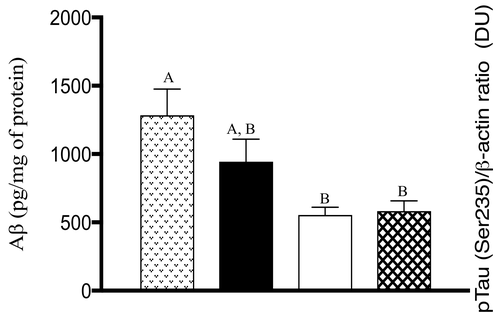


Figure 3. Hippocampal Aβ Levels Following Two Injection Series. SAL/LPS animals had significantly elevated levels of Aβ compared to animals administered SAL/SAL or LPS/SAL. Animals administered two rounds of LPS had intermediary levels of Aβ. Different letters represent significant differences. Mean ± SE

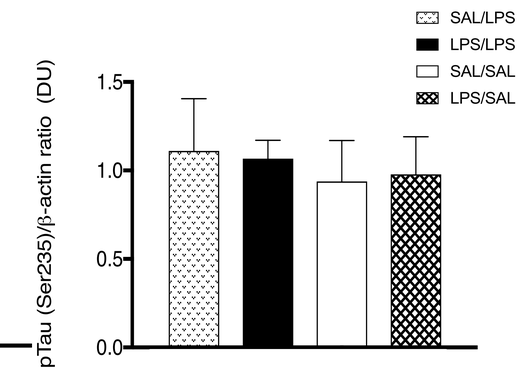


Figure 4. Hippocampal pTau Levels Following Two Injection Series. No significant differences in pTau levels were found between groups. Mean ± SE

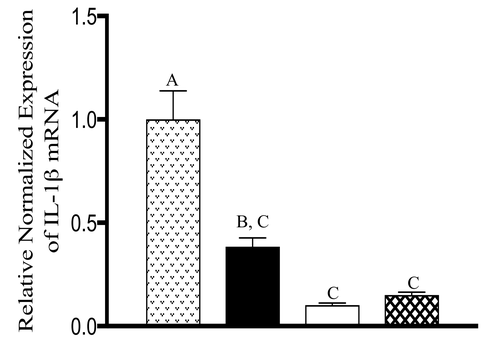
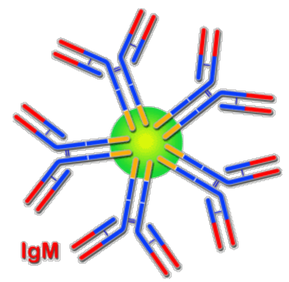


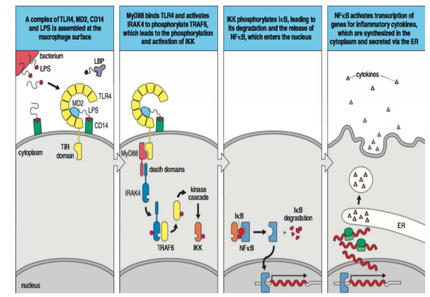
Figure 5. Interleukin – 1β mRNA Concentration in Hippocampal Tissue Following Two Injection Series. SAL/LPS- treated animals had significantly more IL-1β mRNA compared to all other groups. LPS/LPS-treated animals demonstrate a significantly blunted immune response. Different letters represent significant differences. Mean ± SE

Future Directions

Potential Binding Site on IgM antibody



Potential Tolerance Mechanism through NFκB Signaling Cascade



Funding

This research was supported by an intramural undergraduate Science and Engineering Research Center award to S.D.