The Role of GABA-ergic Interneurons in CA1 and Dentate Gyrus for Sequence Learning

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Christy S. Weeden[1], Andrea M. Morris[1], Christina A. Rossi[2], Jared M. Roberts[1], & Raymond P. Kesner[1,2]

University of Utah: Department of Psychology[1], Neuroscience Program[2]

Introduction

- The hippocampus (HPP) is widely accepted as a structure that supports spatial memory. Current interest is focused on temporal processing for sequences of events. It has been demonstrated that HPP lesions disrupt acquisition of a spatial temporal sequence in an 8-arm maze (DeCoteau & Kesner, 2000).
- HPP subregions have been indicated to be critical in spatial temporal sequence processing. The CA1 region has been shown to play a critical role in temporal information processing and CA1 principal cell lesions impair acquisition of 8-arm radial maze sequences (Rolls & Kesner, 2006; Weeden et al, 2009). The dentate gyrus (DG) is also an important region in the processing of new spatial information, but granule cell lesion studies indicate that principal cells are not a necessary component in the learning of sequential events (Weeden et al, 2009).
- Interneurons exhibit inhibitory control over the excitatory principal cells of HPP (Freund & Buzáki, 1996). Their role in temporal processing for spatial locations has yet to be identified. Electrophysiological recording investigations indicate that CA1 and DG interneurons display differential patterns of activation when engaged in identical tasks, such as novel environment exploration (Nitz & McNaughton, 2004). These divergent patterns suggest unique roles for interneurons of different subregions. Within the HPP, inhibitory interneurons exclusively express Substance P receptors (SPR). SPRs have a high affinity for a peptidase-resistant Substance P analog conjugated to the neurotoxin saporin (SSP-Saporin), which allows for selective neurotoxic lesions of inhibitory interneurons that spare surrounding excitatory principal cells (Martin & Sloviter, 2001).
- The present study aims to determine the level of influence HPP interneurons of the CA1 and DG subregions exert on acquisition of spatial temporal sequences compared to excitatory principal cells. We predict that CA1 interneuron lesion subjects but not DG lesion subjects will make more errors during acquisition of sequence information compared to controls.

Methods

Subjects

- Twenty-nine male Long-Evans rats, *M* age = 6 months; *M* weight= 325 g

Lesions

- Subjects were randomly assigned to 1 of 5 conditions: control (saline), dorsal CA1 principal neurons (ibotenic acid), dorsal CA1 GABA-ergic interneuron (SSP-Saporin), dorsal DG principal neurons (colchicine), or dorsal DG GABA-ergic interneuron (SSP-Saporin) lesions. Subjects received postoperative rest for 2 weeks following stereotaxic surgery before commencement of maze exposure.

Apparatus

- 8 arms (10 x 80 cm) radiate from a central platform (Olton & Samuelson, 1976) with sunken food wells at the furthest point of each arm.
- From the central platform, 8 Plexiglas doors are positioned in front of the arms. Access to arms by way of door position are controlled via pulleys operated by experimenters.
- The apparatus was placed in an environment rich with external cues; 3-dimensional objects of various shape and color were hung directly behind food wells.

Sequential Task

- 6 of 8 radial arms were pseudo-randomly assigned to a sequence; all involved arms were baited with Froot Loops cereal.
- Each trial consisted of entrance to all 6 baited arms.
- Subjects received exposure to the task for 10 trials per day, for 10 days with an intertrial interval of 60s.

Measurement

- Doors remained closed until the subject oriented in front of the correct door, at which time the door was opened and the rat was able to gain access to a food reward; the choice was counted as a correct response.
- If the rat oriented to an incorrect door in the sequence, it was allowed to reorient to the correct door and the choice was counted as incorrect.

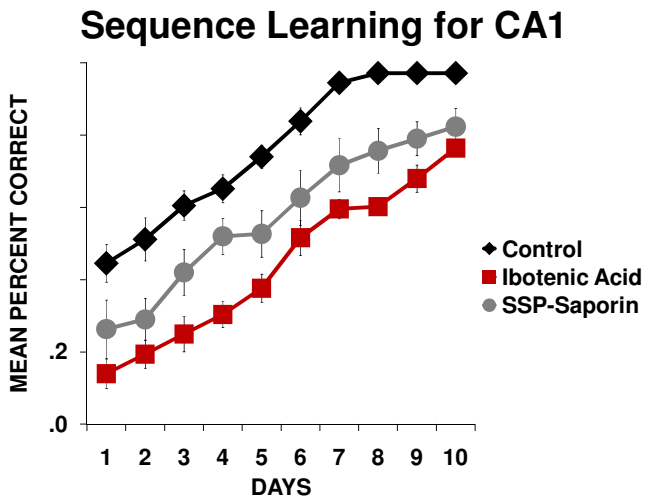

Figure 1. Mean percent correct for the sequence task averaged per day (10 trials each day) for controls, CA1 Ibotenic Acid, and CA1 SSP-Saporin lesions.

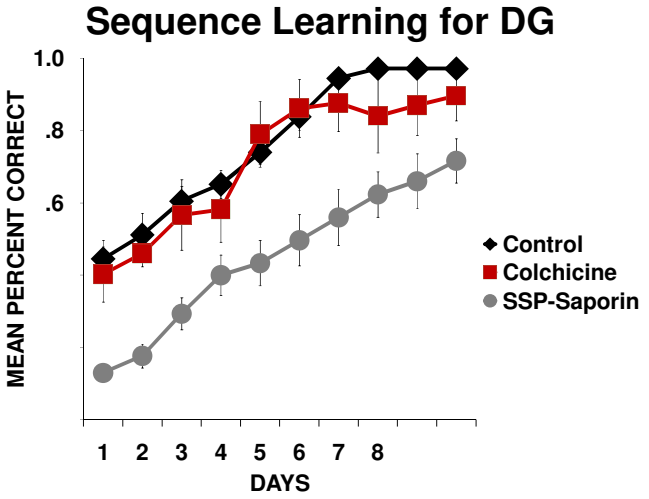

Figure 2. Mean percent correct for the sequence task averaged per day (10 trials each day) for controls, DG Colchicine, and DG SSP-Saporin lesions.

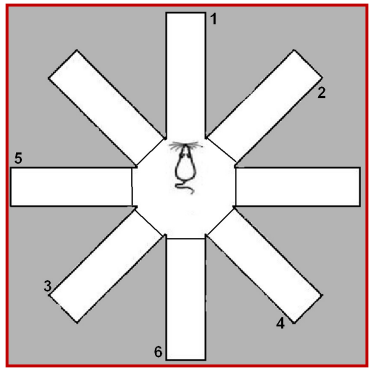

Figure 3. Radial 8-arm maze

Conclusions

- The data suggest HPP subregion CA1 lesions of both principal neurons and interneurons expressing SPRs impair acquisition of the spatial temporal sequence task. These data support other research that suggests the CA1 subregion is involved in temporal processing (Rolls & Kesner, 2006).
- The data also indicate that DG interneuron lesions, but not DG primary excitatory cell lesions impair acquisition on the spatial temporal sequence task.
- DG and CA1 GABA-ergic interneurons appear to have different roles in temporal learning of spatial sequences, which supports other research suggesting differential roles in environment exploration (Nitz & McNaughton, 2004).
- Lesion of DG granule cells reduces overall signal to CA1 via CA3. Because CA1 receives direct input from entorhinal cortex, it is able to conduct temporal sequence learning in the absence of that signal.
- However, DG interneuron lesions serve to prevent inhibition of signal, which may provide for enhanced signal or "noise" to pass from granule cells to CA1 via CA3. This additional signaling may cause interference such that CA1 is impaired in acquiring the temporal sequence for spatial locations.

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