Brain Research Bulletin 127 (2016) 1–10

Contents lists available at ScienceDirect

Brain Research Bulletin

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

Research report

Interaction between dorsal hippocampal NMDA receptors and lithium on spatial learning consolidation in rats

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ARTICLE INFO

Article history:
Received 19 March 2016
Received in revised form 4 July 2016
Accepted 18 July 2016
Available online 18 July 2016

Keywords:
D-AP5
Lithium
Morris water maze
NMDA
Rat

ABSTRACT

Previous investigations have shown that NMDA receptors play an important role in learning and memory process. Lithium is a primary drug for management and prophylaxis of bipolar disorder. It can regulate signal transduction pathways in several regions of the brain and alter the function of several neurotransmitter systems involved in memory processes. The present study aimed to test the interaction of NMDA glutamatergic system of the CA1 region of dorsal hippocampus and lithium on spatial learning. Spatial memory was assessed in Morris water maze task by a single training session of eight trials followed by a probe trial and visible test 24 h later. All drugs were injected into CA1 regions, 5 min after training. Our data indicated that post- training administration of lithium (20 μg/rat, intra-CA1) significantly impaired memory consolidation. Intra- CA1administration of NMDA, a glutamate receptor agonist (0.001 and 0.01 μg/rat) showed spatial learning facilitation. Infusion of D-AP5, a glutamate receptor antagonist (0.05 and 0.1 μg/rat) showed impairment of spatial memory. Our data also indicated that post- training administration of ineffective dose of NMDA (0.0001 μg/rat) significantly decreased amnesia induced by lithium in spatial memory consolidation. In addition, post-training intra-CA1 injection of ineffective dose of D-AP5 (0.01 μg/rat) could significantly increase lithium induced amnesia. It seems probable that signaling cascades of NMDA receptors that regulates synaptic plasticity are targets of anti-manic agents such as lithium. Our results suggest that NMDA receptors of the dorsal hippocampus may be involved in lithium-induced spatial learning impairment in the MWM task.

1. Introduction

Lithium is an important mood stabilizing drug which is used for the treatment of manic-depressive illness. It can potentiate the effects of antidepressant drugs (Schou, 1968). There are several reports showing that lithium treatment decreased learning, memory, and speed of information processing in bipolar patients and in control subjects (Pachet and Wisniewski, 2003; Stip et al., 2000). It seems that lithium effects are due to neuroplastic alterations involving intracellular signaling pathways, transcription factors, and regulation of gene expression (Al Banchaabouchi et al., 2004). The data concerning the effect of lithium on learning and memory are controversial. Some reports introduce lithium as a neuroprotective agent (Creson et al., 2003). However, a number of investigation indicate the memory impairing effect of lithium in both human and animal (Al Banchaabouchi et al., 2004; Parsaei et al., 2011). It has been shown that lithium can regulate signal transduction pathways in several regions of the brain. The drug may also change the function of different neurotransmitter systems (Manji et al., 1995), including acetylcholine (Ach), serotonin (5HT), dopamine (DA), *N*-methyl-D-aspartic acid (NMDA), nitric oxide and neurotrophic factors (Ghasemi and Dehpour, 2011).

In particular, the *N*-methyl-D-aspartate (NMDA) subclass of glutamate receptors was obviously involved in conditioned taste aversion paradigm, an action that was modulated by lithium

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http://dx.doi.org/10.1016/j.brainresbull.2016.07.007
0361-9230/

(Ferreira et al., 2002). There is suggestion that NMDA receptor/nitric oxide (NO) signaling may mediate some responses of lithium in the brain and peripheral tissues (Ghasemi and Dehpour, 2011). NMDA signaling has been shown to be involved in the antidepressant-like effects of lithium (Ghasemi et al., 2010). Acute lithium administration stimulated glutamate release, which was accompanied by an increase in inositol 1,4,5-trisphosphate (IP3) accumulation (Hokin et al., 1996).

It has also been reported that the increase in IP3 accumulation was a result of selective activation of the NMDA receptors by glutamate (Hokin et al., 1996). Hippocampal glutamate levels have been documented to be elevated in stably remitted bipolar patients receiving chronic lithium maintenance therapy for an average of 10 years (Colla et al., 2009).

Considering the above-mentioned points and findings, the present study was designed with the following aims: (i) to determine the effect of acute intra-CA1 administration of lithium on spatial memory consolidation using Morris Water Maze task; (ii) to evaluate whether NMDA glutamatergic receptors of the CA1 region of the hippocampus lead changes of lithium effect on spatial memory consolidation.

2. Materials and methods

2.1. Animals and substances

Adult male albino Wistar rats (200–250 g, aged 10–12 weeks) were obtained from Pasteur Institute of Iran. They were housed in a temperature (25 ± 2 °C) and humidity-controlled room. The animals were maintained under a 12:12-h light/dark cycle, with lights off at 7:00 p.m. Food and water provided ad libitum except for the periods of behavioral testing in Morris water maze (MWM). Each animal was used once only. All experimental procedures were in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

2.2. Drugs

The drugs used in the present study were lithium chloride (LiCl; Merck, Germany), NMDA and D-(−)-2-amino-5-phosphonopentanoic acid (D-AP5; Tocris Cookson Ltd., UK). All drugs were dissolved in sterile 0.9% saline just before using. All drugs were bilaterally injected into the hippocampal CA1 region (intra-CA1), 5 min after training. Control animals received 0.9% physiological saline.

2.3. Surgical procedure

The animals were anaesthetized with intraperitoneal injection of ketamine hydrochloride (50 mg/kg) plus xylazine (5 mg/kg) and placed in a stereotaxic apparatus, while maintaining the incisor bar at approximately 3.3 mm below horizontal zero to achieve a flat skull position. A mid-saggital incision was made to expose the rat skull. Two stainless steel, 22-gauge guide cannulae were placed (bilaterally) 1 mm above the intended site of injection according to the atlas of Paxinos and Watson (Paxinos and Watson, 1997). Stereotaxic coordinates for the CA1 regions of the dorsal hippocampus were: −3 to −3.5 mm (depending on body weight) posterior to bregma, ±1.8 to 2 mm lateral to the midline, and −2.8 to −3 mm ventral to the dorsal surface of the skull. The guide cannula was anchored by a jeweler's screw, and the incision was closed with dental cement. After completing the surgery, two stainless steel stylets (27 gauge) were inserted into the guide cannulae, and left in places until injections were made. All animals were allowed to recover for 1 week after surgery.

2.4. Injection into the CA1 region of dorsal hippocampus

The animals were gently restrained by hand; the stylets were removed from the guide cannulae. For intra-hippocampal CA1 injections of drugs, a 1.0-μl glass Hamilton syringe was used. The injection (inner) cannulae (27-gauge), which projected a further 1 mm ventral to the tip of the guides, were attached with polyethylene tubing to the Hamilton syringe. The injection volume of drugs was 1.0 μl (0.5 μl per side) for all groups. Each dose of drug used/rat was dissolved in 1.0 μl. The injections were made over a 60-s period, and the injection cannulae were left in the guide cannulae for an additional 60 s to facilitate diffusion of the drugs.

2.5. Apparatus

The water maze was a black circular pool with a diameter of 136 cm and a height of 60 cm, filled with 20 ± 1 °C water to a depth of 20 cm. The maze was divided geographically into four equal quadrants and release points that were designed at each quadrant as N, E, S, and W. A hidden circular platform (10 cm in diameter), made of Plexiglas, was located in the center of the southwest quadrant, submerged 1.5 cm beneath the surface of the water. Fixed, extra maze visual cues were present at various locations around the maze (i.e., computer, MWM hard wares, posters). A camera was mounted above the center of the maze and animal motion can be recorded and sent to the computer. A tracking system was used to measure the escape latency, traveled distance and swimming speed.

2.6. Behavioral procedure

Spatial memory was assessed using a 2-day Morris water maze task. The single training session consisted of eight trials with four different starting positions that were equally distributed around the perimeter of the maze (Moosavi et al., 2007). The task requires rats to swim to the hidden platform guided by distal spatial cues. After mounting the platform, the rats were allowed to remain there for 20 s, and were then placed in a holding cage for 30 s until the start of the next trial. Rats were given a maximum of 60 s to find the platform and if it failed to find the platform in 60 s, it was placed on the platform and allowed to rest for 20 s. Latency to platform and distance traveled were collected and analyzed later. After completion of the training, the animals were returned to their home cages until retention testing (probe trial) 24 h later. The probe trial consisted of 60 s free swim period without a platform and the time swum in the target quadrant was recorded. After the probe trial, non-spatial visual discrimination task was done. In this session, the platform was elevated above the water surface and placed in the different positions in the four quadrants. This procedure is believed to provide information on the possible nonspecific effects involving motor, visual, or motivational abilities for learning and memory.

2.7. Drug treatment

Eight animals were used in each experimental group. In the experiments where the animals received one or two injections, the control groups also received one or two saline injections. The intervals of drug administration were based on our previous studies in order to obtain a maximum response (Fig. 1).

2.8. Experimental design

2.8.1. Experiment 1: effect of lithium on spatial memory consolidation

The effect of post-training administration of lithium on memory consolidation was examined. Four groups of animals received