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NMDA receptor antagonists augment antidepressant-like effects of lithium in the mouse forced swimming test

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Abstract

Although there is evidence of the involvement of *N*-methyl-D-aspartate receptors (NMDAR) in the action of lithium, its role in the antidepressant effects of lithium in a behavioural model remains unclear. In this study, we evaluated the effects of NMDAR antagonists on the antidepressant-like effects of lithium in the mouse forced swimming test. Lithium (30 and 100 mg/kg, i.p.) significantly ($P < 0.01$) reduced the immobility times of mice, whereas at lower doses (5 and 10 mg/kg) had no effect. NMDA antagonists ketamine (2 and 5 mg/kg, i.p.), MK-801 (0.1 and 0.25 mg/kg, i.p.) and ifenprodil (1 and 3 mg/kg, i.p.) significantly ($P < 0.05$) decreased the immobility time. Lower doses of ketamine (0.5 and 1 mg/kg), MK-801 (0.01 and 0.05 mg/kg) and ifenprodil (0.1 and 0.5 mg/kg) had no effect. Combined treatment of subeffective doses of lithium (10 mg/kg) and ketamine (1 mg/kg), MK-801 (0.05 mg/kg) or ifenprodil (0.5 mg/kg) robustly ($P < 0.001$) exerted an antidepressant-like effect. The noneffective dose of a NMDA agonist (NMDA, 75 mg/kg, i.p.) prevented the antidepressant-like effect of lithium (30 mg/kg). None of the drugs at subactive doses or in combination with lithium had significant effect on the locomotor activity in the open field test. We for the first time suggested a role for NMDAR signalling in the antidepressant-like effects of lithium, providing a new approach for treatment of depression.

Key words

depression; forced swimming test; ifenprodil; ketamine; lithium; mice; MK-801; NMDA; *N*-methyl-D-aspartate receptor antagonists

Introduction

Lithium was first used as a mood stabiliser in the 19th century and was then rediscovered in 1949 by the Australian psychiatrist John Cade (Cade, 1949; Schou, 2001). Initially lithium was assumed to have a weak antidepressant effect, but several controlled studies have later supported its antidepressant efficacy (Bauer, *et al*., 2000; Bauer and Mitchner, 2004; Heninger, *et al*., 1983; Worrall, *et al*., 1979). Depression associated with bipolar disorder has been regarded to be more severe and difficult to treat, and lithium treatment is beneficial (Bourin and Prica, 2007; Freeman and Freeman, 2006; Mendels, *et al*., 1972). Although antidepressant effects of lithium have been more clearly demonstrated in depressed bipolar patients than in unipolar patients (Baron, *et al*., 1975; Bourin and Prica, 2007), initial open trials (Johnson, 1974; Worrall, *et al*., 1979) and double-blind controlled studies found that lithium is effective for unipolar depression as well (Bauer, *et al*., 2000; Freeman and Freeman, 2006; Goodwin, *et al*., 1972; Mendels, *et al*., 1972; Soares and Gershon, 1998). It was even found to be as effective as antidepressants (Kleindienst and Greil, 2003; Mendels, *et al*., 1972; Soares and Gershon, 1998; Worrall, *et al*., 1979). However, no definitive mechanism for the antidepressant effects of lithium has been established yet. In-vivo and in-vitro studies showed that lithium exerts multiple effects on neurotransmitter/receptor-mediated signalling, ion transport, signal transduction cascades, hormonal and circadian regulation and gene expression (for a review, see Jope, 1999, 2003; Quiroz, *et al*., 2004). In recent years, some investigators have shown that glutamatergic *N*-methyl-D-aspartate (NMDA) receptor signalling could be a target for the action of lithium (Basselin, *et al*., 2006; Hashimoto, *et al*., 2002; Ma and Zhang, 2003; Ma, *et al*., 2004; Nonaka and Chuang, 1998; Nonaka, *et al*., 1998). For instance, it has been shown that pretreatment with different doses of lithium for various periods significantly prevented the glutamate-induced, NMDA-mediated excitation in cultured rat cerebellar granule, cerebral cortical and hippocampal neurons (Nonaka and Chuang, 1998). This effect of

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lithium has been shown to be due to its inhibitory effect on the activity of NMDA receptor and thereby calcium influx into the neurons (Hashimoto, *et al*., 2002; Nonaka and Chuang, 1998). However, the exact role of NMDA receptor signalling in the therapeutic effects of lithium is as yet unidentified.

NMDA receptors are the most complex of the ionotropic receptors. Through this ligand-gated cation channel, Ca^{2+} transfer from extracellular medium into the receptive neurons is mediated, resulting in the activation of several signalling pathways such as activation of nitric oxide synthase (Esplugues, 2002; Paul and Skolnick, 2003). Studies from several laboratories have implicated the NMDA receptors in the pathophysiology of major depression and the mechanism of action of antidepressant treatment (Paul, *et al*., 1994; Petrie, *et al*., 2000). Several lines of evidence also suggest that NMDA receptor signalling could be used as a novel target of antidepressant action (Almeida, *et al*., 2006a,b; Layer, *et al*., 1995; Maj, *et al*., 1992b; Rosa, *et al*., 2003; Trullas, *et al*., 1991; Trullas and Skolnick, 1990) in the mouse forced swimming test (FST), a preclinical behavioural paradigm that is widely used to test compounds for antidepressant activity (Cryan, *et al*., 2002; Porsolt, *et al*., 1977). When animals are exposed to the FST, they typically adopt an immobile posture, which is thought to reflect a state of behavioural despair or helplessness (Porsolt, *et al*., 1977). Antidepressants reduce immobility by increasing escape-motivated behaviours in the FST paradigm (Lucki, *et al*., 2001). Moreover, some studies have also shown that NMDA receptor antagonists display an antidepressant-like behavioural profile in the mouse FST (Almeida, *et al*., 2006a,b; Layer, *et al*., 1995; Maj, *et al*., 1992b; Rosa, *et al*., 2003; Trullas, *et al*., 1991; Trullas and Skolnick, 1990). However, animal behavioural studies using lithium in the FST support the antidepressant properties of lithium (O'Brien, *et al*., 2004; Redrobe and Bourin, 1999a). Pretreatment with lithium can augment the effect of various antidepressants in the FST (Hascoet, *et al*., 1994; Nixon, *et al*., 1994). However, the exact mechanism of action of the antidepressant-like effect of lithium in this model is not fully understood. Therefore, in the current study, using various NMDA receptor antagonists, we investigated whether NMDA receptor signalling is involved in the antidepressant-like effect of acute lithium administration in the mouse FST.

Materials and methods

Animals

Male Naval Medical Research Institute (NMRI) mice weighting 23–30 g (Pasteur Institute) were used throughout the study. Animals were housed in groups of four to five and were allowed free access to food and water except for the short time while animals were removed from their cages for testing. All behavioural experiments were conducted between 12:00–15:00 h with normal room light (12-h regular light/dark cycle) and temperature (22 ± 1 °C). All procedures were carried out in accordance with the institutional animal care and use committee (Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences [TUMS]) guidelines for animal care and use. This study was approved by the Ethics Committee of TUMS. Each animal was used only once, and each experimental group consisted of at least 10 animals.

Open-field locomotor activity

Before the FST, the ambulatory behaviour of mice was assessed in an open-field test (Ghasemi, *et al*., 2008; Kaster, *et al*., 2005) to ensure that alterations in the duration of immobility are not resultant from the changes that occur in motor activity. The apparatus consisted of a wooden box measuring 40 × 60 × 50 cm. The floor of the arena was divided into 12 equal squares. The animals were gently placed in the centre of the field, and the number of squares crossed with all paws (crossing) was counted in a 6-min session.

Forced swimming test

The test was conducted using the method of (Porsolt, *et al*., 1977) and according to our previous study (Ghasemi, *et al*., 2008). Mice were individually placed in an open cylindrical container (diameter 10 cm, height 25 cm), containing 19 cm of water at 23 ± 1 °C. Mice were allowed to swim for 6 min. Each mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water. The duration of immobility was recorded during the last 4 min of the test.

Drugs and treatment

The following drugs were used in the study: lithium chloride, NMDA (*N*-methyl-D-aspartic acid), ketamine hydrochloride, dizolcipine (MK-801) and ifenprodil tartrate (Sigma, Bristol, UK). All drugs were dissolved in saline. All solutions were prepared before the experiments, and all injections were administered intraperitoneally (i.p.) in a constant volume of 5 ml/kg body weight. Lithium chloride (5, 10, 30 and 100 mg/kg) was administered 30 min before the FST in separate groups. At this step, both the per se noneffective and potent doses of lithium were determined for assessment in our next experiments.

For evaluating the effects of MK-801 (0.01, 0.05, 0.1 and 0.25 mg/kg), ifenprodil (0.1, 0.5, 1 and 3 mg/kg) and ketamine (0.5, 1, 2 and 5 mg/kg) in the mouse FST, the drugs were administered 45 min before the test in different experimental groups of animals. In the current study, the doses of these drugs were chosen based on a pilot study and in accordance with previous studies (Ghasemi, *et al*., 2008; Rosa, *et al*., 2003; Trullas and Skolnick, 1990). In these experiments, the noneffective doses of MK-801, ifenprodil and ketamine were determined for the next experiments.

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For evaluating the possible involvement of the activation of NMDA receptors in the effect of lithium in the FST, the non-effective (subactive) doses of each of MK-801, ifenprodil and ketamine were separately administered 15 min before administration of noneffective (subactive) dose of lithium chloride. Thirty minutes after lithium administration, animals were assessed in the FST.

In the last step, we further evaluated the effect of a noneffective dose the NMDA receptor agonist (NMDA, 75 mg/kg, i.p.; Poleszak, *et al*., 2007) on the antidepressant-like effect of a potent dose of lithium in the FST. In this regard, NMDA (75 mg/kg, i.p.) was injected into the animals 30 min before the lithium administration. Thirty minutes after lithium injection, animals were assessed in the FST.

Statistical analysis

Comparisons between experimental and control groups were performed by one-way or two-way ANOVA followed by Newman–Keuls test when appropriate. A value of $P < 0.05$ was considered to be significant.

Results

The results depicted in Figure 1 show that the administration of lithium chloride decreased the immobility time of mice in the FST. ANOVA showed a significant effect of lithium ($F_{4,70} = 4.927$, $P < 0.01$). Lithium chloride at the doses of 30 and 100 mg/kg ($P < 0.01$) significantly decreased the immobility time in the FST, whereas at the doses of 5 and 10 mg/kg produced no significant anti-immobility effect. Different doses of lithium chloride had no significant effect on the locomotor activity of mice in the open field test ($F_{4,70} = 0.643$, $P > 0.05$; data not shown).

As shown in Figure 2A, the administration of different doses of MK-801 had anti-immobility effects on mice in the FST ($F_{4,50} = 3.931$, $P < 0.01$). MK-801 at the doses of 0.1 and 0.25 mg/kg ($P < 0.05$) significantly decreased the immobility time in the FST, whereas at the doses of 0.01 and 0.05 mg/kg produced no significant anti-immobility effect. Figure 2B

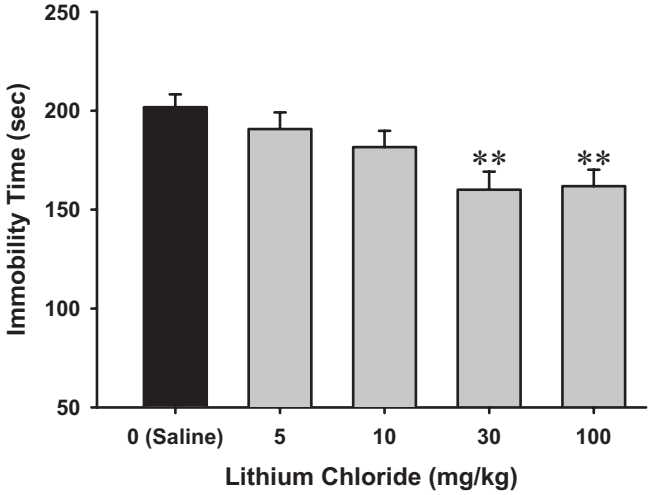

Figure 1 Effect of acute administration of lithium chloride (5–100 mg/kg, i.p.) on the FST in mice. Lithium chloride was administered 30 min before the test. $^{**}P < 0.01$ compared with the saline-treated control. Values are expressed as mean ± SEM ($n = 15$) and were analysed using a one-way ANOVA followed by Newman–Keuls test.

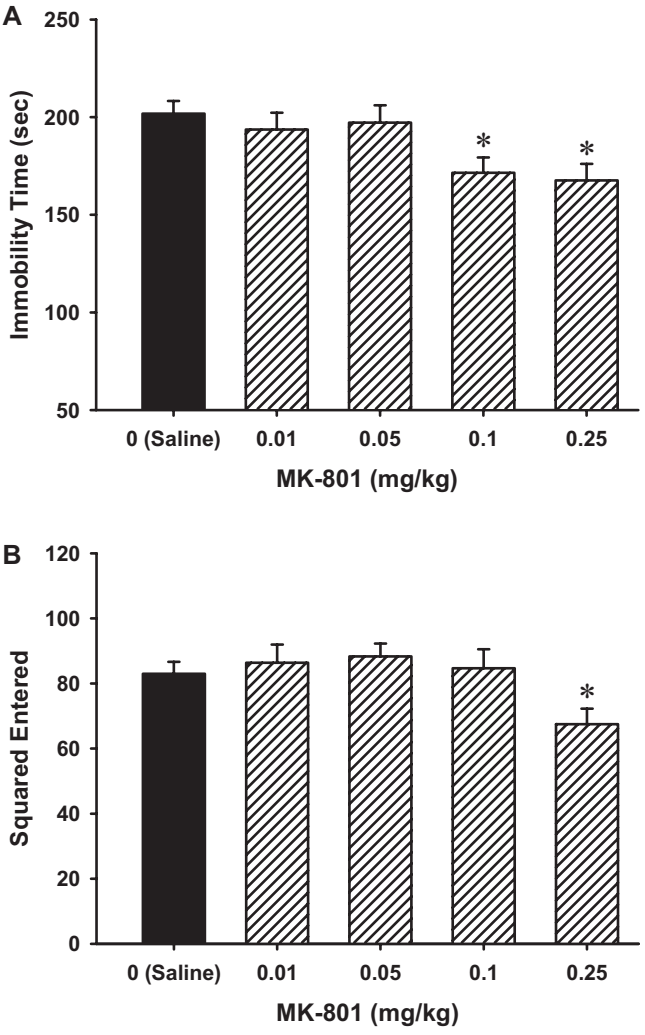

Figure 2 (A) Effect of acute administration of MK-801 (0.01–0.25 mg/kg, i.p.) on the FST in mice. MK-801 was administered 45 min before the test. (B) Effect of acute administration of lithium chloride (0.01–0.25 mg/kg, i.p.) on the locomotor activity of mice in the open field test. Values are expressed as mean ± SEM ($n = 10$) and were analysed using a one-way ANOVA followed by Newman–Keuls test. $^{*}P < 0.05$ compared with the saline-treated control.

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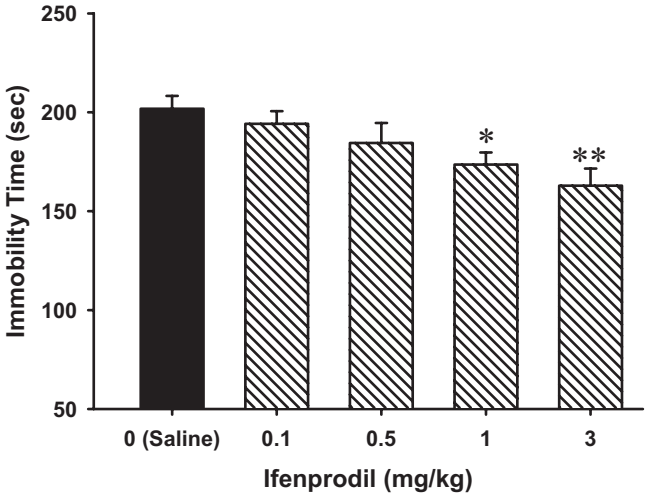

Figure 3 Effect of acute administration of ifenprodil (0.1–3 mg/kg, i.p.) on the FST in mice. Ifenprodil was administered 45 min before the test. Values are expressed as mean ± SEM ($n = 10$) and were analysed using a one-way ANOVA followed by Newman–Keuls test. *$P < 0.05$ and **$P < 0.01$ compared with the saline-treated control.

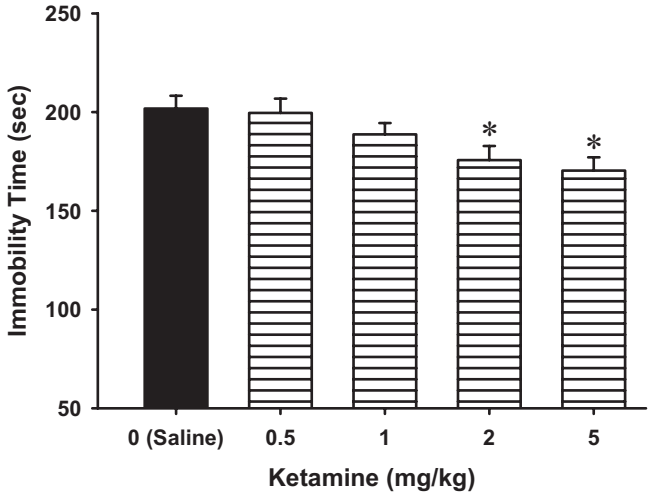

Figure 4 Effect of acute administration of ketamine (0.5–5 mg/kg, i.p.) on the FST in mice. Ketamine was administered 45 min before the test. Values are expressed as mean ± SEM ($n = 10$) and were analysed using a one-way ANOVA followed by Newman–Keuls test. *$P < 0.05$ compared with the saline-treated control.

shows that different doses of MK-801 significantly altered the locomotor activity of mice in the open field test ($F_{4,50} = 2.868$, $P < 0.05$). The dose of 0.25 mg/kg significantly ($P < 0.05$) decreased the locomotor activity, whereas lower doses had no significant effect on the locomotor activity of mice in the open field test.

As shown in Figure 3, the administration of different doses of ifenprodil had anti-immobility effects on mice in the FST ($F_{4,50} = 4.418$, $P < 0.01$). Ifenprodil at the doses of 1 mg/kg ($P < 0.05$) and 3 mg/kg ($P < 0.01$) significantly decreased the immobility time in the FST, whereas at the doses of 0.1 and 0.5 mg/kg produced no significant anti-immobility effect. In addition, different doses of ifenprodil had no significant effect on the locomotor activity of mice in the open field test ($F_{4,50} = 0.634$, $P > 0.05$; data not shown).

As shown in Figure 4A, the administration of different doses of ketamine had anti-immobility effects on mice in the FST ($F_{4,50} = 4.352$, $P < 0.01$). Ketamine at the doses of 2 and 5 mg/kg ($P < 0.05$) significantly decreased the immobility time in the FST, whereas at the doses of 0.5 and 1 mg/kg produced no significant anti-immobility effect. In addition, different doses of ketamine had no significant effect on the locomotor activity of mice in the open field test ($F_{4,50} = 1.369$, $P > 0.05$; data not shown).

Figure 5A shows that combination of per se noneffective doses of MK-801 (0.05 mg/kg) and lithium chloride (10 mg/kg) significantly ($P < 0.001$) exerted an antidepressant-like effect in the FST ($F_{3,36} = 7.690$, $P < 0.001$). Two-way ANOVA showed significant effects for lithium injection ($F_{1,39} = 28.645$, $P < 0.001$), MK-801 treatment ($F_{1,39} = 11.498$, $P < 0.01$), and lithium × MK-801 treatment ($F_{3,39} = 4.317$, $P < 0.05$). A similar result was obtained when both per se noneffective doses of ifenprodil (0.5 mg/kg) and lithium chloride (10 mg/kg) were administered before the FST ($F_{3,36} = 6.647$, $P < 0.01$; Figure 5B). Two-way ANOVA showed significant effects for lithium injection ($F_{1,39} = 27.557$, $P < 0.001$), ifenprodil treatment ($F_{1,39} = 15.445$, $P < 0.01$), and lithium × ifenprodil treatment ($F_{3,39} = 4.117$, $P < 0.05$). Moreover, combination of per se noneffective dose of ketamine (1 mg/kg) and lithium chloride (10 mg/kg) had a significant ($P < 0.001$) antidepressant like effect in the mouse FST ($F_{3,36} = 6.647$, $P < 0.01$; Figure 5C). Two-way ANOVA showed significant effects for lithium injection ($F_{1,39} = 19.808$, $P < 0.001$), ketamine treatment ($F_{1,39} = 11.304$, $P < 0.01$), and lithium × ketamine treatment ($F_{3,39} = 3.865$, $P < 0.05$). Compared with saline/saline-treated animals, concurrent administration of lithium chloride (10 mg/kg) with either MK-801 ($F_{3,36} = 0.605$, $P > 0.05$) or ifenprodil ($F_{3,36} = 0.693$, $P > 0.05$) or ketamine ($F_{3,36} = 0.608$, $P > 0.05$) did not alter the locomotor activity of mice in the open field test (data not shown).

Figure 6 shows that pretreatment with the noneffective dose of the NMDA receptor agonist NMDA (75 mg/kg, i.p.) significantly ($P < 0.05$) prevented the antidepressant-like effect of lithium (30 mg/kg, i.p.) in the FST ($F_{3,36} = 8.059$, $P < 0.001$). Compared with saline/saline-treated animals, concurrent administration of lithium chloride (30 mg/kg, i.p.) with 75 mg/kg NMDA ($F_{3,36} = 0.563$, $P > 0.05$) had no significant effect on the locomotor activity of mice in the open field test (data not shown).

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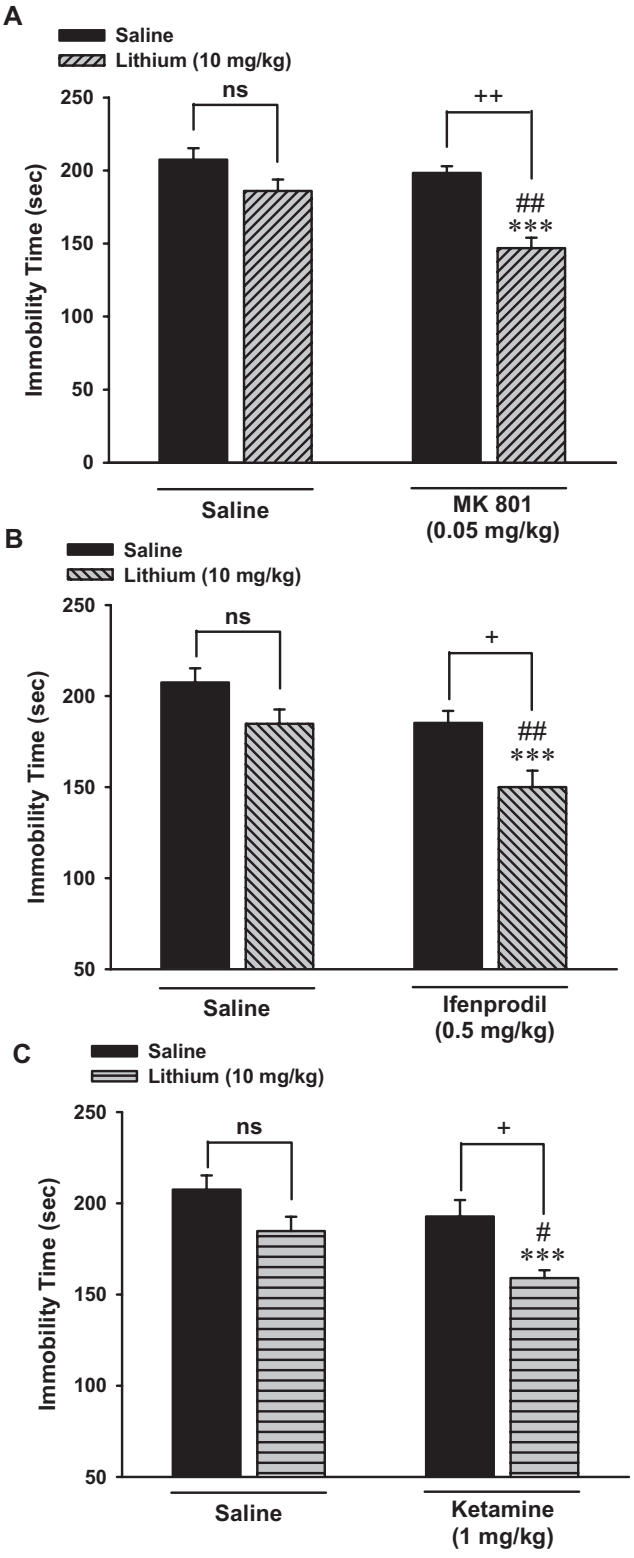

Figure 5 Pretreatment with (A) MK-801 (0.05 mg/kg, i.p.), (B) ifenprodil (0.5 mg/kg, i.p.) or (C) ketamine (1 mg/kg, i.p.) 15 min before administration of lithium (10 mg/kg, i.p.) exerted a significant decrease in the immobility time of mice in the FST at 30 min after lithium administration. $^{***}P < 0.001$ compared with the saline/saline control; $^{\#}P < 0.05$ and $^{\#\#}P < 0.01$ compared with saline/lithium (10 mg/kg) group; $^{+}P < 0.05$ and $^{++}P < 0.01$ compared with saline/corresponding NMDA antagonist; ns means nonsignificant. Values are expressed as mean ± SEM. Each group consisted of ten animals.

Discussion

Using the Porsolt FST, which is the most widely used screening tool for antidepressant activity in rodents (Cryan, *et al.*, 2002; Porsolt, *et al.*, 1977), we demonstrated that acute lithium administration exerted an antidepressant-like effect and caused a decrease in the immobility of mice. This effect of lithium was significant at the doses of 30 and 100 mg/kg, whereas lower doses of lithium (5 and 10 mg/kg) had no significant antidepressant-like effect. These results are in agreement with our recent study (Ghasemi, *et al.*, 2008) and previous studies that have shown that either acute or chronic lithium treatment decreases the immobility time in the FST alone or in combination with other antidepressant agents (Bersudsky, *et al.*, 2007; Cryns, *et al.*, 2007; Gould, *et al.*, 2008; Hascoet, *et al.*, 1994; Nixon, *et al.*, 1994; O'Brien, *et al.*, 2004; Redrobe and Bourin, 1999a,b; Shaldubina, *et al.*, 2006; Silva, *et al.*, 2008). This effect of lithium in the FST could represent a parallel to the mood stabilising action of lithium on the depressive phase of bipolar

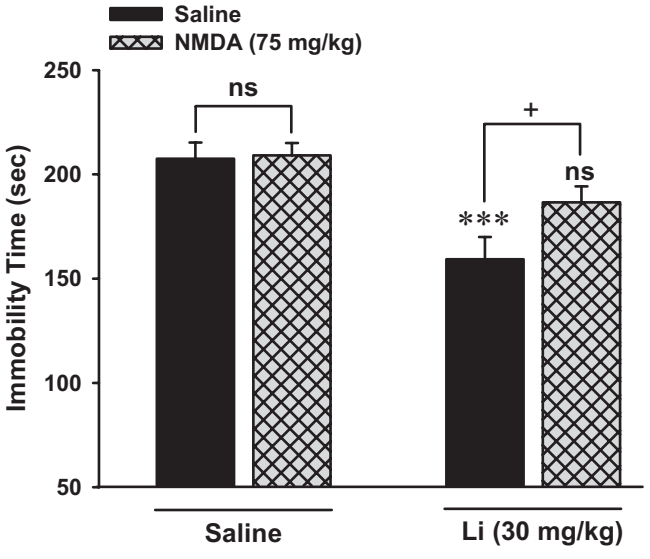

Figure 6 Pretreatment with the NMDA receptor agonist NMDA (75 mg/kg, i.p.) 30 min before administration of lithium (30 mg/kg, i.p.), increased the immobility time of mice in the FST at 30 min after lithium administration. $^{***}P < 0.001$ compared with the saline/saline control; $^{+}P < 0.05$ compared with saline/lithium (Li, 30 mg/kg, i.p.)-treated group; ns means nonsignificant compared with saline/saline group. Values are expressed as mean ± SEM. Each group consisted of ten animals.

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disorder in humans (Bourin and Prica, 2007) and to the effects of antidepressants on learned helplessness (Sherman and Petty, 1980) and immobilisation stress in rats (Hata, *et al*., 1995). Moreover, it was shown that lithium could exert antidepressant-like effect in a variety of animal models of depression including the tail suspension test (TST) (Cryns, *et al*., 2007; Gould, *et al*., 2008), learned helplessness (Faria and Teixeira, 1993; Teixeira, *et al*., 1995), olfactory bulbectomized rat (Song, *et al*., 1994; van Riezen, *et al*., 1977), immobilisation stress (Kofman, *et al*., 1995), muricidal behaviour induced by midbrain lesions in rats (Yamamoto, *et al*., 1985), desynchronisation of reserpine-induced depression (Zamoshchina and Saratikov, 1997; Zamoshchina, *et al*., 1997) and ouabain-induced behavioural changes in rats (Li, *et al*., 1997). However, there are some discrepancies in the antidepressant-like effect of lithium in the FST (Kitamura, *et al*., 2002; Wegener, *et al*., 2003; Tomasiewicz, *et al*., 2006). For example, Gould, *et al*. (2007) have recently reported that intraperitoneal administration of 100 mg/kg of lithium chloride 30 min before the FST did not result in the antidepressant-like action in mice. The differences in these results could be due to a number of factors such as differences in animal species or strain, experimental designs, route and duration of lithium administration. For instance, Gould, *et al*. (2007) used C57BL/6J mice in their experiments, whereas we have used male NMRI mice.

During the past decade, converging lines of evidence have led investigators beyond the monoaminergic synapse for strategies to improve antidepressant therapy. Emerging from these studies is a rapidly changing picture that may provide an entirely new set of potential therapeutic targets. In this regard, studies from several laboratories have implicated the NMDA class of glutamate receptors in the pathophysiology of major depression and the mechanism of action of antidepressant treatment (Paul, *et al*., 1994; Petrie, *et al*., 2000). The initial clue in this regard came from the studies that reported antidepressant effect of D-cycloserine, an antibiotic developed to treat tuberculosis, which is a partial agonist at the glycine site of the NMDA glutamatergic receptor (Crane, 1959, 1961; Papp and Moryl, 1996). Additional work showed that other NMDA receptor antagonists such as amantadine (Huber, *et al*., 1999; Rogoz, *et al*., 2007; Stryjer, *et al*., 2003), memantine (Ferguson and Shingleton, 2007; Muhonen, *et al*., 2008; Munoz, *et al*., 2008) and ketamine (Berman, *et al*., 2000; Goforth and Holsinger, 2007; Kudoh, *et al*., 2002; Liebrenz, *et al*., 2007a,b; Maeng and Zarate, 2007; Ostroff, *et al*., 2005; Zarate, *et al*., 2006) could exhibit antidepressant activity in both unipolar and in bipolar depressed patients. However, Trullas and Skolnick (1990) provided the first evidence of the antidepressant-like effects of NMDA antagonists including 2-amino-7-phosphonoheptanoic acid, Dizolcipine (MK-801) and 1-aminocyclopropanecarboxylicacid in the mouse FST and TST. After that, many studies reported antidepressant-like effects of a variety of NMDA receptor antagonists in animal models of depression such as mouse FST (Almeida, *et al*., 2006a,b; Layer, *et al*., 1995; Maj, *et al*., 1992b; Rosa, *et al*., 2003; Trullas, *et al*., 1991; Trullas and Skolnick, 1990), rat FST (Garcia, *et al*., 2008; Maj, *et al*., 1992a,b,c; Moryl, *et al*., 1993; Przegalinski, *et al*., 1997; Yilmaz, *et al*., 2002), mouse TST (Kos and Popik, 2005; Panconi, *et al*., 1993; Trullas and Skolnick, 1990), learned helplessness behaviour in rats (Meloni, *et al*., 1993), chronic mild stress-induced deficits in sucrose consumption in rats (Papp and Moryl, 1993, 1994, 1996) and olfactory bulbectomized rats (Kelly, *et al*., 1997; Redmond, *et al*., 1997). Consistently, Boyce-Rustay and Holmes (2006) have recently reported that NMDA receptor subunit NR2A knockout mice showed antidepressant-like profiles in the FST and TST, as compared with the wild type controls. In the current study, we also showed that the noncompetitive NMDA antagonist ketamine at 2 and 5 mg/kg, the selective noncompetitive NMDA antagonist MK-801 at 0.1 and 0.25 mg/kg and also the selective polyamine site NMDA antagonist ifenprodil at 1 and 3 mg/kg decreased the immobility time of mice in the Porsolt FST, indicating that these drugs at these concentrations have antidepressant-like effects in the test. Our data also indicated that these agents at active or subactive doses had no effect on the locomotor activity in the open field test, excluding the possibility that their antidepressant-like effects are due to their adverse effects on the locomotor activity.

In the current study, we examined the effect of simultaneous administration of lithium with MK-801, ifenprodil and ketamine in the FST. Our data showed that neither low doses of NMDA antagonists (0.05 mg/kg MK-801, 0.5 mg/kg ifenprodil and 1 mg/kg ketamine) nor low dose of lithium (10 mg/kg), when administered independently, significantly affected the immobility time of mice in the FST. However, when these agents and lithium were combined at the same low doses, they exerted a significant antidepressant-like effect in the FST. We also demonstrated that the NMDA agonist NMDA at a noneffective dose (75 mg/kg) prevented the antidepressant-like effect of a potent dose of lithium (30 mg/kg). These results could reflect the involvement of NMDA receptors in the antidepressant-like effects of lithium in the FST and may also provide a new evidence for the treatment of depression with concurrent administration of low doses of lithium and glutamatergic NMDA receptor antagonists.

Biochemically diverse effects of lithium on the glutamatergic system have been identified by a number of groups (Antonelli, *et al*., 2000; Bauer, *et al*., 2003; Dixon and Hokin, 1998; Dixon, *et al*., 1994; Hokin, *et al*., 1996; Yildiz-Yesiloglu and Ankerst, 2006). Specifically, these effects include evidence suggesting a decrease in glutamate reuptake, decrease in glutamate release and/or modulation of receptor levels. In 1998, Nonaka and his co-workers reported the first evidence of the inhibitory effects of lithium on the NMDA receptors (Nonaka, *et al*., 1998). They showed that pretreatment with different doses of lithium (0.1–5 mM) for various periods (0–7 days) robustly prevented the glutamate-induced, NMDA-mediated, excitation in cultured rat cerebellar granule, cerebral cortical and hippocampal neurons. In subsequent studies, it was found that this protection could be due to the inhibitory effect of lithium on the NMDA-mediated calcium influx into the rat cerebral cortical neurons through attenuation of constitutive tyrosine

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phosphorylation of the NR2B subunit of the NMDA receptor and Src tyrosine kinase (Hashimoto, *et al*., 2002; Nonaka and Chuang, 1998; Nonaka, *et al*., 1998). Moreover, other investigators reported that this effect of lithium can be explained by its reduction of the NR2A tyrosine phosphorylation and its interaction with PyK2 and PSD-95, as well as the interactions of the NR2A subunit with Src and Fyn mediated by PSD-95 in the rat hippocampus (Ma and Zhang, 2003; Ma, *et al*., 2004). Recently, it was also shown that 6-week lithium treatment attenuated the NMDA-induced signalling in the prefrontal, frontal, motor, pyriform, anterior cingulate, somatosensory and visual cortex, preoptic area, superchiasmatic nucleus, globus pallidus, hippocampus, caudate-putamen, habenular nucleus, lateral geniculate, nucleus dorsal, geniculate medial, areas of the thalamus and hypothalamus, substantia nigra and inferior colliculus (Basselin, *et al*., 2006). These results are consistent with the evidence of disturbed markers of NMDA functioning in either the depressed (Clinton and Meador-Woodruff, 2004; Law and Deakin, 2001; Nowak, *et al*., 1995) or the bipolar brain disorder (Mundo, *et al*., 2003; Scarr, *et al*., 2003; Toro and Deakin, 2005; Woo, *et al*., 2004). According to these studies and our present data, it could be suggested that NMDA receptor signalling is involved in the antidepressant-like effect of lithium in the FST. However, it is noteworthy that in the current study we examined the effect of acute administration of lithium in combination with NMDA antagonists. Therefore, more detailed studies are clearly needed to verify the underlying mechanisms in the possible interaction of lithium with NMDA receptor signalling at this level.

Although our data could certainly be amenable to a pharmacodynamic interpretation, it would be reasonable if one supposes that lithium might alter the pharmacokinetic profile of the NMDA antagonist compounds, and they may interact to alter metabolism or brain bioavailability resulting in higher brain levels and thus increased immobility. However, until now no study has evaluated the pharmacokinetic interaction between lithium and NMDA antagonists and this general assumption has to await more detailed studies.

In summary, in the current study, we showed that both lithium and NMDA antagonists (MK-801, ifenprodil and ketamine) exerted antidepressant-like effects in the Porsolt mouse FST. We also showed that low and per se noneffective doses of lithium in combination with low doses of each of the NMDA antagonists significantly decreased the immobility time of mice in the test. Moreover, our data showed that the noneffective dose of the NMDA agonist NMDA attenuated the antidepressant-like effect of a potent dose of lithium in the FST. This indicates the possible interaction between lithium and NMDA receptor signalling in their antidepressant-like effect in the FST and provides a new therapeutic approach for treatment of depression in future studies.

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