Effects of Chronic Sleep Restriction on Amyloid Beta and Cognition in C57BL6/J Mice

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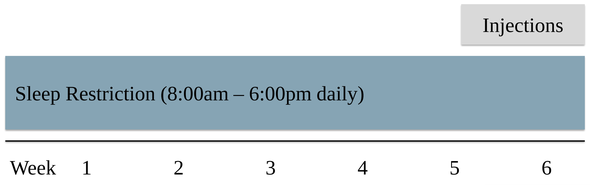
Alzheimer's disease (AD), a form of dementia, is the 6th leading cause of death in the U.S. One of the features associated with AD is a disrupted sleep/wake cycle, and evidence suggests a bidirectional relationship between sleep loss and AD. The aim of the present study was to elucidate the interaction between chronic sleep restriction, inflammation, and AD pathology in C57BL6/J mice. Our data show that chronic sleep restriction was associated with deficits in contextual fear acquisition compared to control groups, suggesting potential deleterious effects of sleep loss over time on cognitive function. Given the large percentage of adults reporting getting less than the minimum recommended 7 hours of sleep per night, combined with the alarming climb in rates of AD and a growing body of work suggesting a link between these trends, investigating the detrimental effects of sleep restriction is an essential area of study.

Introduction

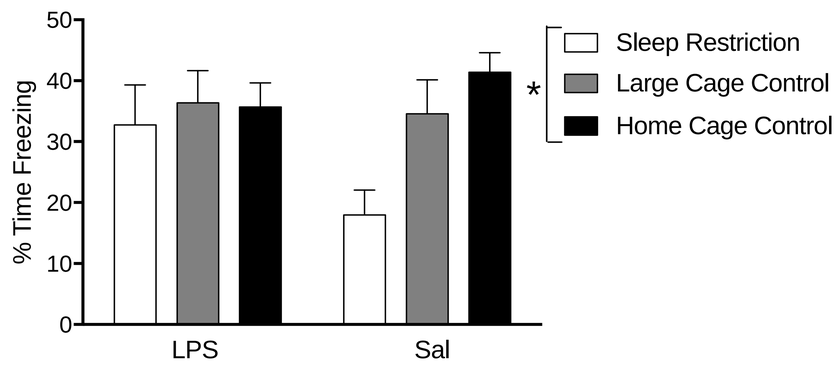
- Alzheimer's disease (AD) is a neurodegenerative disease that affects more than 44 million people worldwide, including around 5.7 million Americans.
- A reported 35.3% of adults in the United States get less than the minimum 7 hours of sleep per night recommended by the National Sleep Foundation.
- Previous research indicates that disruptions in sleep often precede symptoms of AD, such as cognitive impairments and memory loss.
- Chronic sleep loss has been associated with increased amyloid beta and proinflammatory cytokines in the brain.
- Aggregates of amyloid beta form plaques that disrupt neuronal communication are a hallmark of AD.
- Our lab has previously demonstrated that mice administered 7 consecutive days of LPS, a bacterial mimetic, exhibit increases in amyloid beta and proinflammatory cytokines in the hippocampus, as well as cognitive deficits.
- Our lab has also shown that stress can exacerbate the effects of LPS.
- It is hypothesized that chronic sleep restriction will exacerbate LPS-induced AD pathology in C57BL6/J mice.

Methods

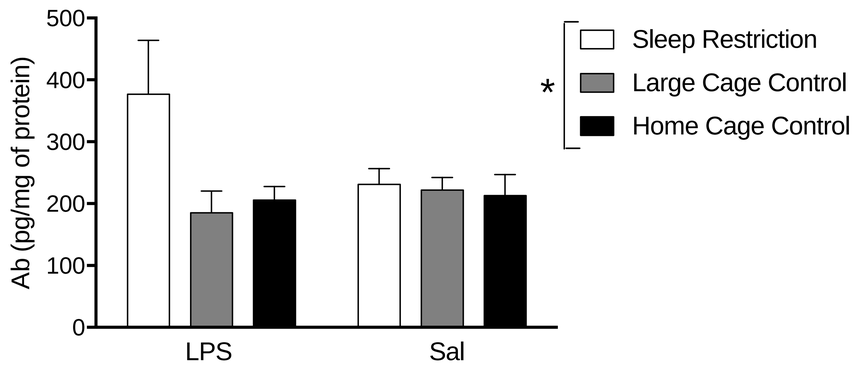


- Healthy C57BL/6 adult male mice were split into three groups – chronic sleep restriction, large cage control, and home cage control.
- Mice in the chronic sleep restriction group were subjected to the multiple platform method of sleep restriction for 10 hours per day for 6 weeks.
- During the final 7 days of sleep restriction, mice received either LPS or saline injections daily.
- After the 7th day of injections, mice were subjected to contextual fear conditioning, consisting of one day of training followed by one day of testing, to assess cognitive function.
- Percent time freezing was measured during the testing session to assess acquisition of contextual fear.
- Following testing, the hippocampus was collected for amyloid beta quantification.

Results



Contextual Fear Conditioning. Two-way ANOVA shows a significant main effect of sleep condition such that mice that underwent chronic sleep restriction froze less than did mice in both control groups (p = .017). There was no effect of treatment and no significant interaction. Bars represent +/- SEM.



Hippocampal Amyloid Beta. Due to a violation in homogeneity of variance, a square root transformation was performed. Two-way ANOVA reveals a main effect of sleep condition (p = .046) such that hippocampal amyloid beta was higher in the mice that underwent chronic sleep restriction compared to that of mice in either control condition. There was no effect of treatment and no significant interaction. Bars represent +/- SEM

Conclusion

- We hypothesized that six weeks of chronic sleep restriction via the multiple platform method coupled with administration of LPS would result in significant deficits in cognitive performance in contextual fear conditioning in sleep-deprived LPS-treated mice relative to controls, as well as significantly increased levels of hippocampal amyloid beta.
- The data obtained support the hypothesis that chronic sleep restriction would be associated with deficits in the contextual fear conditioning paradigm, and sleep restricted mice would freeze more when re-introduced to the context. Results revealed a significant main effect of sleep restriction condition. Mice that underwent chronic sleep restriction exhibited significant deficits in contextual fear conditioning compared to both large cage control and group housed animals.
- There was also a significant main effect of condition such that animals that underwent six weeks of chronic sleep restriction had higher levels of hippocampal amyloid beta than did either control groups.
- The results obtained indicate that chronic sleep loss may be related to exacerbated AD-like pathology, including detrimental effects on learning and memory and increases in amyloid beta.

Future Directions

- Further research will examine the effects of chronic sleep restriction during old age on cognition and amyloid beta using aged mice.
- Future experiments will also attempt to investigate the mechanism through which the observed cognitive deficits and hippocampal amyloid beta increases develop following chronic sleep restriction, including Western blotting for expression of BDNF, BACE, and APP.
- Additionally, as evidence from other studies has demonstrated a diurnal pattern in the expression of pro-inflammatory cytokines in both murine and human subjects, we will assess the impact that chronic sleep restriction may have on these patterns and the extent to which sleep loss over time can alter the inflammatory profile.

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