THE ROLE OF MURINE AMYLOID-BETA IN DISRUPTING DIFFERENT PHASES OF THE LEARNING PROCESS: FROM CONSIOLIDATION TO RETRIEVAL

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Alzheimer's Disease (AD) is a progressive neurodegenerative disease associated with memory loss and cognitive decline. These impairments are thought to be the result of toxic protein build-up in the hippocampus, which is an area in the brain important for memory formation. While the effect of human-Aβ on memory is already known, the specific phases of learning being impaired is less understood. The goal of the current study is to understand whether murine-Aβ infusions impair memory consolidation or retrieval in similar ways to human- Aβ in order to verify that mice are an appropriate animal in which to study AD.

Introduction

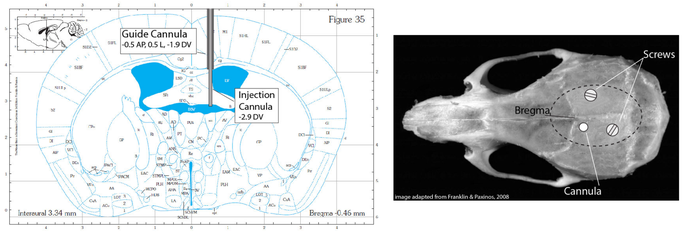
- Alzheimer's is marked by Aβ accumulation (5).
- Soluble Aβ oligomers alter synaptic formation and function (3).
- ICV injections of h-Aβ leads to cognitive deficits (1,2,4).
- The specific phases of learning affected by m-Aβ are not fully understood.
- This study explores how m-Aβ oligomer infusions impact different stages of associative learning.
- A contextual conditioning paradigm was used to determine if consolidation and/or retrieval are impacted in the presence of m-Aβ in two experiments

Objectives

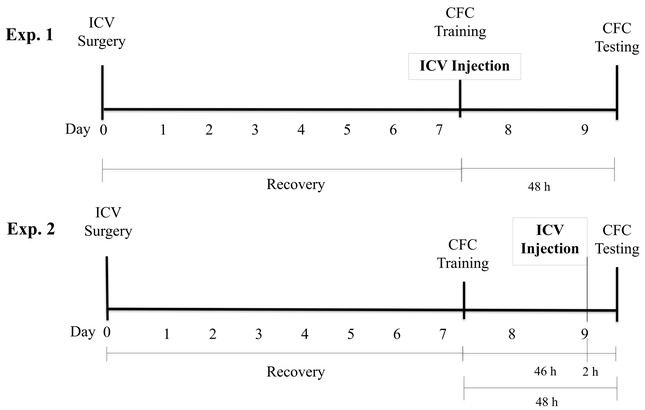
- **Experiment 1** explores whether m-Aβ disrupts consolidation of contextual memories when infused immediately after training in a CFC paradigm.
- **Experiment 2** verifies that any deficit found in Experiment 1 is related to problems with memory consolidation and not memory retrieval.

Methods

Stereotactic Surgery and Intracerebroventricular (ICV) Cannulation:



Contextual Fear-Conditioning (CFC):



Results

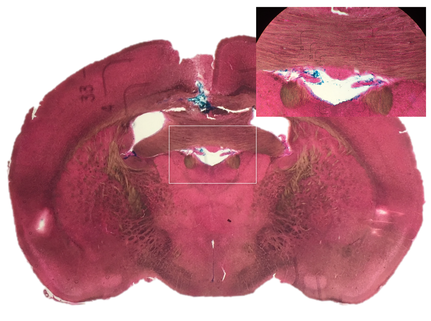


Figure 1. Nuclear Fast Red Stain. Stained 30 µm section of the brain with a visible cannula tract. The blue is injected Indian ink helping in verifying cannula placement. Enlarged picture of the third ventricle from the section demonstrates correct cannula placement

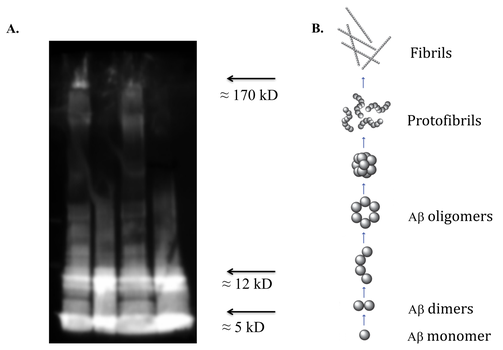


Figure 2. Western Blot Analysis of Injection Assembly State. A.) Four preparations of SDS-stable A β in Sterile Saline were run through electrophoresis to determine assembly state. The preparations contained mostly low-n oligomers and monomers. B.) Cartoon depiction of A β assembly state for clarification.

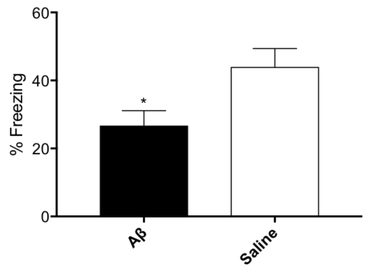


Figure 4. The Influence of Aβ Infusions Immediately After Training in CFC on Freezing Behavior during Testing. Aβ infusions immediately after training phase significantly reduced freezing time during testing phase compared to saline infusions. Mean ± SEM.

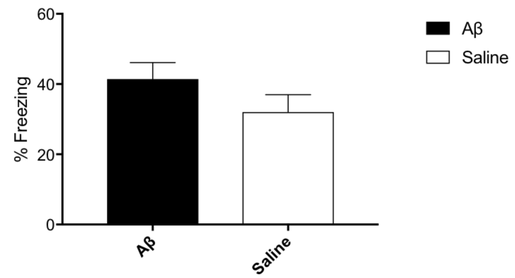


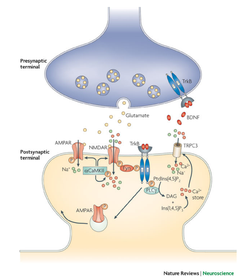
Figure 5. The Influence of Aβ Infusions Two hours before Testing in CFC on Freezing Behavior. No significant difference between Aβ and saline infusions two hours prior to testing phase. Mean ± SEM.

Conclusion

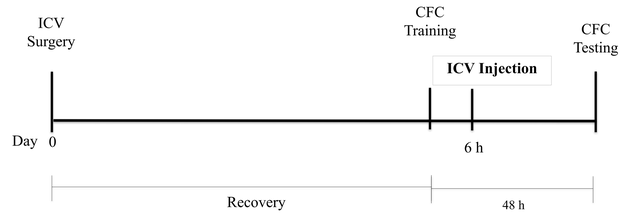
- **Experiment 1:** m-Aβ infusions immediately after training resulted in decreased freezing behavior, indicating that m-Aβ disrupted the consolidation and/or retrieval of the context shock pairing.
- **Experiment 2:** m-Aβ infusions 46 hours post-training had no impact on freezing behavior.
- **Overall:** Together these results indicate that m-Aβ is disrupting the consolidation of new memories and is not impacting the recovery of previously consolidated information.

Future Directions

- Identify potential mechanism by which m-Aβ is affecting consolidation of memory in order to further the understanding of Alzheimer's pathology and its debilitating effects.
  - Consolidation failure may be attributable to:
    - Disrupted BDNF signaling
      - Impaired transcription of Critical genes in cognition
    - Altered synaptic plasticity
      - NMDA and AMPA receptor endocytosis



- Determine whether m-Aβ affects the late phase of memory consolidation by delivering infusions 6 hours post-training.



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Acknowledgments

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