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Original Article

Intra-Dorsal Hippocampal Microinjections of Lithium and Scopolamine Induce a Cross State-Dependent Learning in Mice

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Background: **Lithium, a mood stabilizer, may exert adverse effects on memory. We have previously shown that lithium induces state-dependent learning. Cholinergic systems of the brain may play an important role in memory function and mood regulation. In the present study, the effects of intra-dorsal hippocampal (intra-CA1) injections of lithium and scopolamine on memory and cross state-dependent learning between the two drugs were investigated.**

Methods: **For memory assessment, a one-trial step-down inhibitory avoidance task was used in adult male NMRI mice.**

Results: **Intra-CA1 administration of lithium (0.5 and 1 µg/mouse) after training or injection of the drug (0.5µg/mouse) before testing impaired memory when retrieval was tested 24 hours later. The memory impairment by post-training lithium was reversed by pretest administration of the drug (0.5µg/mouse, intra-CA1) suggesting lithium state-dependent learning. On the other hand, intra-CA1 administration of scopolamine (0.5, 1, and 2 µg/mouse) after training or injection of the drug (2µg/mouse) before testing impaired memory when retrieval was tested 24 hours later. The impairment of memory by post-training injection of scopolamine (2µg/mouse) was restored by the pretest injection of the drug (1 and 2 µg/mouse). Furthermore, memory impairment induced by post-training injection of lithium (0.5 µg/mouse) and scopolamine (2 µg/mouse) was reversed by pretest administration of scopolamine (0.5, 1, and 2 µg/mouse) and lithium (0.5 and 1 µg/mouse), respectively. The impairment by lithium was also reversed by physostigmine.**

Conclusion: **The results suggest that microinjections of both lithium and scopolamine induce state-dependent memory and there may be a cross state-dependency between the two drugs.**

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Keywords: Lithium • mouse • scopolamine • state-dependent learning

Introduction

Lithium administration relieves mania and has long been a primary drug used for treatment and prophylaxis of bipolar disorder. The drug has been suggested to potentiate the effects of other antidepressants. Although its antidepressant effect remains controversial,[1–3] lithium has been shown to be a mood stabilizer, a neuroprotective,[4,5] and an antiapoptotic drug.[6,7] Animal studies may propose lithium effect in the treatment of drug addiction.[8,9] There are reports indicating that lithium may exert adverse effects on memory,[10] including verbal memory,[11] but a number of studies also failed to demonstrate lithium-induced memory deficits.[12] Some investigators have suggested that lithium treatment inhibited learning, memory, and speed of information processing in patients with bipolar disorder and to some extent in control subjects.[11,13–15] It has also been reported that

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lithium enhances memory in some tasks,[16] or attenuates memory impairments induced by other factors.[17]

We have previously shown that lithium restored memory impairment by morphine,[18] and histamine.[19] Despite its clinical use for decades, no definite mechanism for its effect has been established.[20]

Cholinergic systems of the brain may play an important role in memory function and mood regulation.[21–23] Furthermore, failure and cognitive decline associated with aging are related to deterioration of the cholinergic system of the brain.[24,25] The dysfunction of many neurotransmitter systems including the cholinergic system may be involved in bipolar disorder.[26,27] The effects of mood stabilizers, especially lithium, on neurotransmitters and second messenger systems have been extensively investigated.[20,28–32] Many changes in the cholinergic systems produced by lithium have been reported, but it is not clear if these alterations are direct effects which are involved in the therapeutic efficacy of lithium.[22]

Lithium-induced inhibition of the enzyme inositol monophosphatase affects the production of the phosphatidyl inositol (PI)- derived second messengers, diacylglycerol (DAG), and inositol triphosphate (IP3).[8–10] On the other hand, there is evidence indicating that activation of cholinergic receptors by high-dose cholinergic agonist may induce seizures,[33] which can be potentiated by lithium administration. The IP3-induced Ca2+ release may be the mechanism underlying facilitation of the onset of induction by these drugs.[34] The dorsal hippocampus is involved in,[35] thus the present study was carried out to examine state-dependency induced by microinjections of lithium and scopolamine into the CA1 region of dorsal hippocampus of mice and cross state-dependency between the two drugs.

Materials and Methods

Animals

Male albino NMRI mice weighing 25 – 30 g at the time of surgery were used. The animals were kept in an animal house with a 12/12-hour light-dark cycle and controlled temperature (22±2ºC). The animals were housed in groups of 10 in Plexiglas cages and food and water were available ad libitum. Ten animals were used in each group; each animal was used once only. Behavioral experiments were done during the light phase of the light/dark cycles. All procedures were carried out in accordance with institutional guidelines for animal care and use.

Surgical and infusion procedures

The mice were anesthetized with intraperitoneal injection of ketamine hydrochloride (50 mg/kg) plus xylazine (5 mg/kg) and placed in a stereotaxic apparatus. The skin was incised and the skull was cleaned. One 22-gauge guide cannula was placed 1 mm above the intended site of injection according to the Atlas of Paxinos and Franklin (2001).[36] Stereotaxic coordinates for the CA1 region of the dorsal hippocampus were AP: -2 mm from bregma, L: -1.6 from the sagittal suture, and V: -1.5 mm from the skull surface. The cannula was secured to anchor jewelers' screws with dental acrylic. Stainless steel stylet (27-gauge) was inserted into the guide cannula to keep it free of debris. All the animals were allowed one week to recover from surgery and to clear anesthetic.

For drug infusion, the animals were gently restrained by hand, the stylet was removed from the guide cannula, and replaced by 27-gauge injection needle (1 mm below the tip of the guide cannula). The injection solutions were administered in a total volume of 1 µL/mouse over a 60 s period. Injection needle was left in place for an additional 60 s to facilitate the diffusion of the drugs.

Apparatus

The passive avoidance apparatus consisted of a wooden box (30×30×40 cm high) with a steel-rod floor (29 parallel rods, 0.3 cm in diameter, set 1 cm apart). A wooden platform (4×4×4 cm) was set in the center of the grid floor. Intermittent electric shocks (1 Hz, 0.5 s, 40 V DC) were delivered to the grid floor by an insulated stimulator (Grass S44, USA).

Training

A single-trial step-down passive avoidance task was used. Each mouse was gently placed on the wooden platform. When the mouse stepped down from the platform and placed all its paws on the grid floor, intermittent electric shocks were delivered continuously for 15 s. This training procedure was carried out between 10:00 and 15:00 hours. Each mouse was placed on the platform again at 24th hour after training and the step-down latency was measured with a stopwatch as passive avoidance behavior. An upper cut-off time of 300 s was set. The retention test was also carried out between 10:00 and 15:00 hours.

Drugs

Drugs used in the present study were lithium chloride (Merck, Germany) and scopolamine hydrochloride (Tocris, UK). All drugs were dissolved in sterile 0.9% saline just before the experiments and were administered into mouse dorsal hippocampus. The doses of the drugs were chosen according to pilot studies.

Drug treatment

Ten animals were used in each experimental group. Control groups received saline injections.

Experiment 1

This experiment examined the effects of lithium on memory retrieval. One group of animals received saline (1 μL/mouse, intra-CA1) as post-training and pretest treatments. Three other groups received lithium (0.25, 0.5, and 1 μg/mouse) immediately after training and on the test day they received saline (1μL/mouse, intra-CA1) five minutes before testing. A group of animals also received saline as post-training and lithium (0.5 μg/mouse) five minutes before the test.

Experiment 2

In experiment 2, the effect of intra-CA1 administration of lithium before the test on the memory impairment induced by post-training lithium was evaluated. One group of animals received post-training and pretest saline administration. Four other groups received lithium (0.5μg/mouse) after training, and on the test day they received saline (1 μL/mouse) or different doses of lithium (0.25, 0.5, and 1 μg/mouse) five minutes prior to the test.

Experiment 3

This experiment examined the effects of scopolamine on memory retrieval. One group of animals received saline (1 μL/mouse, intra-CA1) as post-training and pretest treatments. Three other groups received scopolamine (0.5, 1, and 2 μg/mouse) immediately after training and on the test day they received saline (1 μL/mouse, intra-CA1) five minutes before testing. A group of animals also received saline as post-training and scopolamine (2 μg/mouse) five minutes before the test.

Experiment 4

In experiment 4, the effect of intra-CA1 administration of scopolamine before the test on the memory impairment induced by post-training scopolamine was evaluated. One group of animals received post-training and pretest saline administration. Three other groups received scopolamine (2 μg/mouse) after training, and on the test day they received saline (1 μL/mouse) or different doses of scopolamine (1 and 2 μg/mouse) five minutes prior to the test.

Experiment 5

In this experiment, the effect of scopolamine administration before testing on the memory impairment induced by lithium given after training was evaluated. One group of animals received post-training and pretest saline administration. Four other groups received post-training lithium (0.5 μg/mouse), and on the test day they received saline or different doses of scopolamine (0.5, 1, and 2 μg/mouse) five minutes before the test.

Experiment 6

In this experiment, the effect of lithium administration before testing on the memory impairment induced by scopolamine given after training was tested. One group of animals received post-training and pretest saline administration. Four other groups received post-training scopolamine (2 μg/mouse), and on the test day they received saline or different doses of lithium (0.5, 1, and 2 μg/mouse) five minutes before the test.

Experiment 7

In this experiment, the effect of physostigmine administration before testing on the memory impairment induced by lithium given after training was tested. One group of animals received post-training and pretest saline administration. Four other groups received post-training lithium (0.5 μg/mouse), and on the test day they received saline or different doses of physostigmine (0.01, 0.1, and 1 μg/mouse) five minutes before the test.

Statistical analysis

Because of individual variations the data were analyzed by using the Kruskal-Wallis non-parametric one-way analysis of variance (ANOVA) followed by a two-tailed Mann-Whitney U test. Holmes Sequential Bonferroni Correction Test was used for the paired comparisons as appropriate. The step-down latencies for ten animals in each experimental group were expressed as median and inter-quartile ranges. In all statistical evaluations $P<0.05$ was used as the criterion for statistical significance.

Results

Effect of lithium on inhibitory avoidance learning

The results of experiment 1 showed that post-training (0.25, 0.5, 1 µg/mouse), or pretest (0.5 µg/mouse) administration of lithium impaired memory retention [Kruskal-Wallis ANOVA, H(4) =21.9, $P<0.0001$] (Figure 1). Experiment 2 indicated that the response induced by post-training lithium (0.5 µg/mouse) was reversed by pretest lithium at the doses of 0.5 and 1 µg/mouse [Kruskal-Wallis ANOVA, H(4)=17.5, $P<0.01$], suggesting state-dependency induced by lithium (Figure 2).

Effect of scopolamine on inhibitory avoidance learning

The results of experiment 3 showed that post-training (0.5, 1, and 2 µg/mouse), or pretest (2 µg/mouse) administration of scopolamine impaired memory retention [Kruskal-Wallis ANOVA, H(4)=17.2, $P<0.01$] (Figure 3). Experiment 4 indicated that the response induced by post-training scopolamine (2 µg/mouse) was reversed by pretest scopolamine at the doses of 1 and 2 µg/mouse [Kruskal-Wallis ANOVA, H(3)=9.1, $P<0.05$], suggesting state-dependency induced by scopolamine (Figure 4).

Effect of intra-CA1 administration of lithium or scopolamine before the test on memory impairment induced by the respective administration of scopolamine or lithium given after training

The results of experiment 5 showed that intra-CA1 administration of scopolamine before the test altered memory impairment induced by post-training lithium [Kruskal-Wallis ANOVA, H(4)= 21.8, $P<0.0001$]. Post-hoc analysis by Mann-Whitney U test indicated that scopolamine (0.5, 1, and 2 µg/mouse) reversed the memory impairment induced by lithium (0.5 µg/mouse; Figure 5). Moreover, the results of experiment 6 showed that pretest administration of lithium also altered memory impairment due to scopolamine given after training [Kruskal-Wallis ANOVA, H(4)=27.5, $P<0.0001$]. Post-hoc analysis revealed that pretest lithium reversed impairment by post-training administration of scopolamine (Figure 6).

Effect of intra-CA1 administration of physostigmine before the test on memory impairment

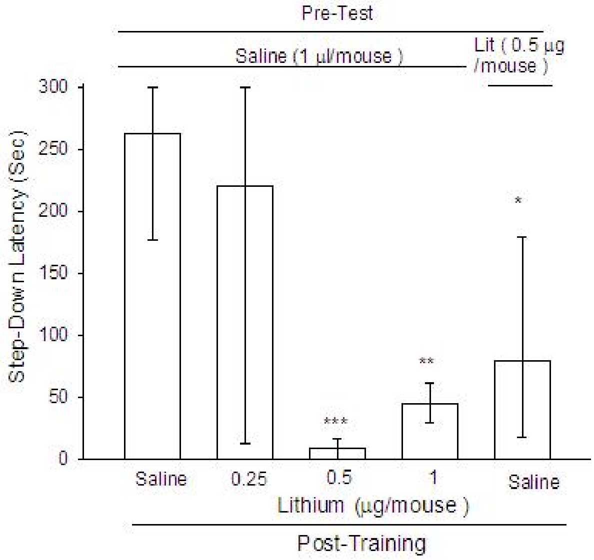

Figure 1. Effect of lithium on memory of inhibitory avoidance task. Five groups of animals were used. One group of animals received post-training and pretest saline (1 µL/mouse, intra-CA1) administration. Three other groups received lithium (0.25, 0.5, and 1 µg/mouse, intra-CA1) immediately after training. On the test day, they received saline (1 µL/mouse, intra-CA1). One other group received saline (1 µL/mouse, intra-CA1) as post-training and lithium (0.5 µg/mouse, intra-CA1) as pretest. Each bar represents median and inter-quartile ranges for 10 animals. $^*P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ compared with saline-saline group.

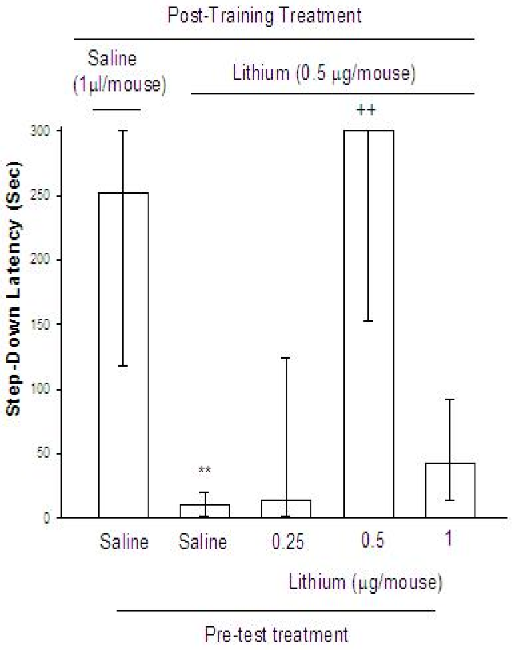

Figure 2. Effect of pretest administration of lithium on memory impairment induced by post-training lithium (0.5 µg/mouse, intra-CA1). Five groups of animals were used. One group of animals received post-training and prerest saline administration. The other groups received post-training lithium (0.5 µg/mouse, intra-CA1). On the test day, the animals received either saline or different doses of lithium (0.25, 0.5, and 1 µg/mouse, intra-CA1) five minutes before the test. Each bar represents median and inter-quartile ranges for 10 animals. **P<0.01 compared with saline-saline group. ++P<0.01 compared with lithium-saline group.

induced by the administration of lithium given after training

The results of experiment 7 showed that intra-CA1 administration of physostigmine before the test altered memory impairment induced by post-training lithium [Kruskal-Wallis ANOVA, H(4)= 23.63, *P*<0.0001]. Post-hoc analysis by Mann-Whitney U test indicated that physostigmine (0.01,

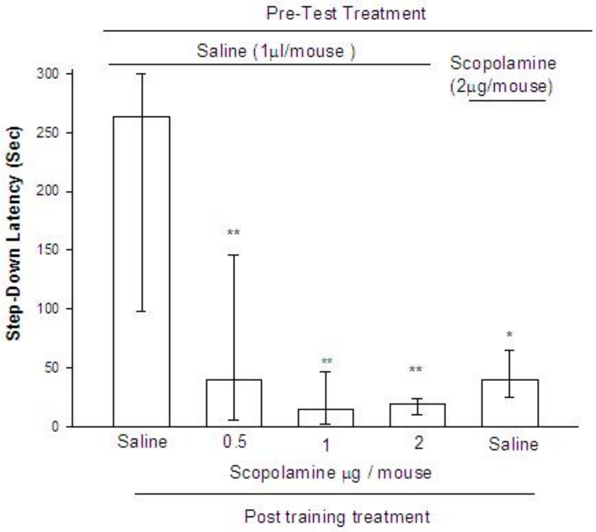

Figure 3. Effect of scopolamine on memory of inhibitory avoidance task. Five groups of animals were used. One group of animals received post-training and pretest saline (1 µL/mouse, intra-CA1) administration. Three other groups received scopolamine (0.5, 1, and 2µg/mouse, intra-CA1) immediately after training. On the test day, they received saline (1 µL/mouse, intra-CA1). One other group received saline (1 µL/mouse, intra-CA1) as post-training and scopolamine (2 µg/mouse, intra-CA1) as pretest. Each bar represents median and inter-quartile ranges for 10 animals. *P<0.05, **P<0.01 compared with saline-saline group (same as above).

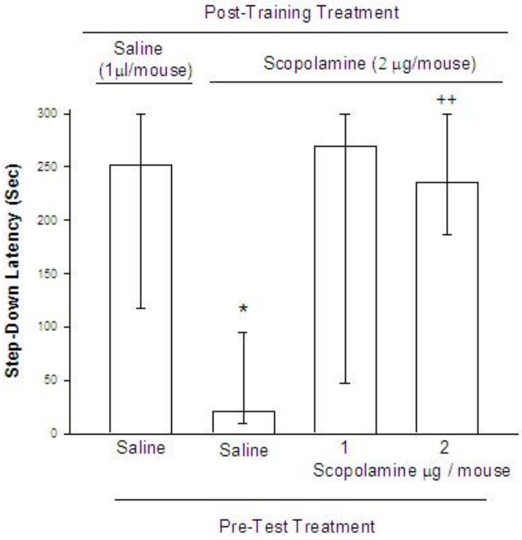

Figure 4. Effect of pretest administration of scopolamine on memory impairment induced by post-training scopolamine (2 µg/mouse, intra-CA1). Five groups of animals were used. One group of animals received post-training and prerest saline administration. The other groups received post-training scopolamine (2 µg/mouse, intra-CA1). On the test day, the animals received either saline or different doses of scopolamine (1 and 2 µg/mouse, intra-CA1) five minutes before the test. Each bar represents median and inter-quartile ranges for 10 animals. *$P<0.05$ compared with saline-saline group. +$P<0.05$, ++$P<0.01$ compared with scopolamine-saline group.

0.1, and 1 µg/mouse) reversed the memory impairment induced by lithium (0.5 µg/mouse; Figure 7).

Discussion

In the present study, it was found that post-training or pretest intra-hippocampal (intra-CA1) administration of lithium impairs memory of inhibitory avoidance task when tested 24 hours later. This was in agreement with our previous data that pretraining administration of lithium impaired inhibitory avoidance response on the test day.[18,19] Since, pretraining administration of drugs may

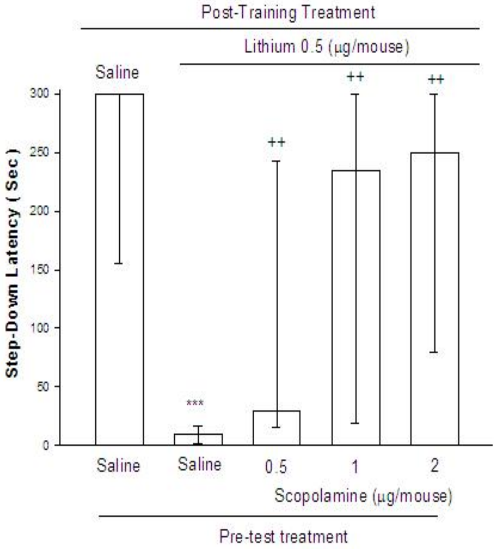

Figure 5. Effect of pretest administration of scopolamine on memory impairment induced by post-training lithium (0.5 µg/mouse, intra-CA1). Five groups of animals were used. One group of animals received post-training and prerest saline administration. The other four groups received post-training administration of lithium (0.5 µg/mouse, intra-CA1). On the test day these animals received saline or different doses of scopolamine (0.5, 1, and 2 µg/mouse, intra-CA1) five minutes before the test. Each bar represents median and inter-quartile ranges for 10 animals. ***$P<0.001$ compared with saline-saline group, ++$P<0.01$ compared with lithium-saline group.

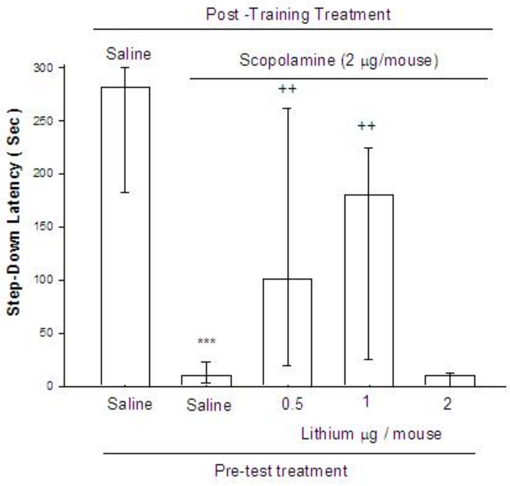

Figure 6. Effect of pretest administration of lithium on memory impairment induced by post-training scopolamine (2 µg/mouse, intra-CA1). Five groups of animals were used. One group of animals received post-training and prerest saline administration. The other four groups received post-training administration of scopolamine (2 µg/mouse, intra-CA1). On the test day these animals received saline or different doses of lithium (0.5, 1, and 2 µg/mouse, intra-CA1) five minutes before the test. Each bar represents median and inter-quartile ranges for 10 animals. ***$P<0.001$ compared with saline-saline group, ++$P<0.01$ compared with lithium-saline group.

influence the animal sensitivity to shock, or the degree of arousal during the original training rather than by directly modifying memory storage processes,[37] in a recent study,[38] and also in the present study lithium was administered after training.

The possibility of inhibition of inositol monophosphatase and inositol polyphosphate 1-phosphatase enzymes by lithium,[39] may account for its response, which needs further experiments to be clarified. Moreover, decrease in hippocampal membrane-associated protein kinase C with lithium may be another possible explanation for the drug-induced memory impairment.[40] Lithium also inhibits the formation of cAMP,[41] which may be related to the drug response.

Our present results also indicate that lithium post-training induced memory impairment was restored by pretest treatment of the drug, suggesting state-dependency of learning. In this

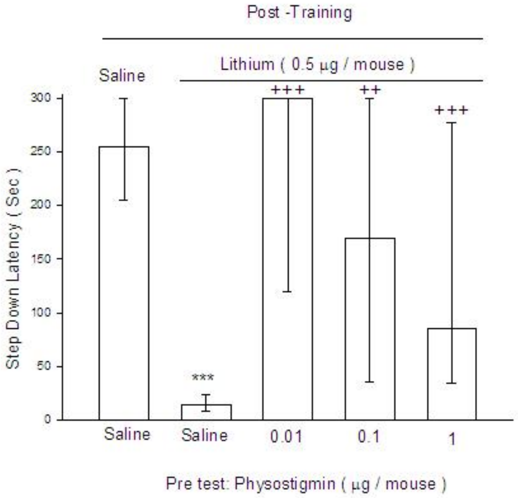

Figure 7. Effect of pretest administration of physostigmine on memory impairment induced by post-training lithium (0.5 µg/mouse, intra-CA1). Five groups of animals were used. One group of animals received post-training and prerest saline administration. The other four groups received post-training administration of lithium (0.5 µg/mouse, intra-CA1). On the test day these animals received saline or different doses of physostigmine (0.01, 0.1, and 1 µg/mouse, intra-CA1) five minutes before the test. Each bar represents median and inter-quartile ranges for 10 animals. ***$P<0.001$ compared with saline-saline group, ++$P<0.01$, +++$P<0.001$ compared with lithium-saline group.

phenomenon, the retrieval of an engram from memory requires that the organism be in a state that is similar to that in which the engram was initially acquired.[42–44] A variety of drugs, including opioids have shown to elicit state-dependent learning.[43] We have also shown this phenomenon with lithium in our previous studies.[18,19]

Lithium can regulate signal transduction pathways in several regions of the rat brain, and alter the function of different neurotransmitter systems.[20,45] Previously we have shown a cross state-dependency between lithium and morphine.[18] Morphine state-dependency could also be influenced by the cholinergic system.[46] Therefore, we expected that influence on the cholinergic system may have an effect on the lithium response. As found with other neural systems, there are many changes reported in the cholinergic systems produced by lithium, but it is not clear if these alterations are direct effects and involved in the therapeutic efficacy of lithium.[22]

The central cholinergic system is involved in learning and memory.[47] The cholinergic agonists and cholinesterase-inhibitors may have beneficial effects on memory,[48] while a cholinergic antagonist scopolamine induced deficits in memory.[49] Patients with Alzheimer's disease have cognitive deficits and a consistence deficit in cholinergic neurotransmission.[50] Furthermore, a decline in the cholinergic neurons and choline acetyltransferase activity in the cerebral cortex and hippocampus have been shown in Alzheimer's disease.[51] Furthermore, involvement of cholinergic function in inhibitory avoidance memory processes has been suggested in our previous studies.[46] In the present study, post-training intra-CA1 injection of the muscarinic receptor antagonist scopolamine impaired memory retrieval when the test was performed 24 hours later. This is in agreement with other data indicating amnesia caused by the drug.[49]

The amnesia induced by post-training administration of scopolamine was reversed by the drug, showing a possible state-dependent learning that has been shown for the drug earlier.[43] In addition, pretest administration of scopolamine reverses the decrease in the step-down latency induced by post-training lithium administration and also pretest lithium restored amnesia induced by post-training scopolamine. These effects may indicate a cross state-dependent learning between the two drugs.

In the present study, in the animals which were under post-training treatment with lithium, pretest injections of anticholinesterase physostigmine prevented the decrease in step-down latency on the test day. Since pretest co-administration of a low dose of scopolamine with the low doses of lithium failed to show any potentiation, one may conclude that the involvement of the cholinergic mechanism(s) in the lithium state-dependent learning seems indirect or unlikely.

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