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Effects of lithium chloride on induction and expression of methylphenidate sensitization

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Abstract

Repeated administration of psychomotor stimulants produces an enduring and progressively enhanced behavioral response known as behavioral sensitization, which has been implicated as a model for psychiatric disorders such as mania, schizophrenia, and drug addiction. The objective of the study was to determine whether lithium chloride (LiCl), an anti-manic agent, is effective in blocking the development and/or the expression of behavioral sensitization to methylphenidate. Male Sprague–Dawley rats ($n = 64$) weighing 170–190 g were randomly divided into seven treatment groups. A computerized animal activity monitor system continuously recorded locomotor activity for 16 days. Effects of LiCl on induction of methylphenidate sensitization were studied by giving LiCl before or during six daily methylphenidate administrations. Effects of LiCl on the expression of methylphenidate sensitization were studied by injecting LiCl after sensitization to methylphenidate was induced. It was shown that LiCl treatment modulated the acute methylphenidate effects by transiently attenuating the locomotor response to methylphenidate during the six daily methylphenidate administrations but neither single nor multiple treatments with LiCl blocked the development or the expression of behavioral sensitization. © 2001 Published by Elsevier Science B.V.

Keywords: Locomotor activity; Behavioral sensitization; Psychostimulant; Methylphenidate; Lithium chloride

1. Introduction

Repeated intermittent administration of psychostimulants, such as cocaine, amphetamine, and methamphetamine, results in behavioral sensitization (Segal and Mandell, 1974; Post and Rose, 1976; Post et al., 1984; Kalivas, 1995; Pierce and Kalivas, 1997; Sax and Strakowski, 1998), which is characterized by an increase in locomotor and/or stereotypic behaviors (Robinson and Becker, 1986; Segal and Kuczenski, 1987). Behavioral sensitization also occurs with repeated intermittent administration of methylphenidate (commonly known as Ritalin) (Shuster et al., 1982; Gaytan et al., 1996, 1997a,b; Crawford et al., 1998; Sripada et al., 1998), a psychomotor stimulant widely used in the treatment of attention deficit/hyperactivity disorder in children and adults (Goldman et al., 1998; Safer et al., 1996). Psychostimulants produce effects, such as behavioral sensitization, that are similar in some respects to the symptoms of mania and bipolar disorder in humans (Smith and Davis, 1977; Cappeliez and Moore, 1990; Gessa et al., 1995). It has been shown that repeated administration of psychostimulants can induce manic states and enhance the chance of relapses in psychotic patients who are in remission (Janowsky et al., 1973; Snyder, 1973; Gessa et al., 1995). Moreover, it has been suggested that repetitive use of psychostimulants changes the catecholamine system that causes behavioral sensitization and psychosis induced by psychostimulants. Changes in the level of catecholamine output by the neurons, which are associated with manic or mixed episodes, can alter illness course or treatment response by mechanisms related to behavioral sensitization (Gessa et al., 1995; Robinson and Becker, 1986). Hence, behavioral sensitization is also used as a model to study bipolar disorders. Studying drugs that modulate behavioral sensitization may provide further insight on the mechanisms underlying these disorders.

Lithium chloride (LiCl) is the preferred treatment for mania and bipolar disorder (Schou, 1968; Gershon and Shopsin, 1973; Prien et al., 1984; Cappeliez and Moore, 1990). Repeated treatment with LiCl has been shown to reduce the hyperactivity induced by D-amphetamine and

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methamphetamine (Borison et al., 1978; Namina et al., 1998). Attention deficit/hyperactivity disorder patients often have other psychiatric disorders such as mania and depression (Spencer et al., 1999) for which they may take LiCl in addition to methylphenidate for attention deficit/hyperactivity disorder. Little is known about interactions between LiCl and sensitization resulted from repetitive methylphenidate treatment. In the present study, sensitization was used as a model for bipolar disorder to determine the effects of LiCl on behavioral sensitization to methylphenidate in rats. The study had two parts: the first was concerned with LiCl's ability to prevent the development of sensitization; the second was to determine whether LiCl, given after sensitization to methylphenidate was developed, prevents the expression of methylphenidate-sensitization. To test these possibilities, six different LiCl regimens were given to the rats before, during and after methylphenidate treatment.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats ($n = 64$, Harlan, Indianapolis, IN), weighing 170–190 g, were housed in groups of four in the experimental room at an ambient temperature of 21 ± 2 °C and a relative humidity of 37–42%. Animals were maintained on a 12/12-light/dark cycle with food and water provided ad libitum.

2.2. Apparatus

The computerized animal activity monitoring system (AccuScan, Columbus, OH) was used to continuously record locomotor activity (Dougherty et al., 1990; Gaytan et al., 1996, 1997a,b, 1998, 2001). The activity chambers consisted of clear acrylic open field boxes ($40.5 \times 40.5 \times 31.5$ cm) with infrared motion sensors 6 and 12.5 cm above the floor of the cage. The activity monitoring system checked for interruptions of each infrared beam at a frequency of 100 Hz. The interruption of any beam was recorded as an activity score. Interruptions of two or more consecutive beams separated by at least 1 s were recorded as a movement score. Cumulative counts of scores were compiled and downloaded every 10 min into OASIS data collection software, and organized into motor indices.

The following representative indices were analyzed: (1) total distance, which measures the amount of forward ambulation; (2) vertical activity, which measures the amount of rearing; (3) horizontal activity, which measures the overall motor activity in the lowest tier of the test cages and is used to assess the overall amount of locomotor activity; and (4) number of stereotypic movements, which measures the number of repetitive episodes with at least one second interval before the beginning of another episode. Number of stereotypic movements is used to assess the effect of drug treatment on general stereotyped behavior (sniffing, grooming, and other repetitive behaviors).

2.3. Drugs

Methylphenidate hydrochloride was a gift from Mallinckrodt (Hazelwood, MO) and LiCl was obtained from Sigma (St. Louis, MO). Methylphenidate (2.5 mg/kg) was dissolved in 0.9% saline and injected subcutaneously (s.c.). The dose of methylphenidate was selected based on previous dose–response studies on methylphenidate-induced sensitization (Gaytan et al., 1997b). LiCl (50 mg/kg) was dissolved in water and injected intraperitoneally (i.p.). The 50 mg/kg LiCl concentration was chosen because in a dose–response study [unpublished data], this dosage had no independent motor effect and caused no changes of the injection site, while the 100 and 200 mg/kg LiCl produced a slight increase in the animals' locomotor activity as well as a noticeable irritation (e.g., a small hairless region at the site of injection). All injections were of equal volume (0.8 cm^3) and given between 12:00 and 14:00 h.

2.4. Protocol

After 48-h habituation to the experimental room, the animals were weighed and randomly divided into a control group ($n = 12$), three groups to study whether LiCl prevents the development of sensitization, and three groups to determine whether LiCl modulates the expression of sensitization. Each rat was individually housed in test cage for at least 24 h before recording locomotor activity.

2.4.1. Control group I

Baseline levels of locomotor activity were obtained for each rat on day 1. On days 2 and 3, animals were injected with 0.9% saline (s.c.), which served to establish the handling and injection controls. On days 4–9, rats were weighed and given daily injection of 2.5 mg/kg methylphenidate (s.c.). On days 10–14, no drug treatment was given (i.e., washout period). Methylphenidate re-challenge was given on day 15 (Table 1).

2.4.2. LiCl's effects on the induction of methylphenidate sensitization

Three groups of rats had the same methylphenidate protocol described above but were given LiCl during the methylphenidate treatment period (see Table 1, Groups II–IV). On day 4, rats in Group III ($n = 8$) received an injection of 50 mg/kg LiCl (i.p.) 1 h prior to methylphenidate challenge, and rats in Groups II ($n = 8$) and IV ($n = 8$) received 0.9% saline (i.p.) 1 h prior to the initial methylphenidate challenge. On day 5, rats in Group III received 0.9% saline (i.p.) 1 h prior to methylphenidate challenge, while rats in Groups II and IV were given 50

Table 1
Schedule of drug treatment[a]

Group	Induction phase			Expression phase				
	Day 4	Day 5	Days 6–9	Day 10	Days 11–13	Day 14	Day 15	Day 16
I	MPD	MPD	MPD	No drugs	No drugs	No drugs	MPD	
II	Saline + MPD	LiCl + MPD	LiCl + MPD	No drugs	No drugs	No drugs	Saline + MPD	
III	LiCl + MPD	Saline + MPD	Saline + MPD	No drugs	No drugs	No drugs	Saline + MPD	LiCl + MPD
IV	Saline + MPD	LiCl + MPD	Saline + MPD	No drugs	No drugs	No drugs	Saline + MPD	
V	MPD	MPD	MPD	LiCl	LiCl	LiCl	MPD	
VI	MPD	MPD	MPD	LiCl	No drugs	No drugs	MPD	
VII	MPD	MPD	MPD	No drugs	No drugs	LiCl	MPD	

[a]Baseline recordings for all rats were done on day 1. They received saline injections on days 2–3. Injections of 50 mg/kg LiCl and/or saline (i.p.) were given at 13:00 h, and all injections of 2.5 mg/kg methylphenidate (MPD) (s.c.) were given at 14:00 h.

mg/kg LiCl (i.p.) 1 h prior to methylphenidate injection. On days 6–9, rats in Groups III and IV received saline injections 1 h prior to methylphenidate and rats in Group II received daily injections of LiCl 1 h prior to methylphenidate treatment. From days 10 to 14, rats in all four groups received no treatment. On day 15, rats were re-challenged with 2.5 mg/kg methylphenidate (s.c.). On day 16, Group III received the same treatment as on day 4 (Table 1) to determine whether methylphenidate sensitization was still present.

2.4.3. LiCl's effects on the expression of methylphenidate sensitization

Three groups of rats had the same protocol described above, i.e., the first 9 days were identical to the control methylphenidate group (Group I, Table 1). Starting on day 10, the rats were divided randomly into three groups that received one of three LiCl treatments. Group V ($n = 10$) was administered five daily injections of 50 mg/kg LiCl (i.p.) on experimental days 10–14. Group VI ($n = 10$) was given a single injection of 50 mg/kg LiCl (i.p.) on experimental day 10 and received no further drug treatment from days 11 to 14. Group VII ($n = 8$) was given a single 50 mg/kg LiCl (i.p.) dose on experimental day 14. All rats were re-challenged with a 2.5-mg/kg injection (s.c.) of methylphenidate on day 15 (Table 1).

2.5. Data analysis

Acute drug effects were assessed by comparing the difference between activity during the 2 h immediately following injection of either methylphenidate or LiCl and the 2 h immediately following injection of saline in the same rats. Presence of sensitization was determined by comparing the activity scores from the initial methylphenidate challenge (day 4) to the activity scores of the other methylphenidate injection days (5–9 and 15). Results were analyzed using repeated measures of analysis of variance (ANOVA) (two levels: treatment day and 10-min sample bins) and post-hoc Fischer's method. Statistical significance was set at $^{*}P < 0.05$ or $^{**}P < 0.01$ for all comparisons. In addition, the difference in the magnitude of motor responses was also determined by calculating the ratio of the absolute change in activity between methylphenidate challenge (day 4) and methylphenidate re-challenge (day 15). Results were analyzed using ANOVA (one-way: treatment group). Significance for this comparison was set at $^{*}P < 0.05$.

3. Results

3.1. Control

Time control (16 days) and saline effects on an identical experimental protocol were previously reported and demonstrated that the motor indices studied had remained similar over the 16 days and were not affected by repeated saline injections, so any deviation from the saline treatment was the result of drug(s) used (Gaytan et al., 1996, 1997b, 1998). The effects of daily repeated injections of 2.5 mg/kg methylphenidate (Group I) on horizontal activity, total distance, vertical activity, and number of stereotypic movements are summarized in Fig. 1. The bar graph shows the difference in activity score for the 2 h after methylphenidate injection for that day as compared to day 3 (saline injection, Table 1). Sensitization to methylphenidate was established in all four motor indices by the fourth methylphenidate injection (day 7) and persisted on day 15. The line graph represents the temporal response over the 2 h following methylphenidate injection for days 4 and 15. Locomotor activities on day 15 increased significantly 10 min after methylphenidate injection and remained elevated throughout the first 60 min after methylphenidate injection, then gradually descended to non-significant levels as compared to day 4.

3.2. LiCl's effects on the induction of methylphenidate sensitization

Fig. 2 summarizes the effects of multiple injections of LiCl administered (Group II) 1 h prior to daily meth-

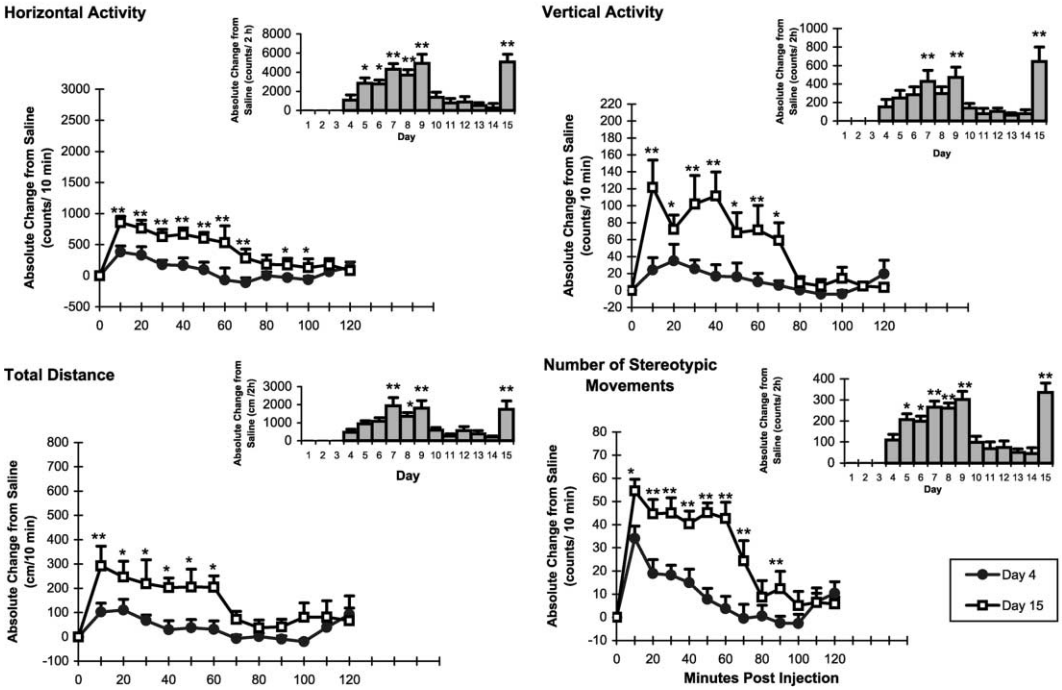

Fig. 1. The effects of multiple methylphenidate (2.5 mg/kg, s.c.) treatment on locomotor activity. Temporal response in 10-min samples for 120 min after methylphenidate injection (line graph) and 2-h total activity (bar graph) for the four motor indices studied: horizontal activity, vertical activity, total distance, and number of stereotypic movements following administration of methylphenidate. Sensitization to locomotor activities resulted from daily injection of methylphenidate was well established by the fourth methylphenidate injection (day 7) and was still expressed several days later (day 15). Presence of sensitization to methylphenidate was determined by comparing results obtained after the second to the sixth injection with that obtained at day 4. Values are presented as the mean ± S.E.M. for each 10-min or 2-h sample. $^{*}P < 0.05$ or $^{**}P < 0.01$ compared to day 4.

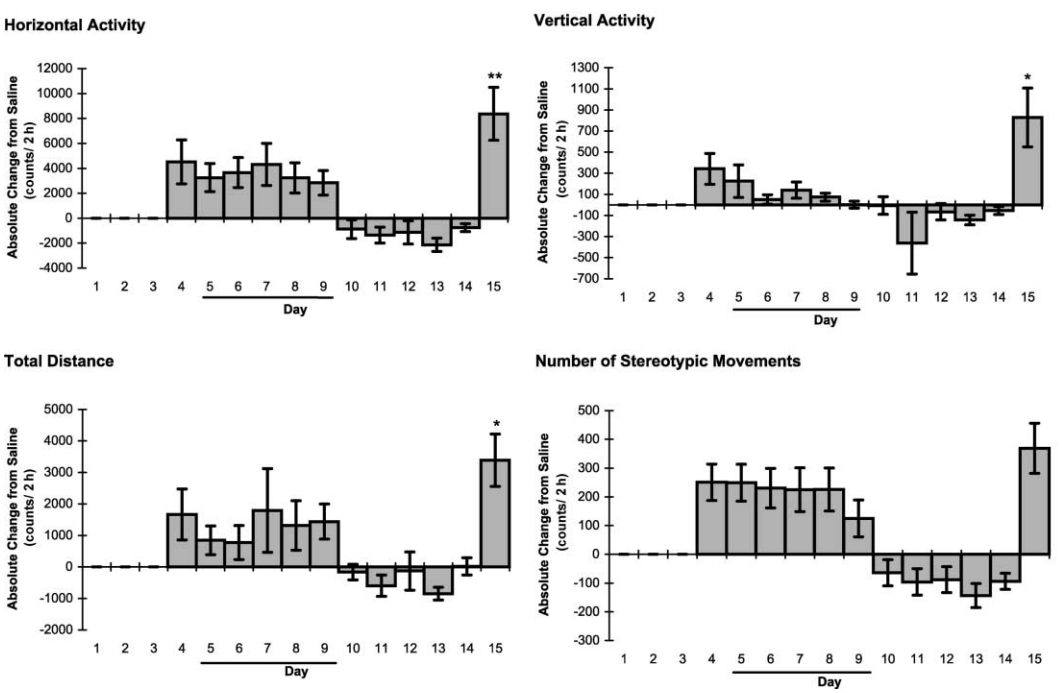

Fig. 2. The effects of multiple LiCl (50 mg/kg, i.p.) administration ("—" indicates days of LiCl injection) 1 h prior to methylphenidate injection on days 5–9. A 2-h total for horizontal activity, total distance, vertical activity, and number of stereotypic movements following repeated administration of 2.5 mg/kg methylphenidate is shown. All days are compared to the methylphenidate challenge (day 4). No evidence of sensitization is seen on days 5–9, but a sensitized response is observed on day 15 in horizontal activity, total distance, and vertical activity. Multiple LiCl administration given 1 h prior to methylphenidate treatment on days 5–9 did not prevent the induction of methylphenidate-elicited sensitization on day 15. Values are presented as the mean ± S.E.M. for the 2-h samples. $^{*}P \leq 0.05$ or $^{**}P \leq 0.01$ as compared to day 4.

ylphenidate on days 5–9 (induction phase). When LiCl was given 1 h before methylphenidate on days 5–9, there was no progressive increase in motor activity, i.e., LiCl prevented methylphenidate augmentation on days 5–9 compared to that of Group I. However, when methylphenidate was re-administered on day 15, augmentation of locomotor activity was observed when compared to the methylphenidate effects on day 4. LiCl injections given during days 5–9 did not prevent the induction of methylphenidate-elicited sensitization on day 15 because the locomotor indices studied exhibited an enhanced locomotor response. Horizontal ($P < 0.01$) and vertical ($P < 0.05$) activities and total distance ($P < 0.05$) were significantly increased upon methylphenidate re-challenge (day 15) as compared to day 4, the initial day of methylphenidate injection. Methylphenidate re-challenge on day 15 also produced an increase in number of stereotypic movements, but this increase was not significant.

A single dose of LiCl administered 1 h prior to the initial methylphenidate challenge on day 4 (Group III) or 1 h prior to the second methylphenidate challenge on day 5 (Group IV) had similar effects to multiple administrations of LiCl, as it prevented the progressive increase in locomotion during the five repetitive methylphenidate injections, while methylphenidate re-challenged on day 15 exhibited sensitization when compared to day 4, the initial day of methylphenidate treatment. Therefore, LiCl exerted an acute effect on motor stimulation by methylphenidate and only transiently attenuated the sensitized response to methylphenidate since sensitization was still evident upon methylphenidate re-challenge on day 15.

3.3. LiCl's effects on the expression of methylphenidate sensitization

Fig. 3 summarizes the effect of daily LiCl injection (Group V) on days 10–14 (i.e., after sensitization was induced). Repeated injections of methylphenidate on days 4–9 elicited locomotor sensitization as demonstrated by the gradual increase in motor activities after each methylphenidate injection. Sensitization was established by the third injection of methylphenidate (day 6) for horizontal activity, total distance, and vertical activity and by the fifth injection of methylphenidate (day 8) for number of stereotypic movements. LiCl given daily on days 10–14, i.e., during methylphenidate washout period, had no effect on the four motor indices studied and when methylphenidate was re-challenged on day 15, the 5 days of LiCl treatment did not prevent methylphenidate-elicited sensitization on day 15 as evident in horizontal activity ($P < 0.01$), total distance ($P < 0.01$), vertical activity ($P < 0.05$), and the number of stereotypic movements ($P < 0.01$). Similar mo-

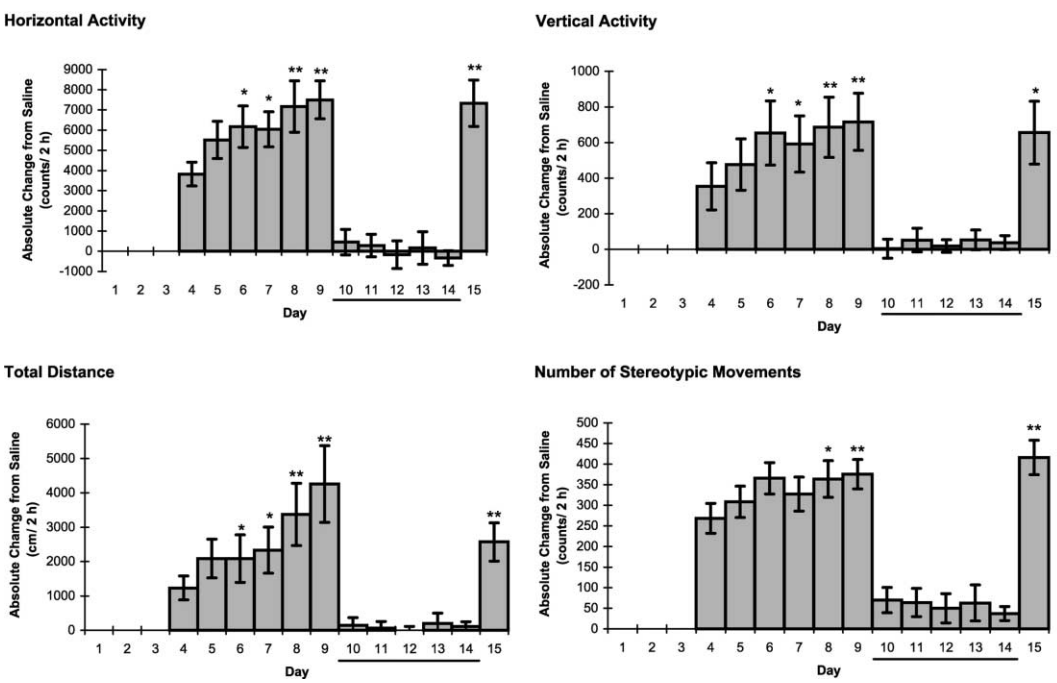

Fig. 3. The effects of daily LiCl (50 mg/kg) administration ("—" indicates days of LiCl injection) on days 10–14. A 2-h total for horizontal activity, total distance, vertical activity, and number of stereotypic movements following repeated administration of 2.5 mg/kg methylphenidate is shown. All days are compared to the methylphenidate challenge (day 4). Repeated injections of methylphenidate on days 4–9 elicited locomotor sensitization as demonstrated by the gradual increase in motor activities after each methylphenidate injection. Sensitization was established by the third injection of methylphenidate (day 6) for horizontal activity, total distance, and vertical activity and by the fifth injection of methylphenidate (day 8) for a number of stereotypic movements. LiCl given everyday during the washout period (days 10–14) had no effect on the four motor indices studied and did not prevent methylphenidate-elicited sensitization on day 15. Values are presented as the mean ± S.E.M. for the 2-h samples. $^{*}P \leq 0.05$ or $^{**}P \leq 0.01$ as compared to day 4.

Table 2
MPD response magnitude[a]

Group	Horizontal activity	Total distance
I	4.5 ± 1.5	3.5 + 2.8
II	2.0 ± 1.3	2.0 ± 1.0
V	2.0 ± 2.0	2.1 ± 1.8

[a]Methylphenidate response magnitude of horizontal activity and total distance for Groups I, II, and V. Group I received six daily injections of methylphenidate, Group II received multiple LiCl treatment on experimental days 5–9, and Group V received multiple LiCl treatment on experimental days 10–14 (washout phase). The methylphenidate response magnitude is represented by the ratio of the absolute change in activity between methylphenidate challenge (day 4) and methylphenidate re-challenge (day 15) (i.e., ratio ± S.E.M.). Analysis of this methylphenidate response magnitude further supports the results summarized in Figs. 1–3 that neither single nor multiple treatments with LiCl prevented the development or the expression of methylphenidate sensitization on day 15.

tor responses were seen in the other two groups in which a single injection of LiCl was given either 1 day after the last methylphenidate injection (Group VI, day 10) or 1 day before methylphenidate re-challenge (Group VII, day 14).

3.4. Magnitude of sensitization among groups

Because of variability in response to drug effect among groups and sensitization is normally defined by a difference in response magnitude, the response magnitude to methylphenidate for Groups I (daily methylphenidate for 6 days), II (multiple LiCl treatment during the induction phase), and V (multiple LiCl during washout phase) is summarized in Table 2. The methylphenidate response magnitude is represented by the ratio of the absolute change in activity between methylphenidate challenge (day 4) and methylphenidate re-challenge (day 15). Table 2 summarizes the response magnitude of methylphenidate sensitization for horizontal activity and total distance. Repeated methylphenidate treatment (Group I) beginning on day 4 produced about a 4.5- and a 3.5-fold increase in horizontal activity and total distance (i.e., methylphenidate sensitization) by day 15, respectively. LiCl given during days 5–9 (Group II) or given daily during the washout period (Group V) did not significantly modulate methylphenidate sensitization as compared with that of Group I. These evaluations further support results summarized in Figs. 1–3 that neither single nor multiple treatments with LiCl prevented the development or the expression of methylphenidate sensitization on day 15.

4. Discussion

Behavioral sensitization consists of two phases: induction and expression. The induction or developmental phase is the immediate cellular and/or molecular effects induced by a psychostimulant that leads to changes responsible for the increased behavioral response (Kalivas and Stewart, 1991). The expression phase refers to the long-term behavioral consequences of cellular and/or molecular effects of a psychostimulant (Kalivas and Stewart, 1991). The present study is aimed at determining whether single and/or repeated injections of LiCl chloride prevent the induction and the expression of methylphenidate-induced behavioral sensitization.

A preliminary dose–response study showed that chronic administration of 50, 100, and 200 mg/kg LiCl alone had no effect on the locomotor behavior in rats, an observation supported by other studies (Berggren et al., 1981; Engel and Berggren, 1980). Methylphenidate and other psychostimulants such as amphetamine and cocaine are thought to induce behavioral sensitization by elevating extracellular dopamine in structures of the motive circuit, which causes enhanced locomotion (Robinson and Berridge, 1993; Jones et al., 1998). Thus, dopamine is believed to play a crucial role in behavioral sensitization. The present study also found that single and repeated administration of 50 mg/kg LiCl transiently blocked the progressive increase in locomotor behavior during the induction phase, but it did not prevent the development of methylphenidate-induced behavioral sensitization because sensitization was expressed when the animals were re-challenged with methylphenidate on day 15. This observation suggests that LiCl may have acutely interfered with the catecholaminergic mechanisms, such as reducing the release of dopamine at the presynaptic region that leads to a decrease in locomotor activity. A similar phenomenon was reported with amphetamine-induced behavioral sensitization in rats that were repeatedly treated with LiCl (Berggren, 1985). Berggren (1985) interpreted this observation as a decrease of the synthesis and release of dopamine and this decrease in dopamine attenuated the locomotor activity. This observation is consistent with suppression of amphetamine-induced locomotor stimulation by LiCl. The involvement of dopamine in the behavioral sensitization is further supported by another study that found that a precursor of dopamine reversed the LiCl suppressed amphetamine-induced locomotor stimulation (Berggren et al., 1978).

Although repeated administration of 50 mg/kg LiCl transiently attenuated the acute effect of methylphenidate during days 5–9, the repeated administration of LiCl did not prevent the induction or the expression of methylphenidate sensitization. The locomotor activity on day 15 (methylphenidate re-challenge) was significantly higher than the locomotor activity produce by methylphenidate in naïve animals (experimental day 4). This suggests that the effect of LiCl on the catecholamine receptors may be transient and that the effect of LiCl cannot reverse the more permanent changes at these receptors resulting from chronic methylphenidate treatment. In other words, LiCl apparently cannot reverse the sensitization produced by multiple methylphenidate treatment once it had developed. The acute effect of LiCl may also explain why a single

administration of 50 mg/kg LiCl given during or after the methylphenidate-induction phase was not robust enough to prevent the expression of methylphenidate sensitization.

The fact that LiCl acutely attenuated methylphenidate-induced hyperactivity, while it did not prevent the induction or the expression of methylphenidate sensitization is consistent with other studies on the effects of LiCl on amphetamine- and cocaine-induced behaviors. LiCl was reported to attenuate amphetamine-induced hyperactivity in rats and mice (Borison et al., 1978; Engel and Berggren, 1980; Berggren, 1985; Berggren et al., 1981; Rubin and Wooten, 1984), but other studies demonstrated that LiCl did not affect the stereotypes and locomotion induced by amphetamine (Fessler et al., 1982; Cappeliez and Moore, 1990). Pretreatment with LiCl has also been reported to prevent the induction of cocaine-elicited behavioral sensitization (Post et al., 1984). These different results could be due to differences in experimental parameters such as the route of LiCl administration (e.g., diet vs. intraperitoneal injection), duration of LiCl treatment, and method of behavioral or locomotor quantification. It could also be that the LiCl concentration used in the present study was too low to prevent the induction of methylphenidate-elicited sensitization. However, higher doses of LiCl (100 and 200 mg/kg) were not well tolerated by the rats; hence, we did not use these dosages.

Sodium valproate is another drug used in the treatment of mania. Previous studies in our lab have shown that repeated administration of valproate, which enhances γ-aminobutyric acid (GABA) activity, prevented the induction and the expression of methylphenidate sensitization (Yang et al., 2000a,b). It is believed that valproate may have prevented sensitization to methylphenidate by increasing GABAergic function (Yang et al., 2000a,b) because GABA participates in the regulation of dopamine neurons by reducing dopamine release and inhibiting dopaminergic action (Agmo et al., 1996). Because LiCl only acutely attenuated methylphenidate-induced hyperactivity and did not prevent the induction or the expression of methylphenidate sensitization, it seems unlikely that the LiCl's acute effect is mediated via increases in GABAergic function.

It has also been suggested that LiCl's efficacy is due to its inhibition of the enzyme myoinositol 1-phosphate, which influences several inositol phospholipid pathways. Interference in inositol synthesis causes decreases in intracellular calcium and protein kinase C, which affect the efficiency of cell signaling (Tohen and Grundy, 1999). Other researchers have suggested that LiCl targets the cyclic nucleotide metabolism, as it has been shown to prevent catecholamine-induced increases in adenylate cyclase activity (Divish et al., 1991). Because LiCl's effects are broad in the brain, it is possible that the drug exerts its effects through all these mechanisms, as well as through the catecholaminergic systems, and does not involve any one particular route or site of action.

Pharmacologic interference of the induction and the expression of sensitization to psychostimulants may provide information about the mechanism of behavioral sensitization. Behavioral sensitization has been implicated as an experimental model of psychiatric illnesses, such as bipolar disorders. Therefore, the results suggest that LiCl can acutely attenuate behavioral responses to methylphenidate, but LiCl does not prevent the induction or the expression of behavioral sensitization to methylphenidate. These data are consistent with the fact that LiCl appears less effective in patients with bipolar disorder who have many episodes of this illness (Swann et al., 1999). Mechanisms by which LiCl exerts its effects may provide clues about the process by which transiently increased motor activity becomes persistent sensitization.

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