Medial septal nucleus theta frequency stimulation improves spatial memory and increases seizure threshold

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Introduction

Epilepsy often leads to persistent cognitive deficits. Spatial memory deficits have been correlated with hippocampal dysfunction and reduced hippocampal theta oscillations. Previously, we demonstrated that hippocampal theta is reduced following status epilepticus. Furthermore, we showed that continuous medial septal nucleus (MSN) theta stimulation improves spatial memory in pilocarpine treated rats during the epileptogenic period. In the following study we assessed the effects of MSN theta stimulation on cognition and seizure threshold in chronic pilocarpine-induced epileptic rats.

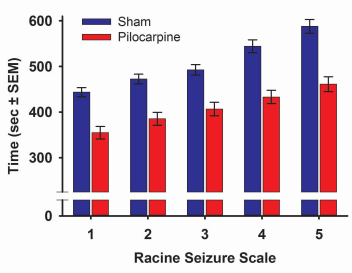
Methods

Status epilepticus was induced in 61 adult male Sprague-Dawley rats (300-350 grams) using pilocarpine. Baseline flurothyl testing was performed at 5 weeks, and rats were then equally distributed into two groups based on seizure thresholds. A MSN stimulating/recording electrode as well as hippocampal and pre-frontal cortex recording electrodes were implanted the subsequent day.

Methods (CONTINUED)

At week 6, rats received continuous MSN theta (7.7Hz; 80μA) stimulation, 1 minute of theta stimulation throughout the task or no stimulation during the Barnes Maze task. Flurothyl testing was assessed again at 9 weeks after SE with or without MSN theta stimulation.

5-Week Seizure Threshold



Stage 5 Seizures

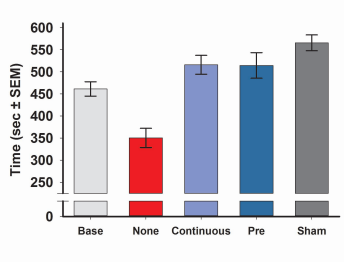
Results

Theta stimulation increased seizure threshold following status epilepticus (SE). Theta stimulation increased both Racine stage 3 and stage 5 seizure thresholds in SE rats. Between weeks 5 and 9, non-stimulated SE rats had a significant decrease in seizure threshold for both Stage 3 ($p<0.001$; $F(3,37)=15.8$) and Stage 5 seizures ($p<0.001$; $F(3,37)=16.0$). Stimulation improved spatial working memory on the Barnes maze.

Results (CONTINUED)

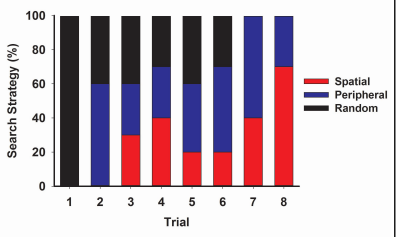
During the Barnes maze task, both pre-task stimulation and continuous stimulation pilocarpine rats had improved search strategies compared to pilocarpine rats without stimulation. Moreover, MSN theta stimulated rats had significantly fewer errors on the Barnes maze ($p<0.05$). Rats stimulated during the flurothyl test, however, had significantly higher seizure thresholds as compared to their baseline ($p<0.05$).

9-Week Seizure Threshold

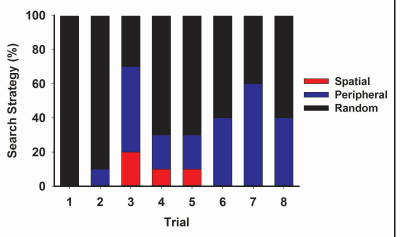


Stage 5 Seizures: Sham compared to pilocarpine (red)

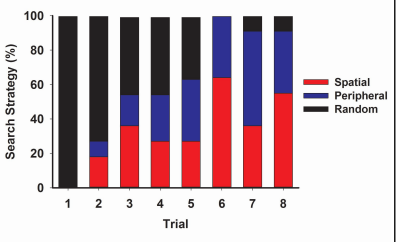
Barnes Maze Sham Strategies



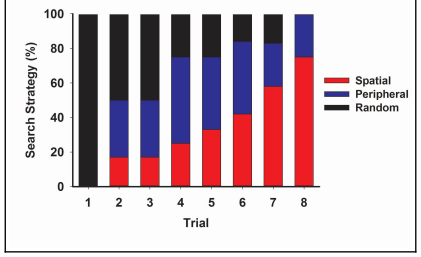
Barnes Maze Pilocarpine Strategies



Barnes Maze Pilocarpine Pre-Task Stimulation



Barnes Maze Pilocarpine Continuous Stimulation



Conclusions

Deep brain MSN theta stimulation improves spatial learning, and increases seizure threshold in pilocarpine-induced epileptic rats. This suggests that MSN theta stimulation may be an effective neuromodulatory technique for treatment of cognitive deficits and seizures in epilepsy patients.

Learning Objectives

1. Status epilepticus results in spatial and working memory deficits.
2. Medial septal nucleus theta stimulation improves spatial working memory in status epilepticus rats.
3. Following status epilepticus, medial septal nucleus theta stimulation increases seizure threshold.