Original Article

Involvement of cholinergic system in state-dependent learning induced by lithium in mice

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Objective: The influence of cholinergic drugs on lithium-induced state-dependent learning has been investigated in adult male mice.
Method: A single-trial step-down inhibitory avoidance task was selected. The drugs used in the study were lithium chloride physostigmine , nicotine hydrogen tartrate and scopolamine hydrobromide, atropine sulphate. The drugs were administrated through the peritoneal route. Control animals received saline or respective vehicle for nicotine. Ten animals were used in each experimental group. on day 1 or training session, the animals being trained in the step-down inhibitory avoidance task, and then immediately received post-training treatment of lithium or atropine or scopolamine. On day 2 or testing session, the animals firstly received pre-test administration of drugs (for nicotine 30 min, for lithium 45 min and for cholinergic antagonists 60 min before the test), and then were tested for step-down latency.
Results: The results showed that post-training and pre-test intraperitoneal (i.p.) administration of lithium (10 mg/kg) induced state-dependent learning. In addition, pre-test administration of an anticholinesterase, physostigmine (0.3 and 0.6 mg/kg, i.p.) and nicotinic acetylcholine receptor agonist, nicotine (0.1 and 0.5 mg/kg) could substitute for pre-test lithium. Pre-test co-administration of an ineffective dose of physostigmine (0.1 mg/kg) but not nicotine (0.01 mg/kg), with lower doses of lithium (2.5 and 5 mg/kg) potentiated the effect of the latter drug on step-down latency. Post-training administration of a nonselective antagonist of muscarinic acetylcholine receptors, atropine, decreased the step-down latency, but pre-test administration of the same dose of the drug and also lithium, could not reverse the decrease of step-down latency. On the other hand, pre-test atropine at higher doses (0.3 and 0.6 mg/kg) disrupted lithium-induced state-dependent learning. On the contrary, the decrease of step-down latency due to post-training administration of another nonselective muscarinic antagonist, scopolamine (1 mg/kg, i.p.) reversed by pre-test administration of not only the same dose of the drug, but also lithium (10 mg/kg). Interestingly, pre-test administration of scopolamine (1 mg/kg) also reversed the decrease of step-down latency induced by post-training lithium (10 mg/kg).
Conclusion: cholinergic system(s) may be involved in the lithium-induced state-dependent learning and the involvement of muscarinic receptors is more possible than nicotinic ones.

Keywords*: Atropine, Learning, Lithium chloridel, Mice, Nicotine, Physostigmine, Scopolamine*

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Although, lithium has been used as an important mood stabilizing agent in the treatment of bipolar mood disorders (1, 2), a neuroprotective role (3), and an antiapoptotic effect for lithium (4, 5) have also been reported. Animal studies may also suggest to investigate lithium effect in the treatment of drug addiction (6, 7). However, the drug's side effects can not be tolerated by many patients (8). Lithium's primary effects on memory in general are debatable. In particular, inhibition of learning, memory, and speed of information processing in patients with bipolar disorders and to some extent in control subjects has been reported (9-12). On the contrary, it has been shown that lithium enhances memory in some tasks (13), or attenuates memory impairments induced by other factors (14).

Brain cholinergic systems are thought to play an important role in memory function and mood regulation (15-19). Moreover, deterioration of the cholinergic system also contributes to memory failure and cognitive decline associated with aging (20, 21). It has also been hypothesized that dysfunction of many neurotransmitter systems including the cholinergic system is involved in bipolar disorder (22, 23). The

effects of mood stabilizers, especially lithium, on neurotransmitters and second messenger systems have been extensively investigated (16, 17, 24-27). As found with other neural systems, there are many reported changes 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 (19).

We have shown in our previous studies that lithium (10 mg/kg) induced state-dependent learning, and the involvement of different mechanisms in this process have been investigated (28-31). Considering the involvement of cholinergic systems in some responses induced by lithium, in the present study the effect of cholinergic agents on retrieval of the state-dependent learning induced by lithium was investigated.

Materials and Method

Animals

Male albino Naval Medical Research Institute (NMRI) mice weighing 22–30 g were used. The animals were maintained under a 12/12-h light–dark cycle (light beginning at 7 a.m.) and in a controlled temperature (22±2 °C), with *ad libitum* access to food and water. Ten animals were housed per cage and used in each experiment. Each animal was used once. All procedures were carried out in accordance with institutional guidelines for animal care and use.

Inhibitory avoidance task

The inhibitory (passive) avoidance apparatus consisted of a wooden box (30×30×40 cm^3) with steel-rod floor (29 parallel rods, 0.3 cm in diameter set 1 cm apart). A wooden platform (4×4×4 cm^3) was placed in the center of the grid floor. Electric shocks (1 Hz, 0.5 sec and 50 V DC) were delivered to the grid floor by an isolated stimulator (Grass S44, West Warnick, RI,USA).

In the training session, animals were gently placed on the wooden platform and their latencies to step down on the grid floor with all four paws were recorded. Immediately after stepping down on the grid, each animal received an electric shock continuously for 15 s. Retention test session was carried out 24 h after training session and was procedurally identical to it, except that no shock was given. After each test, the apparatus was cleaned by cotton embedded in saline. Step-down latency was used as an indication of inhibitory avoidance memory retention. An upper cut-off time of 300 s was set. The training and testing sessions were carried out between 8:00 a.m. and 2:00 p.m.

Drugs

The drugs used in the study were lithium chloride (LiCl; Merck, Germany), physostigmine (Sigma-Aldrich Co. Ltd, Gillingham, England), nicotine hydrogen tartrate and scopolamine hydrobromide (Sigma Cookson Ltd. UK), atropine sulphate (Sina-Daru Pharmaceutical Co. Ltd. Tehran, Iran). All drugs were dissolved in sterile saline except nicotine which was dissolved in sterile saline and then the pH of the solution was adjusted to 7.2 with NaOH (0.1 normal solution). The drugs were administrated through the peritoneal (i.p.) route. Control animals received saline or respective vehicle for nicotine.

Experimental design

Ten animals were used in each experimental group. For intraperitoneal (i.p.) injections the doses were adjusted so that each animal received a volume of at most 10 ml/kg. The protocol and time of drug administration used were as following schematic diagram i.e. on day 1 or training session, the animals being trained in the step-down inhibitory avoidance task, and then immediately received post-training treatment of lithium or atropine or scopolamine. On day 2 or testing session, the animals firstly received pre-test administration of drugs (for nicotine 30 min, for lithium 45 min and for cholinergic antagonists 60 min before the test), and then were tested for step-down latency. We have used this protocol in our previous studies (29-31).

Experiment 1

This experiment examined effects of pre-test lithium, anticholinesterase physostigmine and nicotinic acetylcholine receptor agonist, nicotine on the decrease of step-down latency induced by post-training lithium. In this experiment, 11 groups of animals were used. One group of animals as control received both post-training and pre-test injections of saline (10 ml/kg). The other ten groups of animals received lithium (10 mg/kg) after training, and on the test day four groups of them received saline or lithium (2.5, 5 and 10 mg/kg), the other three groups received physostigmine (0.1, 0.3 and 0.6 mg/kg), and the last three groups received nicotine (0.01, 0.1 and 0.5 mg/kg) before the test.

Experiment 2

In experiment 2, effects of pre-test co-administration of an ineffective dose of physostigmine or nicotine with lower doses of lithium on the decrease of step-down latency induced by post-training lithium were evaluated. Thirteen groups of animals were used. One group of animals received injections of saline (10 ml/kg) both post-training and pre-test. The other twelve groups of animals received lithium (10 mg/kg) after training, and on the test day these animals in three sets of four groups received saline or lithium (1.25, 2.5 and 5 mg/kg) plus saline (10 ml/kg) or physostigmine (0.1 mg/kg) or nicotine (0.01 mg/kg) before testing.

Experiment 3

In this experiment twelve groups of animals were divided in two sets of six groups. In the first set, one group received injections of saline (10 ml/kg) both post-training and pre-test. The other five groups received muscarinic cholinergic antagonist, atropine (0.1 mg/kg) after training. On the test day, one group of these animals received saline, one group received

atropine (0.1 mg/kg), and the other three groups received lithium (2.5, 5 and 10 mg/kg) before the test. In the second set of animals, one group received injections of saline (10 ml/kg) both post-training and pre-test. The other five groups received lithium (10 mg/kg) after training. On the test day, one group of these animals received saline, one group received lithium (10 mg/kg), and the other three groups received lithium (10 mg/kg) plus atropine (0.1, 0.3 and 0.6 mg/kg) before the test.

Experiment 4

In this experiment, seven groups of animals were used. One group of the animals received injections of saline (10 ml/kg) both post-training and pre-test. Three groups of animals received injections of a muscarinic cholinergic antagonist, scopolamine (1 mg/kg) after training, and on the test day they received saline or scopolamine (1 mg/kg) or lithium (10 mg/kg) before testing. The other three groups received lithium (10 mg/kg) after training, and they received saline or lithium (10 mg/kg) or scopolamine (1 mg/kg) before testing.

Data analysis

Because of individual variations, the data were analyzed using the Kruskal–Wallis nonparametric one-way analysis of variance (ANOVA) followed by a two-tailed Mann–Whitney's 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±quartile ranges. In all statistical evaluations $p<0.05$ was used as the criterion for statistical significance.

Results

Effect of pre-test lithium, physostigmine and nicotine on the decrease of step-down latency induced by post-training lithium

The result of experiment 1 showed that post-training lithium (10 mg/kg) decreased step-down latency on the test day, and pre-test administration of not only lithium, but also physostigmine and nicotine reversed the decrease of step-down latency induced by post-training lithium (Kruskal–Wallis non-parametric ANOVA, $H(10)=59.39$, $P<0.001$). Post hoc analysis by Mann-Whitney's U-test indicated that lithium at doses of 5 and 10 mg/kg partly or fully reversed the decrease of step-down latency induced by post-training lithium (10 mg/kg), indicating state-dependent learning. Interestingly, physostigmine at doses of 0.3 and 0.6 mg/kg, and nicotine at doses of 0.1 and 0.5 mg/kg, could mimic the effect of pre-test lithium (Fig. 1).

Effects of pre-test co-administration of an ineffective dose of physostigmine or nicotine with lower doses of lithium on the decrease of step-down latency due to lithium given after training

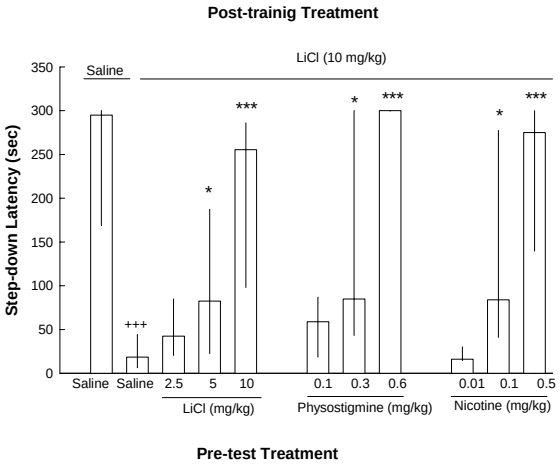

Figure1. The effects of pre-test lithium, physostigmine and nicotine on the decrease of step-down latency induced by post-training lithium. One group of animals received injections of saline (10 ml/kg) both post-training and pre-test. Ten groups of animals received lithium (10 mg/kg) after training, and on the test day, four groups received saline or lithium (2.5, 5 and 10 mg/kg), the other three groups received physostigmine (0.1, 0.3 and 0.6 mg/kg), and the last three groups received nicotine (0.01, 0.1 and 0.5 mg/kg) before the test. Each value represents the median±quartiles for 10 animals. +++P<0.001 compared to saline-saline group. *P<0.05 and ***P<0.001 compared to lithium-saline group.

The results of experiment 2 indicated that in the animals which received post-training lithium (10 mg/kg), the pre-test co-administration of the ineffective dose of physostigmine (0.1 mg/kg) with lower doses of lithium (1.25, 25 and 5 mg/kg) altered step-down latency (Kruskal–Wallis ANOVA, $H(8)=45.55$, $P<0.001$). Post hoc analysis revealed that physostigmine (0.1 mg/kg) in combination with lithium (25 and 5 mg/kg) increased the step-down latency on the test day (Fig. 2).

On the contrary, the ineffective dose of nicotine (0.01 mg/kg) did not alter the effect of lower doses of lithium before the test on step-down latency (data not shown).

Effects of post-training and pre-test administration of atropine on step-down latency and evaluation of its cross-effect with lithium.

The results of experiment 3 showed that there was a significant decrease of step-down latency due to post-training administration of atropine (Kruskal–Wallis ANOVA, $H(5) = 18.56$, $P<0.01$). Post hoc analysis by Mann-Whitney's U-test indicated that post-training injection of atropine (0.1 mg/kg) decreased step-down latency on the test day, and administration of neither the same dose of atropine nor lithium (2.5, 5 and 10 mg/kg) reversed the effect of post-training atropine.

On the other hand, pre-test administration of atropine at

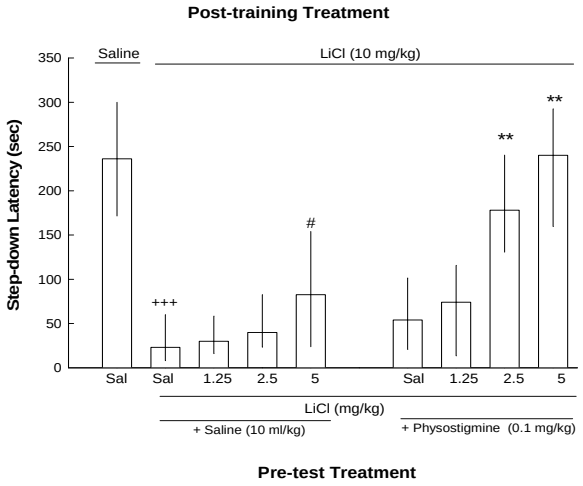

Figure 2. The effects of pre-test co-administration of an ineffective dose of physostigmine with lower doses of lithium on the decrease of step-down latency induced by post-training lithium. The control group received injections of saline (10 ml/kg) both post-training and pre-test. The other eight groups of animals received lithium (10 mg/kg) after training, and on the test day in two sets of four groups they received saline or lithium (1.25, 2.5 and 5 mg/kg) plus saline (10 ml/kg) or physostigmine (0.1 mg/kg). Each value represents the median±quartiles for 10 animals. +++*P*<0.001 compared to saline-saline group. #*P*< 0.05 compared to lithium-saline group. ***P* < 0.01 compared to lithium-(saline+physostigmine) group.

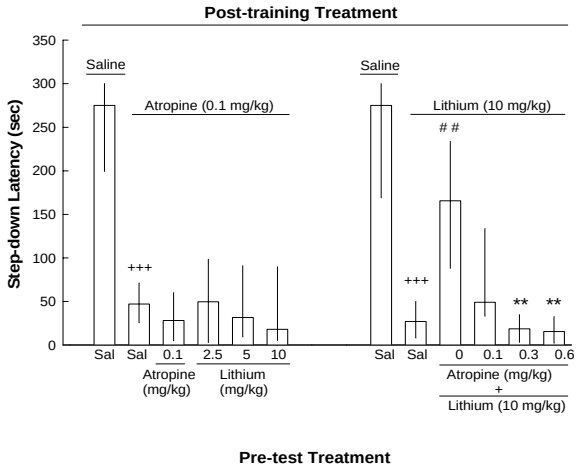

Figure 3. The effects of post-training and pre-test atropine on step-down latency on the test day and its interaction with lithium-induced state-dependent learning. In two sets of six groups of animals, one group received injections of saline (10 ml/kg) both post-training and pre-test. The other five groups in the first set received atropine (0.1 mg/kg) after training, and on the test day, they received saline, atropine (0.1 mg/kg) and lithium (1.25, 2.5 and 5 mg/kg) before the test. In the second set of animals, five groups received lithium (10 mg/kg) after training, and on the test day, they received saline, lithium (10 mg/kg), and the other three groups received lithium (10 mg/kg) plus atropine (0.1, 0.3 and 0.6 mg/kg) before the test. Each value represents the median±quartiles for 10 animals. +++P<0.001 compared to saline-saline group. ##P<0.01 compared to lithium-saline group, and **P<0.01 compared to lithium-(lithium+saline) group.

doses of 0.3 and 0.6 mg/kg disrupted the state-dependent learning induced by lithium 10 mg/kg (Kruskal–Wallis ANOVA, H(5)=32.85, P<0.001) (Fig. 3).

Effects of post-training scopolamine on the step-down latency and evaluation of its cross-effect with lithium

The results of experiment 4 indicated that in the animals which received post-training scopolamine, decreased the step-down latency on the test day (Kruskal–Wallis ANOVA, H (6)=37.89, P<0.001). Post hoc analysis indicated that scopolamine (1 mg/kg) decreased step-down latency on the test day, which reversed by pre-test administration of the same dose of scopolamine (partly) and lithium 10 mg/kg (almost fully). On the other hand, pre-test administration of lithium (10 mg/kg) and scopolamine (1mg/kg) reversed the decrease of step-down latency induced by post-training lithium (Fig. 4).

Discussion

Consistent with our previous studies (29, 30), the present data show that post-training administration of lithium decreased step-down latency of inhibitory avoidance task in mice, which was fully or partly reversed by pre-test administration of the drug. This effect of lithium on inhibitory avoidance memory seems to be due to state-dependent learning (29-31). In state-dependent learning when pre- or post-training administration of a drug decreases memory for a task, administration of the drug prior to testing reinstates the memory for the task (32, 33).

Accumulated data has been shown that memory impairment in several tasks, including inhibitory avoidance tasks, by pre- or post-training administration of some drugs and hormones could be reversed by their administration before testing (34-38). With the idea of state-dependent learning, the decrease of step-down latency in animals which received post-training lithiumand pre-test saline may not to be due to impairment of memory by lithium but rather the animals are not in the 'lithium state' when the retrieval test is done. However, the exact mechanism of state-dependent learning induced by drugs including lithium will require more investigations.

Previously, we have shown that cholinergic function is involved in inhibitory avoidance memory processes and morphine-induced state-dependent learning (39). We have also shown cross state-dependene between lithium and morphine (40). Therefore, we expected that cholinergic system(s) may also influence lithium-induced state-dependent learning .

The present results show that in the animals which were under post-training treatment of lithium, pre-test injections of an anticholinesterase, physostigmine and nicotinic acetylcholine receptor agonist, nicotine reversed the decrease in step-down latency induced by post-training lithium. Interestingly, pre-test co-administration of an ineffective dose of physostigmine with the lower doses of lithium potentiated the effect of pre-test lithium on step-down latency.

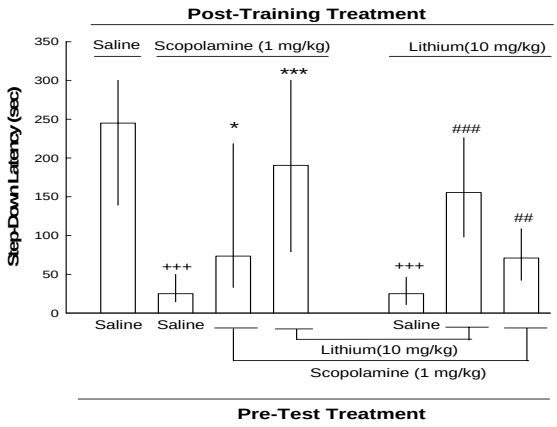

Figure 4. The effects of post-training and pre-test administration of scopolamine on step-down latency on the test day and its interaction with lithium-induced state-dependent learning. Seven groups of animals were used. One group of the animals received injections of saline (10 ml/kg) both post-training and pre-test. Three groups of animals received injections of scopolamine (1 mg/kg) after training, and on the test day they received saline or scopolamine (1 mg/kg) or lithium (10 mg/kg) before testing. The other three groups received lithium (10 mg/kg) after training, and they received saline or lithium (10 mg/kg) or scopolamine (1 mg/kg) before testing. Each value represents the median±quartiles for 10 animals. +++*P*<0.001 compared to saline-saline group. **P*<0.05, ****P*<0.001 compared to scopolamine-saline group. ##*P*<0.01 and ###*P*<0.001 compared to lithium-saline group.

It has been shown that pre-test administration of physostigmine and nicotine improved state-dependent retrieval of ethanol and morphine (41, 42). Improvement of cognitive and memory dysfunctions have also been reported in other investigation (43, 44). The potentiation effect of pre-test physostigmine on lithium response may support the involvement of cholinergic mechanism(s) in state-dependent learning induced by lithium .

On the contrary, pre-test co-administration of an ineffective dose of nicotine with lower doses of lithium had no effect on step-down latency on the test day. Therefore, it seems that in the present study nicotine had no interaction with lithium response on the test day. It has been revealed that neuronal nicotinic systems play an important role in learning, memory, and cognition (45). Therefore, improvement of state-dependent retrieval by nicotine may be mediated through its effects on cognition and attention not a direct interaction with lithium effect. Thus, in the last of the study we examined the effects of blockade of muscarinic cholinergic receptors on state-dependent learning induced by lithium.

Our present data indicate that post-training administration of a nonselective antagonist of muscarinic acetylcholine receptors, atropine, decreased the step-down latency on the test day. Furthermore, the same dose of atropine could not reverse the decrease of step-down latency and did not show state-dependent learning. In addition, lithium caused also no change in the decrease of step-down latency induced by post-training atropine. On the other hand, pre-test co-administration of atropine with lithium prevented the response of the effective dose of lithium. One may propose that the decrease of step-down latency due to atropine or lithium administration results from different mechanism(s), and the disruption effect of atropine on lithium may be due to its impairing effects on memory (41, 42).

The present results also show that post-training administration of another nonselective muscarinic antagonist, scopolamine decreased the step-down latency on the test day which was partly reversed by the pre-test administration of the drug, suggesting state-dependent learning induced by scopolamine. In support of our results, it has been shown that post-training administration of scopolamine induced amnesia in a passive avoidance task (46, 47), and state-dependent learning was also observed by scopolamine (48). Furthermore, the present data show that there was cross state-dependent retrieval of memory which acquired under post-training treatment of lithium or scopolamine. Therefore, it can further be supported that the muscarinic cholinergic receptors may be involved in the state-dependent learning induced by lithium. But, the difference which was observed between responses of atropine and scopolamine in the present study is not clear and will require more investigations.

In conclusion, it can be suggested that cholinergic receptor stimulation by physostigmine or nicotine has an influence on state-dependent learning induced by lithium, but their influence on lithium effects seems to be mediated through different mechanisms. Blockade of the muscarinic acetylcholine receptors by atropine and scopolamine showed the involvement of muscarinic acetylcholine receptors in lithium-induced state-dependent learning, but mechanisms of their effects needs more investigations.

Acknowledgments

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