Effects of MRK-016 on Aß-induced learning deficits in mice in a contextual conditioning paradigm

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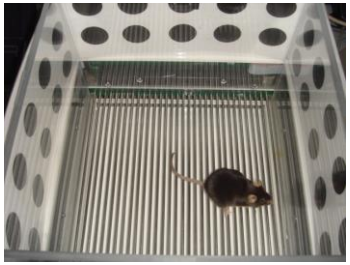
INTRODUCTION

• Our lab has shown that initiating peripheral inflammation through administration of a bacterial mimetic (LPS) for 7 consecutive days leads to an increase in amyloid-beta (Aß)
•Elevated levels of Aß led to cognitive dysfunction in mice, specifically in contextual conditioning
•Amyloid-beta plaques are a hallmark of Alzheimer's disease pathology
•MRK-016 (MRK) is a benzodiazepine inverse agonist (Fig. 1) that decreases the flow of inhibitory chloride ions across the membrane
•We have found MRK to be protective against LPS-induced memory acquisition and consolidation errors in a hippocampus-dependent task

•In the present study, we used the 7-day LPS injection model to examine the protective effects of MRK on the cognitive deficits associated with an accumulation of Aß, followed by tissue analysis of two biological markers linked to learning outcomes

METHODS

• C57BL/6J mice received i.p. injections of either LPS (200 µg/kg) or saline (200 µg/kg) once a day for 7 consecutive days
• 24 hours after the final injection (day 8), mice were trained in a contextual conditioning paradigm
• Immediately after training, mice were given an injection of MRK-016 or saline
• Testing was performed 24 hours after training and the degree of animal freezing was measured
• 4 hours after training, tissue was collected to follow-up significant behavioral results with RNA-isolation and qRT-PCR
• Targets of interest for qRT-PCR were Arc and TrkB



Contextual Conditioning: Peppermint odor and dotted pattern walls.

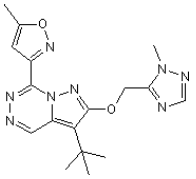


Figure 1. Chemical structure of MRK-016.

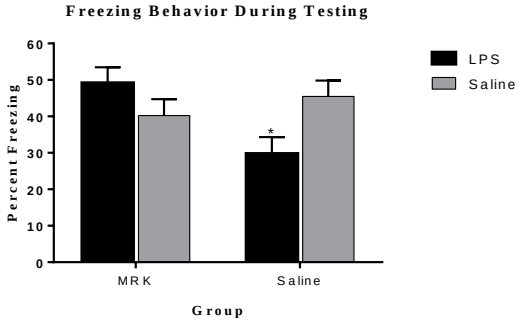


Figure 2. Mean (±SEM) percent time freezing during testing.

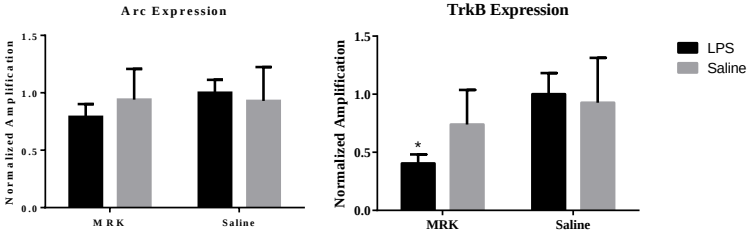


Figure 3. qRT-PCR results for Arc and TrkB mRNA expression.

RESULTS

•As expected, there were no significant differences in freezing behavior between groups during the training period
•During testing, there were no differences in freezing behavior between animals in the MRK/Saline, MRK/LPS, and Saline/Saline conditions; however, those in the LPS/Saline condition froze significantly less than the other animals (Fig. 2)
• Results of the ELISA confirming elevated Aß levels in LPS-treated animals are pending
•Treatments had no effect on Arc mRNA expression (Fig. 3)
•TrkB expression was found to be significantly decreased in the LPS/MRK condition compared to all other conditions (Fig. 3)

CONCLUSIONS

• MRK-016 has a protective effect against the consolidation errors experienced by mice with elevated levels of Aß in a hippocampus-dependent task
• Modulation of central GABAergic transmission can rescue impaired cognition, reversing the learning deficits incurred by Aß accumulation
• MRK-016 does not employ an Arc-dependent rescue mechanism for learning
• Results suggest some relationship between the action of MRK-016 and regulation of the BDNF/TrkB pathway

FUTURE DIRECTIONS

• Elevated TrkB expression in the LPS/Saline group compared to the LPS/MRK group was an unforeseen finding
• Current work on this project is addressing the mechanism behind this difference in TrkB and the potential involvement of other relevant targets