Behavioural Brain Research 323 (2017) 124–132

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Effects of dorsal hippocampus catecholamine depletion on paired-associates learning and place learning in rats

Corinna Roschlau, Wolfgang Hauber*

Department Animal Physiology, University of Stuttgart, D-70550 Stuttgart, Germany

HIGHLIGHTS

- We tested spatial learning of rats with hippocampus catecholamine (CA) depletion.
- Rats with CA depletion showed intact object-location learning in a touchscreen task.
- Rats with CA depletion preferred a response strategy in a maze spatial learning task.
- Hippocampus CA depletion may alter the balance between place and response learning.

ARTICLE INFO

Article history:
Received 26 September 2016
Received in revised form 20 January 2017
Accepted 24 January 2017
Available online 31 January 2017

Keywords:
Hippocampus
Dopamine
Noradrenaline
Spatial learning
Paired-associates learning
Place learning
Rat

ABSTRACT

Growing evidence suggests that the catecholamine (CA) neurotransmitters dopamine and noradrenaline support hippocampus-mediated learning and memory. However, little is known to date about which forms of hippocampus-mediated spatial learning are modulated by CA signaling in the hippocampus. Therefore, in the current study we examined the effects of 6-hydroxydopamine-induced CA depletion in the dorsal hippocampus on two prominent forms of hippocampus-based spatial learning, that is learning of object-location associations (paired-associates learning) as well as learning and choosing actions based on a representation of the context (place learning). Results show that rats with CA depletion of the dorsal hippocampus were able to learn object-location associations in an automated touch screen paired-associates learning (PAL) task. One possibility to explain this negative result is that object-location learning as tested in the touchscreen PAL task seems to require relatively little hippocampal processing. Results further show that in rats with CA depletion of the dorsal hippocampus the use of a response strategy was facilitated in a T-maze spatial learning task. We suspect that impaired hippocampus CA signaling may attenuate hippocampus-based place learning and favor dorsolateral striatum-based response learning.

1. Introduction

Hippocampus-based spatial memory processes include many forms of spatial learning and navigation, i.e. memory of places of events and things in the environment, map-like or paired-associate representations, and representations of routes to navigate from the present to a remembered location [1]. Emerging findings suggest that hippocampus catecholamine (CA) transmission supports some forms of hippocampus-based spatial learning and memory. For instance, a recent rodent study demonstrates that optogenetic stimulation of mesohippocampal dopamine (DA) fibers during spatial learning of new goal locations improved later recall of neural representations of space and alleviated memory performance [2]. Also, blockade or stimulation of hippocampus DA receptors prior to or immediately after spatial learning reduced or enhanced performance of rats in complex radial maze tasks [3,4]. Likewise, lesions of mesohippocampal DA fibers impaired retrieval of spatial information in rats tested in the Morris water-maze task [5].

Moreover, growing evidence indicates that noradrenaline (NA) released from fibers originating in the locus coeruleus (LC) influences spatial memory formation in the hippocampus. For instance, β-adrenergic receptor activation facilitated induction of hippocampal long term potentiation (LTP) [6]. In addition, spatial learning in a holeboard task facilitated LTP at hippocampal synapses, an effect that was prevented by a β-adrenoreceptor blockade [7].

Despite considerable progress, forms of hippocampus-mediated spatial learning that do or do not require CA modulation in the

* Corresponding author at: University of Stuttgart, Department Animal Physiology, Pfaffenwaldring 57, D–70550 Stuttgart, Germany.
E-mail address: wolfgang.hauber@bio.uni-stuttgart.de (W. Hauber).

http://dx.doi.org/10.1016/j.bbr.2017.01.038
0166-4328/

hippocampus are still poorly characterized. Therefore, in the current study, we examined the effects of 6-hydroxydopamine (6-OHDA)-induced CA depletion in the dorsal hippocampus (dHIPP) on two prominent forms of hippocampus-based spatial learning, that is learning of object-location associations (paired-associates learning, PAL) as well as learning and choosing actions based on a representation of the context (place learning).

In Experiment 1 we used an automated touch screen PAL task for rodents that demands learning that a particular object, i.e. one out of three symbols, is only correct in a particular location, i.e. one out of three positions on the touchscreen [8,9]. On a given trial, two symbols are displayed, one in its correct, another one in an incorrect position, and the rat has to respond to the symbol in the correct position. Performance on the PAL task is sensitive to hippocampal dysfunction. For instance, intra-hippocampal microinfusions of lidocaine, muscimol or NMDA and AMPA receptor antagonists impaired PAL performance in rats [8,10]. Moreover, systemic administration of CA and glutamatergic drugs can alter performance in the PAL task [9,11–13]. In humans, performance in a related PAL task is predictive of the conversion from mild cognitive dysfunction to Alzheimer's disease [14]. Furthermore, in mild cognitive impairment, PAL performance is correlated with hippocampal volume [15]. Remarkably, in an arena-based spatial memory task for rats, DA D1 receptor blockade in the hippocampus compromised the persistence of memory for novel paired-associates between food flavors and locations in space [16]. In view of these findings, we hypothesized that hippocampal CA depletion should impair object-location learning in the PAL task (Experiment 1).

In Experiment 2, we used a spatial learning task employed in earlier studies [17,18]. This task can be solved either by hippocampus-mediated place learning, i.e. learning and choosing actions based on a representation of the context or allocentric coordinates or by striatum-based response learning that involves body-centered or egocentric coordinates, such as a right-turn response. For instance, rats were trained for several days to retrieve a reward from the west arm of a cross maze starting from the south, i.e. to make a left turn at the choice point [18]. On a subsequent test day, a probe test was given in which the starting arm was inserted as the north arm. Control rats with intra-hippocampus vehicle injections made a right turn on the probe test and approached the rewarded west arm indicating that those rats adopted a place strategy. By contrast, most animals with intra-hippocampus lidocaine injections made a left turn to the unrewarded east arm suggesting that those rats used a response strategy [18]. If hippocampal CA signaling supports learning and choosing actions based on allocentric coordinates, hippocampus CA depletion should induce a preference for a response over a place strategy (Experiment 2).

2. Material and methods

We examined in rats the effects of dHIPP CA depletion on PAL in an automated touchscreen task (Experiment 1) and on place and response learning in a T-maze task (Experiment 2). Animal experiments were conducted according to the German law of animal protection and were approved by the proper authorities.

2.1. Experiment 1: dHIPP CA depletion and PAL

2.1.1. Subjects

Male Lister Hooded rats (N = 14, Charles River Laboratories, UK) were used for this experiment weighting between 230 g and 270 g at the beginning of the experiment. They were housed in groups of 3–4 in transparent plastic cages (60 cm × 38 cm × 20 cm, Tecniplast, Milan) in a 12:12-h light-dark cycle with lights on at 7 A.M. All experiments were conducted during the light phase, temperature (22 ± 2 °C) and humidity (50 ± 10%) were kept constant. Animals had ad libitum access to water and were supplied with standard laboratory chow for rodents (Altromin, Lage, Germany) ad libitum for the first 7 days after arrival. Thereafter, laboratory chow was restricted to 15 g per animal and day to maintain them on approximately 85% of their free-feeding weight. For environmental enrichment, a plastic tube (20 cm, Ø 12 cm) was fixed at the lid of each cage and nesting material was provided.

2.1.2. Apparatus

Operant boxes (Med Associates, Vermont USA; 31.8 cm × 25.4 cm × 26.7 cm) were employed with one end of the chamber equipped with a touch-sensitive, flat-screen LCD monitor equipped with an infrared sensor. A black aperture plate (29 × 19 cm) was attached in front of the monitor made of stainless steel with 3 rectangular response windows (6 cm × 9 cm; lower edge 4 cm above box grid floor). The plate was attached to the monitor leaving a 0.5-cm space between the plate and monitor. A shelf (6 cm × 20.5 cm) was attached above the grid floor. The wall opposite the LCD monitor was equipped with a food magazine with a built-in magazine light and head entry detector. Above the food magazine there was a house light (3 W). Each operant box was kept in a sound-attenuating chamber. The testing apparatus was controlled by the K-Limbic software (Med Associates, Vermont, USA).

2.1.3. Task and training

Animals were trained and tested on the dPAL task (*"different Paired Associate Learning"*) according to a previous protocol [8] usually on 5 days per week.

2.1.3.1. Habituation. In brief, animals were placed in the operant chambers for 2 subsequent days for 20 min each to habituate them to the boxes baited with peanut butter and food pellets (45 mg Dustless Precision Pellets #F00231-J, Bio-Serv, Frenchtown, USA) scattered throughout the chamber.

2.1.3.2. Pretraining. Next, we trained animals to pick up food pellets from the magazine. On Day 1, for 100 trials, the magazine light was switched on upon pellet delivery (every 30 s) and switched off after a head entry into the magazine. On Day 2, white squares were presented in all three of the response windows. If the animal did not touch the monitor, a one-pellet reward was always given after 30 s, if the animal touched the monitor, a three-pellet reward was given on top. Then, the next trial was initiated; the session ended after 100 trials or 30 min whichever came first.

Subsequently, rats were required to touch any area of the monitor to earn a reward. On Day 3 and 4, one session was given per day, a session ended after 100 trials or 30 min whichever came first. Again, white squares were presented in all three of the response windows. The screen remained active until a response occurred. Once a response occurred, one food pellet was delivered and the touchscreen deactivated. The next trial began 5 s after the pellet was collected.

Next, to avoid a development of a response bias, in daily sessions on Days 5 and 6 (including 99 trials each), one of the three response locations was randomly illuminated and the rat was required to poke at this location to earn a food pellet. Pokes at other locations had no programmed consequences.

2.1.3.3. PAL task training. As shown in Fig. 1, the following symbols were used as stimuli on the touch screen: flower, plane and spider. Each symbol was correct (S+) in one particular position on the screen (left (1), middle (2) or right (3)) and incorrect in the other two positions (S-). Correct positions for each symbol differed within