Behavioural Brain Research 297 (2016) 141–149

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Evidences of the role of the rodent hippocampus in the non-spatial recognition memory

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HIGHLIGHTS

- The hippocampal lesion impairs contextual habituation.
- Insufficient habituation causes low concentration to objects.
- Hippocampal lesion impairs object recognition memory when fully habituated.
- Object recognition test with full habituation occluded hippocampal LTP.

ARTICLE INFO

Article history:
Received 3 May 2015
Received in revised form
30 September 2015
Accepted 6 October 2015
Available online 20 October 2015

Keywords:
Recognition memory
Hippocampus
Habituation
Long-term potentiation

ABSTRACT

The hippocampus is a key region responsible for processing spatial information. However, the role of the hippocampus in non-spatial recognition memory is still controversial. In the present study, we performed hippocampal lesioning to address this controversy. The hippocampi of mice were disrupted with bilateral cytotoxic lesions, and standard object recognition (non-spatial) and object location recognition (spatial) were tested. In the habituation period, mice with hippocampal lesions needed a significantly longer time to fully habituate to the test box. Interestingly, after 4 days of habituation (insufficient habituation), the recognition index was similar in the sham and hippocampal lesion groups. However, exploration time was significantly shorter in mice with hippocampal lesions compared with that in control mice. Interestingly, if mice were subjected to a 10-days-long period of habituation (full habituation), the recognition index was significantly lower in mice with hippocampal lesions compared with that in control mice; however, total exploration time was similar in both groups. Furthermore, the object recognition test after full habituation occluded hippocampal long-term potentiation, a cellular model of memory. These results indicate that sufficient habituation is required to observe the effects of hippocampal lesions on object recognition memory.

1. Introduction

Recognition memory is the ability to distinguish novel and familiar stimuli. Recognition memory depends on the integrity of the medial temporal lobe [1], which includes the hippocampus, perirhinal cortex, entorhinal cortex, and parahippocampal cortex [2]. In fact, the impaired recognition of familiar objects/locations and difficulties in distinguishing them from novel objects/locations

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http://dx.doi.org/10.1016/j.bbr.2015.10.018
0166-4328/

is one of the early traits of cognitive decline, which is observed in patients with Alzheimer's disease [3] and schizophrenia [4], who have an impaired declarative memory [5–7]. Therefore, it is important to explore the exact characteristics of this type of memory, which might help in understanding the related pathologies and in developing new drugs for various neurodegenerative and neuropsychological diseases.

The hippocampus receives information from various parts of the medial temporal lobe, which is an important region for memory formation in mammals [8]; however, its role in object recognition memory is still controversial. Several previous studies showed that object recognition memory is impaired in animals with perirhinal cortical lesions, but not in animals with hippocampal lesions [9,10]. However, other studies suggested that the hippocampus plays a role in object recognition memory [11–13]. This discrepancy may be explained with the different spatial or contextual information available during the tests [14].

The aim of this study was to uncover the role of the hippocampus in recognition memory. Several previous studies reported that object recognition memory is affected by habituation [15,16]. These results suggest that the extent of habituation may be a key factor that defines the involvement of the hippocampus in object recognition memory. Therefore, we hypothesized that hippocampal lesions could affect the context-specific habituation. To test this hypothesis, we introduced an extensive habituation protocol to familiarize experimental animals to the experimental context. In these experiments, hippocampal lesions significantly prolonged the time necessary for the fully habituation to the experimental context. After full habituation, hippocampal lesions significantly impaired both spatial and non-spatial object recognition memories.

2. Materials and methods

2.1. Animals

Forty male ICR mice (25–30 g, 7 weeks old) were purchased from the Orient Co. Ltd., a branch of Charles River Laboratories (Seoul, Korea). Ten mice were used for each group (Sham–normal habituation, lesion–normal habituation, sham–long habituation, lesion–long habituation). Mice were housed 5 per cage, provided with food and water ad libitum, and kept under a 12 h light/dark cycle (light on 07:30–19:30) at room temperature. Animal treatment and maintenance were carried out in accordance with the Animal Care and Use Guidelines issued by Kyung Hee University, Korea. The experimental animal protocols were approved by the Institutional Animal Care and Use Committee of Kyung Hee University, Korea (approved No. KHP 2010-03-02). All animals were anesthesized with Zoletil 50 (1 mg/kg, i.m.) for surgery and sacrifice. All efforts were made to minimize suffering.

2.2. Surgery

Mice were placed in a stereotaxic frame (David Kopf Instruments, Tujunga, CA) under Zoletil 50® anesthesia (10 mg/kg, i.m.). Ibotenic acid (IBO, Sigma, St. Louis, MO) was dissolved in 0.1 M phosphate-bufferd saline to provide a solution with a concentration of 4 mg/mL, pH 7.4. The syringe needle was lowered to the target coordinate and left in place for 1 min before beginning the injection. Following the injection, the syringe needle was left in place for a further 2 min to reduce the spread of IBO up the needle tract. For the hippocampal lesion group, a total of 4 μL of IBO was injected into 8 sites (0.5 μL/site, 0.1 μL/min) within each hippocampus following stereotaxic coordinates: (1) 1.50 mm posterior to bregma, 1.00 mm lateral to midline, and 2.00 ventral from dura, (2) 2.00 mm posterior to bregma, 2.00 mm lateral to midline, and 2.20 mm ventral from dura, (3) 3.00 mm posterior to bregma, 3.00 mm lateral to midline, and 2.00 and 3.50 mm ventral from dura. Following surgery, mice were allowed to recover for 7 days. After the behavioral experiments, lesion volume was verified by postmortem histological analysis (Fig. 1).

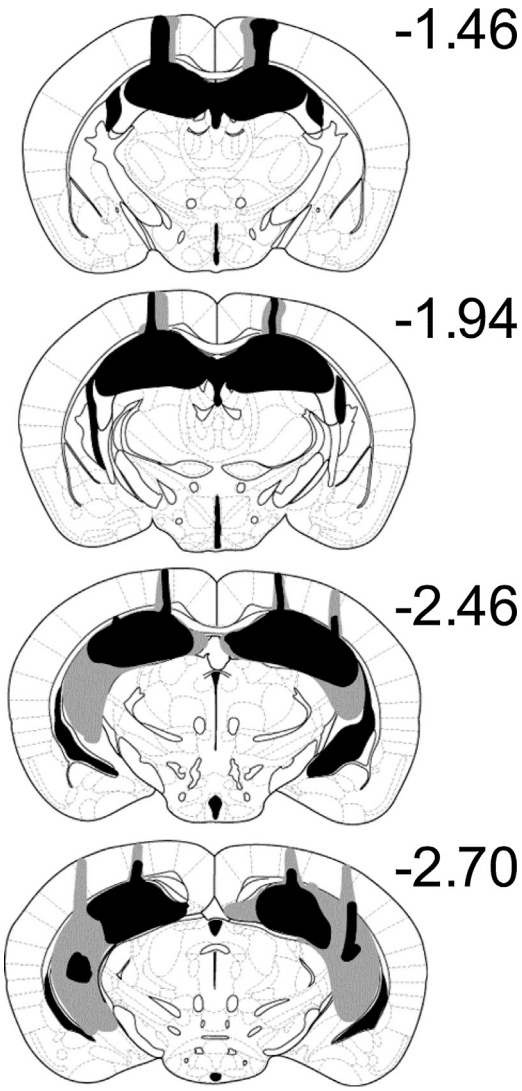

Fig. 1. Reconstructions of coronal sections through the hippocampus showing the smallest (black) and largest (gray) lesion. Numbers (right) represent the distance (mm) posterior to bregma.

2.3. Recognition memory test

The experimental apparatus consisted of a black rectangular open field (25 cm × 25 cm × 25 cm) with a visual cue placed on the arena wall. The object recognition task was carried out as described elsewhere [17]. Habituation training took place by exposing the animal to the experimental apparatus for 5 min in the absence of objects for indicated period. During the training phase, mice were placed in the experimental apparatus in the presence of two identical objects and allowed to explore for 5 min. After a retention interval of 24 h, mice were placed again in the apparatus, where a novel one replaced one of the objects. Mice were allowed to explore for 5 min. Preference for the novel and familiar object were expressed as the percent time spent exploring the novel object relative to the total time spent exploring both objects. The objects were