

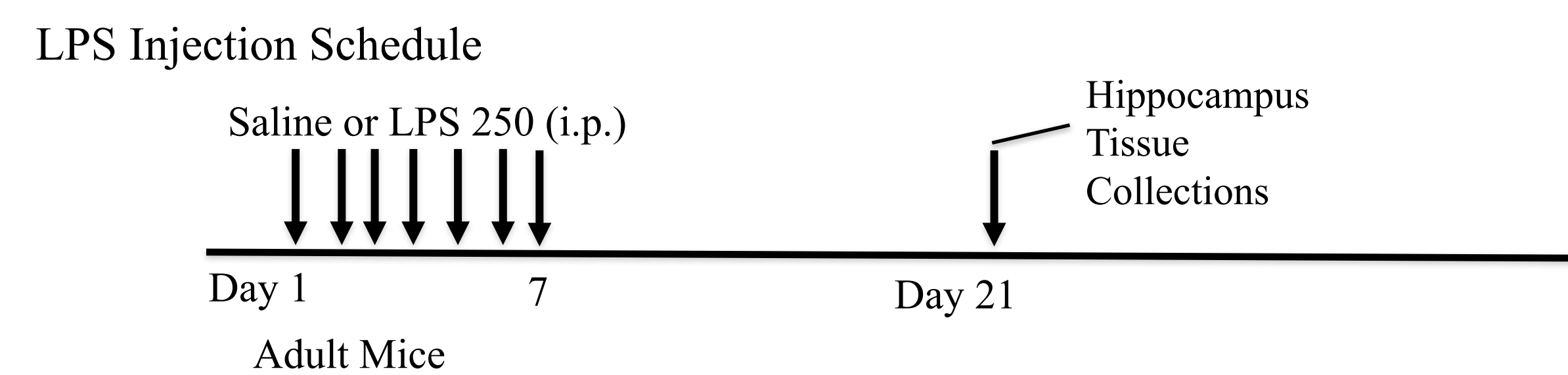
Alzheimer's Disease is a neurodegenerative disease characterized by decline of cognitive function. This correlates with accumulation of neurofibrillary tangles and A $\beta$  protein fragment plaques, which can initiate an inflammatory response. Injections of LPS can lead to an inflammatory response that stimulates production of A $\beta$ . 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, A $\beta$  levels were not exacerbated. This was related to a decreased inflammatory response shown by a decrease in IL-1 $\beta$  mRNA in animals given two rounds of LPS. Our lab is now evaluating what mechanism leads to this result.

## Introduction

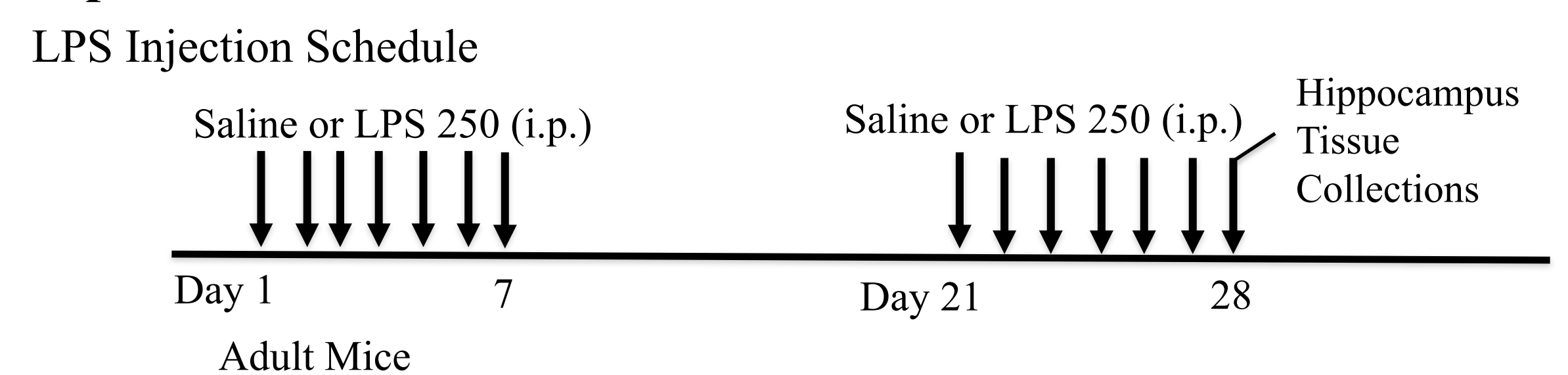
- Alzheimer's disease (AD) is a neurodegenerative disease affecting nearly 5.5 million Americans, and there is currently no cure (1).
- AD is characterized by A $\beta$  plaques of A $\beta$  protein fragments and neurofibrillary tangles of hyperphosphorylated tau protein (pTau) in the brain, predominantly in the hippocampus (2).
- The presence of A $\beta$  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 A $\beta$ 1-42 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



### Experiment 2



## Conclusion

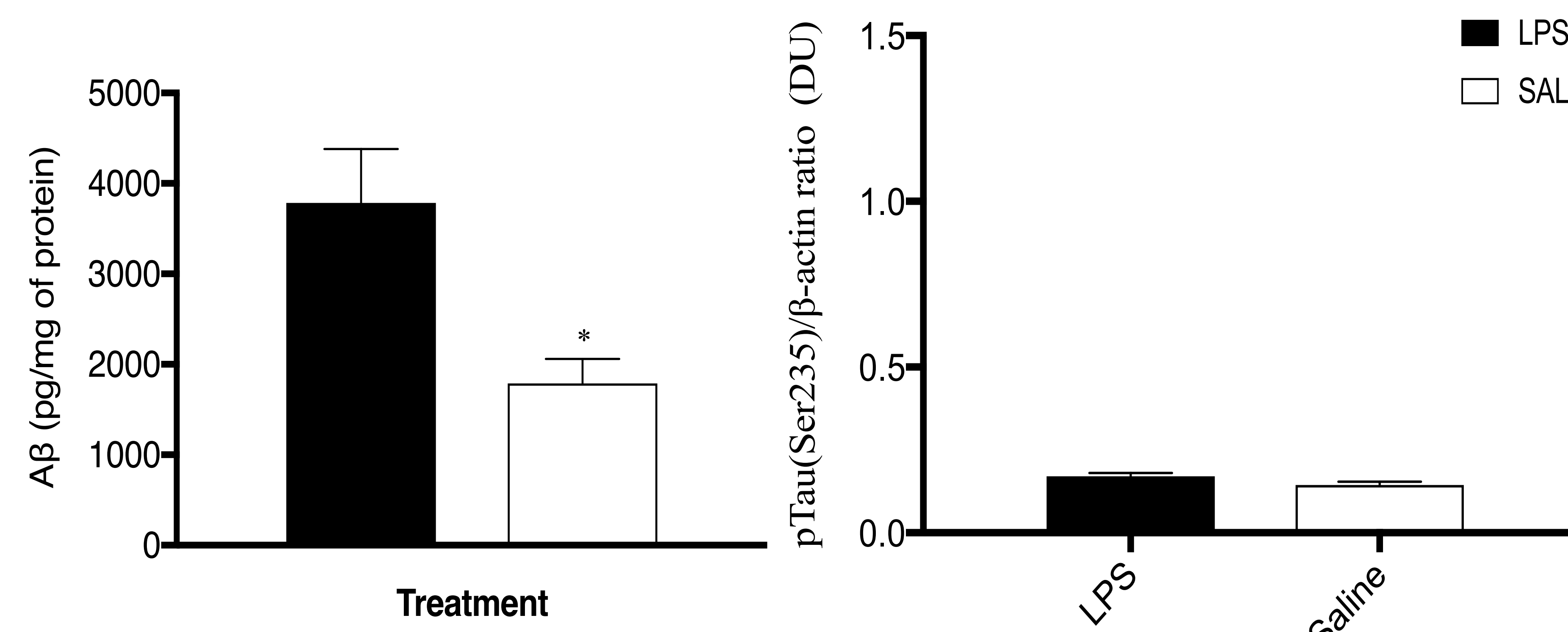
- 14 days after the last injection, animals administered LPS still have significantly higher levels of A $\beta$  in the hippocampus compared to saline-treated animals. This pattern is not replicated in levels of phosphorylated tau within the hippocampus.
- Contrary to our hypothesis, A $\beta$  levels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

## References

- Fact and figures
- Mattson MP. Pathways towards and away from Alzheimer's disease. *Nature*. 2004 Aug 5;430(7000):631-9. Review.
- 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
- Kahn M, Kranjac D, Alonzo C, Haase J, Cedillos R, McLinden K, et al. Prolonged elevation in hippocampal A $\beta$  and cognitive deficits following repeated endotoxin exposure in the mouse. *Behavioural brain research* 2012; 229: 176-84.

## Results

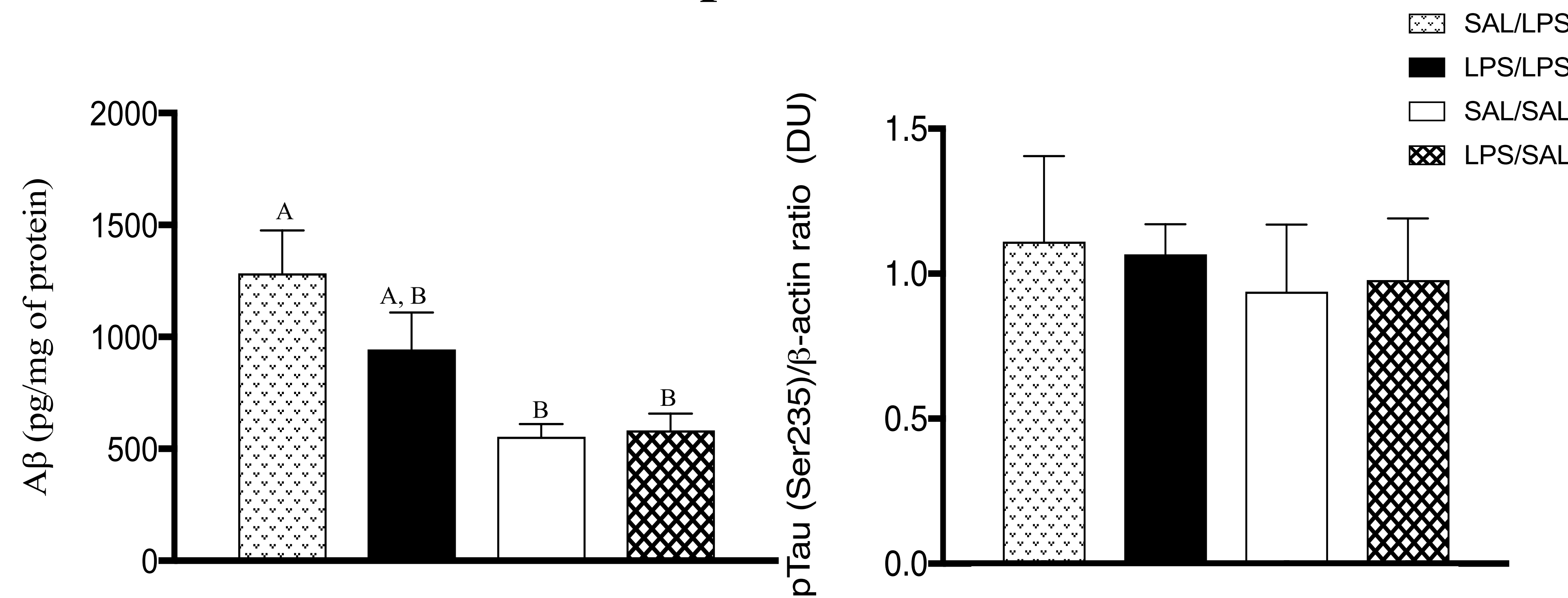
### Experiment 1



**Figure 1. Hippocampal A $\beta$  Levels 14 days after the last LPS Injection.** LPS-treated animals had significantly more A $\beta$  than SAL-treated controls. Mean  $\pm$  SE

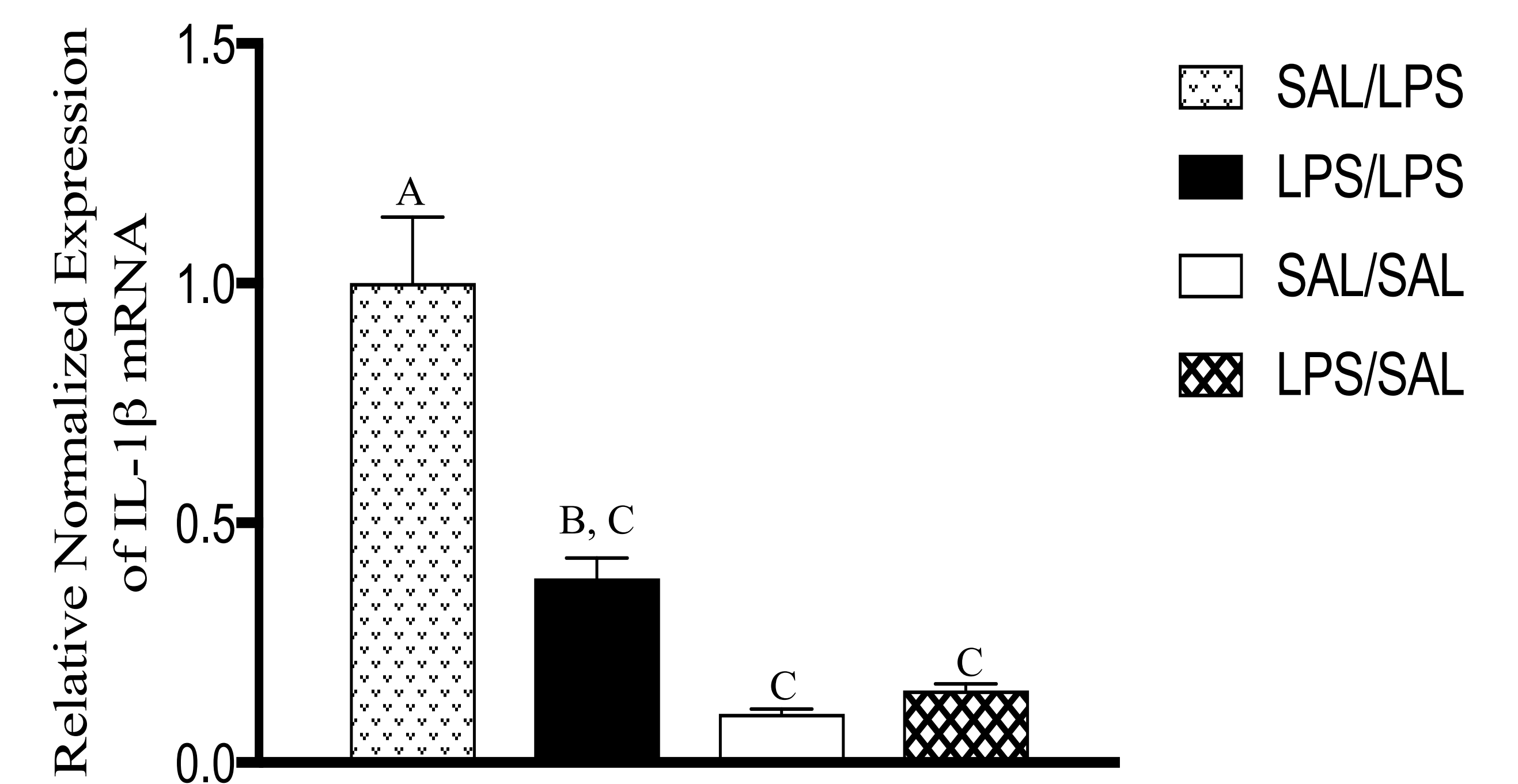
**Figure 2. Hippocampal pTau Levels 14 days after the last LPS Injection.** LPS-treated animals had significantly more pTau than SAL-treated controls. Mean  $\pm$  SE

### Experiment 2



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

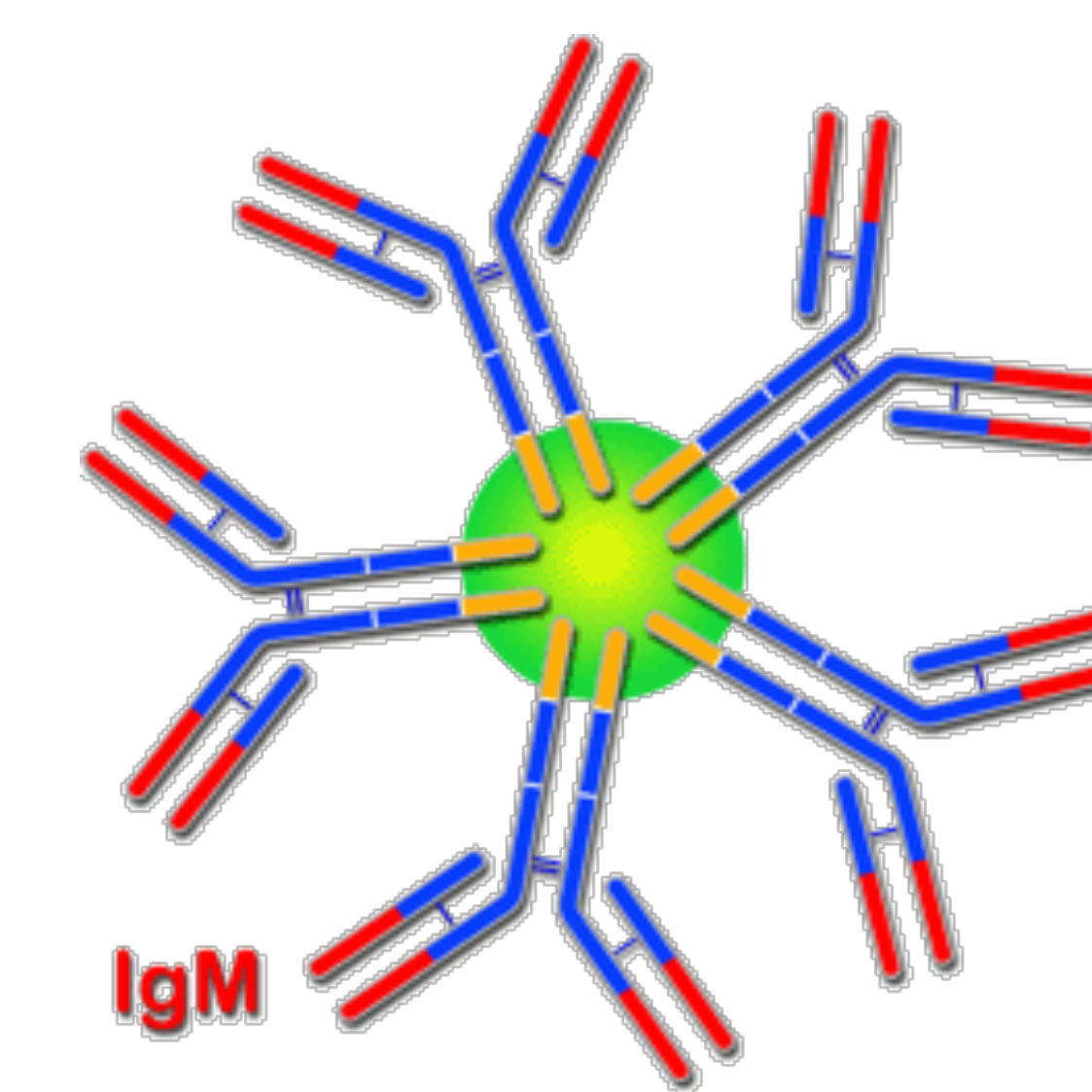
**Figure 4. Hippocampal pTau Levels Following Two Injection Series.** No significant differences in pTau levels were found between groups. Mean  $\pm$  SE



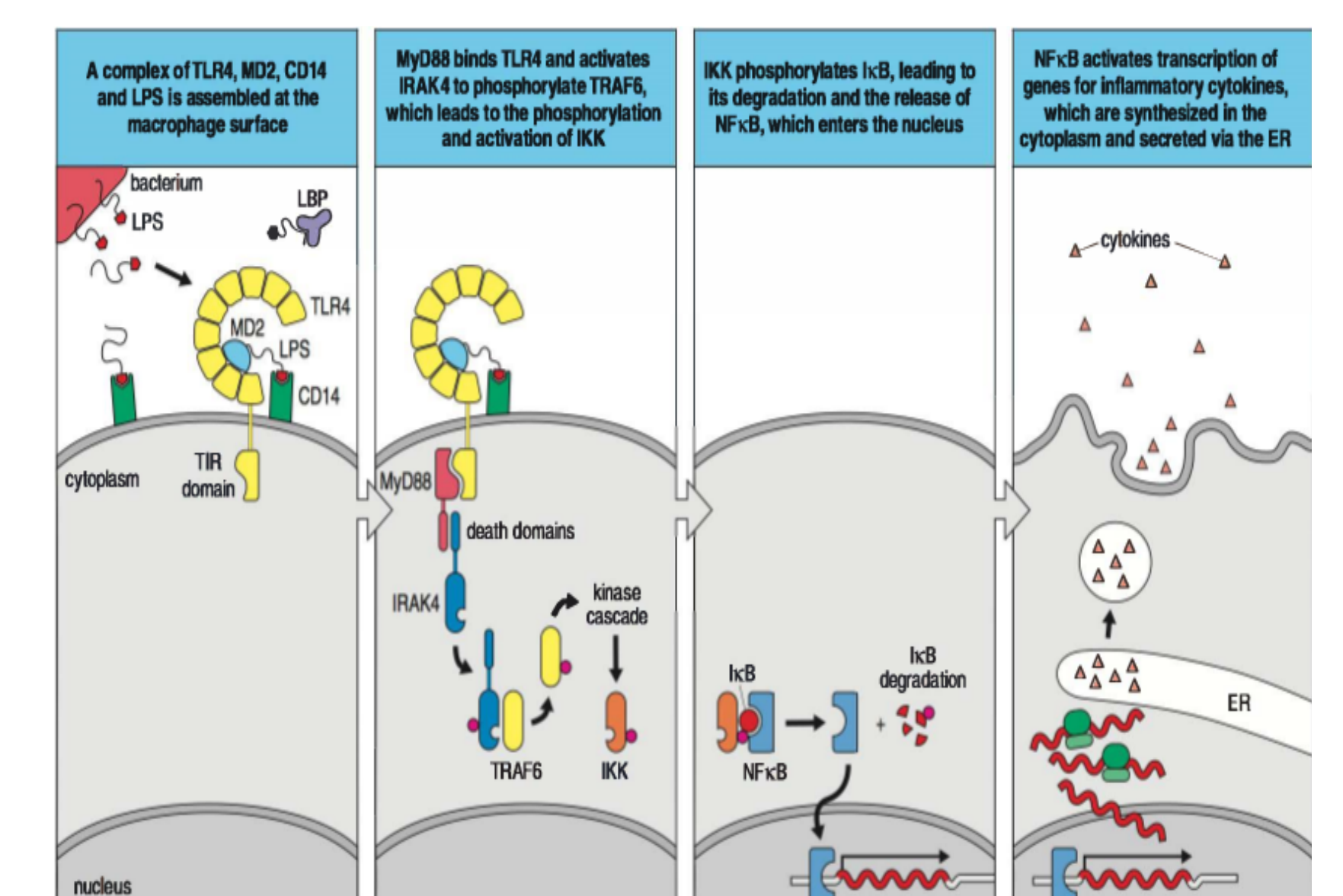
**Figure 5. Interleukin-1 $\beta$  mRNA Concentration in Hippocampal Tissue Following Two Injection Series.** SAL/LPS-treated animals had significantly more IL-1 $\beta$  mRNA compared to all other groups. LPS/LPS-treated animals demonstrate a significantly blunted immune response. Different letters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

## Future Directions

### Potential Binding Site on IgM antibody



### Potential Tolerance Mechanism through NF $\kappa$ B Signaling Cascade



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