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Repeated administrations of dopamine receptor agents affect lithium-induced state-dependent learning in mice

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Abstract

The influence of repeated administration of dopamine receptor agents on the effect of lithium on lithium-induced state-dependent learning was examined in mice. Immediate post-training intraperitoneal (i.p.) administrations of lithium (10 and 20 m/kg) decreased the step-down latency of a single-trial inhibitory avoidance task. This was fully or partly reversed by pre-test administration of the same doses of the drug, with maximum response at the dose of 10 mg/kg, suggesting state-dependent learning was induced by lithium. Here, it has also been shown that repeated intracerebroventricular administrations of a mixed D1/D2 dopamine receptors agonist apomorphine (once daily injections of 0.5 μg/mouse for three consecutive days followed by five days of no drug treatment) increased the effect of lower doses of pre-test lithium (1.25, 2.5 and 5 mg/kg, i.p.) on the reinstatement of the step-down latency decreased by post-training lithium (10 mg/kg). On the contrary, not only repeated administrations of the dopamine D1 receptor antagonist SCH 23390 (0.5 and 1 μg/mouse) but also the dopamine D2 receptor antagonist sulpiride (0.3 and 1 μg/mouse) disrupted the state-dependent learning induced by lithium. These results suggest that state-dependent learning induced by lithium may be altered by repeated pretreatment of dopamine receptor agents.

Key words
apomorphine; lithium; memory; mouse; SCH23390; sulpiride

Introduction

Lithium has been accepted as an important mood-stabilising agent in the treatment of bipolar mood disorder (Bone, et al., 1980), though the drug treatment inhibited learning, memory and speed of information processing in patients with bipolar disorder and to some extent in control subjects (Honig, et al., 1999; Kocsis, et al., 1993; Pachet and Wisniewski, 2003; Stip, et al., 2000). However, the definitive mechanism(s) for the effect of drug has not been established.

Although much data indicate the involvement of serotonin and noradrenaline in the pathogenesis of mood disorders, the role of dopamine cannot be overlooked (Brugue and Vieta, 2007). The findings on dopamine in mood disorders suggest that a decreased dopamine activity is involved in depression, whereas increased dopamine function contributes to mania (Diehl and Gershon, 1992). The lithium efficacy in controlling behaviours related to dopamine stimulants and manic states has also been proposed (Barnes, et al., 1986; van Kammen, et al., 1985). Thus, lithium’s action may be mediated at least partly through the dopamine receptors (Acquas and Fibiger, 1996; Carli, et al., 1997; Gottberg, et al., 1989; Gottberg, et al., 1988). Considering the above-cited data, it is also logical to suggest that the dopamine receptors to be involved in the effects of lithium on memory.

State-dependent learning is a phenomenon in which the retrieval of memory of newly acquired information requires that the organism be in a state similar to that in which the information was initially acquired (Carlezon, et al., 1995; Colpaert, 1990; Shulz, et al., 2000). This phenomenon was firstly described in 1978 and has been shown with different drugs including adreno-corticotropic hormone , epinephrine and opioids (Bruins Slot...
and Colpaert, 1999a,b; Izquierdo and Dias, 1983a,b; Izquierdo, et al., 1984; Zornetzer, 1978). We have also reported this phenomenon with morphine and lithium in our previous studies (Khavandgar, et al., 2002; Khavandgar, et al., 2003; Zarrindast, et al., 2006a,c; Zarrindast, et al., 2005).

In our previous studies, we found that morphine-induced state-dependent learning was enhanced by repeated administrations of morphine (Zarrindast and Rezayof, 2004). Repeated morphine administration reportedly induces locomotor sensitisation through enhancement of the dopamine D1 and D2 receptor function (Jeziorski and White, 1995; Serrano, et al., 2002) and has been shown to increase the dopamine D2 receptor mRNA (Heidari, et al., 2006). This evidence suggests that the enhancement of state-dependent learning by repeated administrations of morphine may involve changes in dopamine receptor function. Interestingly, we have found that there is a cross-state dependency between lithium and morphine in an inhibitory avoidance task (Zarrindast, et al., 2006c), suggesting that lithium may act via similar mechanisms to morphine.

Therefore, the aim of the present study was to investigate the effects of repeated pretreatment with the dopamine receptor agents and possible subsequent changes in the dopamine receptors sensitivity on lithium-induced state-dependent learning.

Materials and methods

Animals

Male albino Naval Medical Research Institute (NMRI) mice weighing 18–23 g, at the time of surgery, were used. The animals were maintained under a 12/12-h of light-dark cycle (light beginning at 7:00 a.m.) and in a controlled temperature (22 ± 2°C). They had ad libitum access to food and water. The animals were housed 10 per cage. Ten animals were used in each experimental group. Each animal was used once. All procedures were performed in accordance with institutional guidelines for animal care and use.

Surgery

The animals were anesthetised with a mixture of ketamine- xylazine (100 mg/kg–10 mg/kg, respectively) and placed in a stereotaxic apparatus. A middle incision was made in the scalp, and underlying connective tissue and periosteum were removed. Then, a 22-gauge stainless steel guide cannula was implanted until 0.5 mm above the right lateral ventricle to prevent damage to the ventricle before the intracerebroventricular (i.c.v.) injections and then anchored to the skull by dental cement. The coordinates were 0.9 mm posterior to the bregma, 1.5 mm lateral to the midline and 2 mm below the top of the skull. A stylet was inserted into the cannula to keep it patent prior to injections. The surgery was performed five days before the repeated drug administrations. After the surgery until recovery from the anesthesia, each animal was housed in a clean box under a 100 W electric bulb to maintain body temperature, and then they were returned to their home cage.

Drugs

The drugs used in this study were lithium chloride (Merck, Darmstadt, Germany), apomorphine hydrochloride (Sigma, Poole, UK), SCH 23390 (R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride), sulpiride (Sigma, St Louis, California, USA). All drugs were dissolved in sterile 0.9% saline just before the experiments except for sulpiride, which was dissolved in one drop of glacial acetic acid and made up to a volume of 2 mL with sterile 0.9% saline and then was diluted to a required volume.

Intracerebroventricular injections

Following recovery from the surgery (five days after surgery), repeated administrations of the drugs were performed. The dopaminergic agents were injected into the lateral ventricle for three consecutive days (days 1–3) followed by five days (days 4–8) of no drug treatment. For i.c.v. drug administration, each animal was gently restrained by hand, and the stylet was withdrawn from the guide cannula. Then, a 27-gauge injection needle, which was attached with a polyethylene tube to a 5-μL Hamilton syringe, was inserted into the guide cannula. The injection solution was administered in a total volume of 2 μL per mouse during 60 s injection time followed by an additional 60 s to facilitate diffusion of the drugs into the cerebral ventricle.

Inhibitory avoidance task

The inhibitory avoidance apparatus was a (30 × 30 × 40 cm³) plexiglas box. The floor of which consisted of parallel stainless steel bars (0.3 cm diameter spaced 1 cm apart). A wooden platform (4 × 4 × 4 cm³) was placed on the centre of the grid floor; this means a 4 × 4 cm² platform, 4 cm off the floor.

In the training session, each animal was placed on the platform, and its latency to step down on the grid floor with all four paws was recorded. Immediately after stepping down on the grid floor, the animal received an electric shock (1 Hz, 0.5 s, 45 v DC) continuously for 15 s. The shock was delivered to the grid floor by an isolated stimulator (Grass S44, West Warnick, RI, USA). Because pre-training administration of drugs may influence the animal sensitivity to shock or the degree of arousal during the original training rather than by directly modifying memory storage processes (Castellano, et al., 2001), thus lithium was administered after training in the present study.

The retention test session was carried out 24 h after the training and was procedurally identical to the training except that no shock was given. The step-down latency for each animal was used as a measure of inhibitory avoidance memory.
An upper cut-off time of 300 s was set. The training and testing sessions were performed between 8:00 a.m. and 2:00 p.m.

**Drug treatment**

Ten animals were used in each experimental group. Apomorphine, SCH 23390 and sulpiride were infused through i.c.v. route for three consecutive days followed by five days washout. We have used this schedule of repeated administrations for some other drugs such as morphine and the dopamine receptors agents (Zarrindast, et al., 2006d), and changes in the expression of the dopamine D2 receptor mRNA in the brain was detected, suggesting receptor sensitisation (Heidari, et al., 2006). In the animals those did not receive repeated administrations of drugs, the inhibitory avoidance test was performed following recovery from the surgery, but in those with repeated administrations of drugs, the inhibitory avoidance test was carried out after 5 days washout period. Post-training and pre-test injections were given through intraperitoneal route (i.p.) immediately after training and 45 min before testing, respectively.

**Experiment 1** This experiment examined the effect of post-training lithium on the step-down latency when tested 24 h later. One group of animals received injections of both post-training and pre-test saline (10 mL/kg). The other groups of animals received post-training lithium (5, 10 and 20 mg/kg) and pre-test saline (10 mL/kg).

**Experiment 2** This experiment examined lithium state-dependent learning. One group of animals received injections of both post-training and pre-test saline (10 mL/kg). The other groups received lithium (10 mg/kg) after training and saline or different doses of lithium (5, 10 and 20 mg/kg) prior to the test.

**Experiment 3** This experiment examined the effect of repeated administrations of apomorphine on the effect of lithium on the inhibitory avoidance memory. One group of animals received injections of both post-training and pre-test saline (10 mL/kg). Four groups of the animals received repeated administrations of saline (2 μL/mouse) as control, and the other four groups received apomorphine (0.5 μg/mouse). On the training day, all of these animals received post-training lithium (10 mg/kg), and they received saline or lower doses of lithium (1.25, 2.5 and 5 mg/kg) before testing.

**Experiment 4** This experiment examined the effect of repeated administrations of the dopamine receptor antagonists on state-dependent learning induced by lithium. One group of animals received injections of both post-training and pre-test saline (10 mL/kg). Two groups of animals received lithium (10 mg/kg) after training and saline or lithium (10 mg/kg) before testing. Other groups of animals with repeated administrations of either SCH23390 (0.25, 0.5 and 1 μg/mouse) or sulpiride (0.1, 0.3 and 1 μg/mouse) received injections of both post-training and pre-test lithium (10 mg/kg). We have also used these doses of the drugs in our previous studies (Zarrindast, et al., 2006b).

**Statistical analysis**

Because of the large individual variations, the data were analyzed by using the Kruskal–Wallis nonparametric one-way analysis of variance (ANOVA) followed by a two-tailed Mann–Whitney U-test. The Holmes–Bonferroni Correction test was used for the paired comparisons. The step-down latencies on the test day for 10 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**

**Effects of post-training and pre-test lithium on the step-down latency on the test day**

The result of experiment 1 showed that post-training administration of lithium altered the step-down latency on the test day [Kruskal–Wallis nonparametric ANOVA, H(3) = 14.27, P < 0.01]. Post hoc analysis by Mann-Whitney U-test indicated that lithium at the doses of 10 and 20 mg/kg decreased the step-down latency on the test day (Figure 1).

The result of experiment 2 showed that pre-test administration of lithium reversed the decrease in the step-down latency induced by post-training lithium [Kruskal–Wallis nonparametric ANOVA, H(4) = 18.45, P < 0.01 (Figure 2)].

**Influence of repeated administrations of the D1/D2 dopamine receptor agonist apomorphine on lithium-induced state-dependent learning**

As shown in Figure 3, repeated injection of apomorphine appears to have sensitised the animals to the pre-test doses of lithium so that the lower doses (1.25, 2.5 and 5 mg/kg) of pre-test lithium substitute partly or fully for 10 mg/kg post-training lithium [Kruskal–Wallis ANOVA, H(8) = 41.79, P < 0.001].

**Influence of repeated administration of selective D1 and D2 dopamine receptor antagonists on lithium-induced state-dependent learning**

The results of experiment 4 indicated that repeated pretreatment with SCH 23390 or sulpiride significantly disrupted state-dependent learning induced by lithium [Kruskal–Wallis ANOVA, H(8) = 39.7, P < 0.001]. Thus, whilst in animals those were given both post-training and pre-test lithium but no i.c.v. injection, the median step-down latency was 130 s, and in animals those had received i.c.v. SCH 23390, the step-down latency was markedly and dose dependently reduced. A similar
pattern was seen in animals those received i.c.v. sulpiride (Figure 4).

Discussion

Pharmacological studies of memory usually involve training animals, such as mice, in simple learning tasks and testing their memory in a day or so later (McGaugh and Izquierdo, 2000). In the step-down model of an inhibitory avoidance task, animals learn that stepping down from a platform is followed by a footshock, and on subsequent exposures to the task, they will stay much longer on the safe platform before eventually stepping down (Izquierdo and McGaugh, 2000; Izquierdo and Medina, 1997). The testing session in an inhibitory avoidance task should be in the same state as the training session, thus a state-dependent learning may be involved in the learning of the task.

The findings of the present study are, first, post-training administration of lithium decreased the step-down latency on the test day, which was fully or partly reversed by pre-test administra-
that encoded in a ‘saline state’ had poor retrieval when in the ‘lithium state’. However, the exact mechanism of state-dependent learning induced by drugs, including lithium, has not been fully elucidated and will require more investigations.

It has been suggested that a component of the anti-manic effect of lithium may be its ability to decrease the dopamine release in the nucleus accumbens (Ichikawa, et al., 2005). Given that repeated administrations of drugs affect animal’s behaviours through changes in the receptor sensitivity, the present study was designed to investigate whether repeated intracerebroventricular administrations of the dopamine receptor agents affect lithium-induced state-dependency.

The present results showed that repeated administrations of apomorphine (a mixed D1/D2 dopamine receptors agonist), compared with saline, improved retrieval of inhibitory avoidance memory by pre-test administration of lower doses of lithium. One may propose that repeated administrations of apomorphine have influenced the dopamine receptor sensitivity and thereby affected the changes in the step-down latency induced by lithium. Therefore, the involvement of a dopaminergic mechanism in state-dependent learning induced by lithium may be suggested.

Other studies have also reported the interactions between lithium and apomorphine in different methods. For example, apomorphine inhibited passive avoidance retention when given during training or in a defined 10–12 h post-training period (Doyle, et al., 1996). However, chronic lithium treatments in rats decreased yawning (Sharifzadeh, et al., 2000) and sniffing behaviour induced by apomorphine (Fazli-Tabaei, et al., 2002).

Lithium also reversed the disruption of prepulse inhibition through the apomorphine (Umeda, et al., 2006).

The present results also indicated that repeated pretreatment with the dopamine D1 receptor antagonist SCH23390 or the dopamine D2 receptor antagonist sulpiride disrupted the state-dependent learning induced by lithium. Therefore, both the dopamine D1 and D2 receptor mechanisms may be involved in the state-dependent learning induced by lithium in the inhibitory avoidance task. However, more experiments will require to determine the exact mechanisms.

It has also been reported that the dopamine D1 and D2 receptor antagonist injections in the prefrontal cortex selectively impaired spatial learning in mice (Rinaldi, et al., 2007). Immediate and long-term memories were also inhibited by injections of SCH 23390 into the prefrontal cortex (Izquierdo, et al., 2007). It has been indicated that pre-trial intra nucleus accumbens administration of the SCH 23390 impaired acquisition of a lever-pressing response (Hernandez, et al., 2005). Bilateral microinjections of sulpiride into the medial prefrontal cortex 30 min before the administration of corticosterone attenuated the glucocorticoid-induced impairment of memory retrieval (Pakdel and Rashidy-Pour, 2007).

An overall interpretation of the data is that repeated administrations of apomorphine shift the lithium dose response to the left, whereas both the dopamine D1 and D2 receptor antagonists shift the lithium dose response to the right. It can be concluded that the repeated schedule of administration of the dopamine receptor agents may well interfere with whatever that lithium

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**Figure 4** The influence of repeated administrations of selective dopamine receptor antagonists on lithium-induced state-dependent learning. One group of animals received injections of both post-training and pre-test saline (10 mL/kg). Two groups of animals received lithium (10 mg/kg) after training, and saline or lithium (10 mg/kg) before testing. Other groups of animals with repeated administrations of either SCH23390 (0.25, 0.5 and 1 μg/mouse) or sulpiride (0.1, 0.3 and 1 μg/mouse), received injections of both post-training and pre-test lithium (10 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 < 0.05 and **P < 0.01 compared to lithium-lithium group.

Consistent with our previous studies, the present results indicated that post-training administration of lithium decreased the step-down latency (an index of the inhibitory avoidance memory) on the test day. Interestingly, pre-test injection of the same dose of the drug compensated the decrease of the step-down latency on the test day. Our suggestion to describe the same dose of the drug compensated the decease of the memory on the test day. Interestingly, pre-test injection of the step-down latency (an index of the inhibitory avoidance dependent learning induced by lithium.

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does for acquisition, and the effect of lithium in the present study depends, at least partly, on both the dopamine D1 and D2 receptor mechanisms.

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References


