Pharmacology, Biochemistry and Behavior xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Effects of chronic lithium exposure in a modified rodent ketamine-induced hyperactivity model of mania

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ARTICLE INFO

Keywords:
Lithium
Animal model
Mania
Ketamine
Locomotor activity

ABSTRACT

Bipolar illness is characterized by periods of "mania" — high energy, irritability, and increased psychomotor activation. While the neurobiological investigation of mania has been limited by the lack of reliable animal models, researchers have recently reported that daily subanesthetic doses of ketamine produce a lithium-reversible increase in rodent locomotor activity. Such studies have typically employed short-term (2 week) exposure to daily intraperitoneal-injected lithium and extremely brief (i.e., 5-min) open-field tests of hyperactivity. To increase the translational utility of the model, the effects of 70-days of orally administered lithium were examined on ketamine-induced hyperlocomotion during 30-min test sessions. Rats consumed 2.0 mEq/kg lithium chloride (LiCl) presented daily in a high incentive food (10 g of peanut butter). Control animals ingested peanut butter infused with an equimolar concentration of sodium chloride (NaCl). After 60 days of treatment, a 30-min baseline revealed no differences in the locomotor activity of LiCl and NaCl animals. During the next 10 days, animals received single daily supplemental injections of 25 mg/kg IP ketamine. A subset of animals was injected daily with saline and served as non-ketamine controls. Behavioral testing on the final two days of treatment confirmed that ketamine administration produced a profound increase in locomotor activity that was significantly attenuated in the LiCl group. Additionally, blood plasma levels of lithium were found to be comparable to low-moderate human therapeutic levels. These data confirm the viability and utility of ketamine-induced hyperlocomotion as a rodent model of mania.

1. Introduction

Bipolar illness is a serious psychiatric disorder affecting 2–4% of the world's population (Miklowitz and Johnson, 2009; Murray and Lopez, 1996). The disorder increases the probability of financial struggle, suicide, homelessness, incarceration, and drug abuse (Copeland et al., 2009; Miklowitz and Johnson, 2009) and is reported to decrease life expectancy by an average of 8.5 to 9 years (Crump et al., 2013; Nock et al., 2009). The disorder is characterized by unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks. As the name implies, if left untreated, bipolar illness typically entails two distinct oscillating and opposing periods of affective disorder — a manic phase characterized by states of irritability, high energy, hyperlocomotion, and impulsive behavior alternating with periods of depressed mood, energy and activity (American Psychiatric Association, 2013).

The use of animal models has proven useful for the study of the underlying neurobiological mechanisms associated with psychiatric disorders and for the development of effective pharmacotherapies (e.g. see reviews by Flint and Shifman, 2008; Koob, 2012; Phillips et al., 2018). Note, however, that animal behavioral "models" are distinguishable from behavioral "screens" in that the latter has strong "predictive validity" but not necessarily "face validity" while the former is expected to have both. Thus, a behavioral "screen" can be employed to identify a behavioral response to a drug that predicts clinical efficacy even if the response being measured has little if anything in common with the clinical state. So, for example, a drug's ability to decrease active avoidance responding, while not altering escape responding, has been shown to predict both anti-dopaminergic action and clinical efficacy for the treatment of schizophrenia, while having little if anything in common with the behavioral characteristics of the disease (e.g., Wadenberg and Hicks, 1999; Porsolt et al., 2010). In contrast, behavioral "models" attempt to simulate some aspect of the clinical pathology, and hence have both predictive and face validity. Note that the

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https://doi.org/10.1016/j.pbb.2019.01.003
Received 21 November 2018; Received in revised form 9 January 2019; Accepted 15 January 2019

development of such animal models is not intended to mimic the complete phenotype of a human psychiatric illness, but rather to identify and study a particular aspect of the illness that is responsive to treatments known to be effective in human subjects. For example, there are several viable animal models of depression and anxiety that are responsive to antidepressant or anxiolytic medications and hence provide a means for the assessment of potential new pharmacotherapies. (e.g., see reviews by Abelaira et al., 2013; Bourin, 2015; Campos et al., 2013; Einat et al., 2018; Krishnan and Nestler, 2011; Kumar et al., 2013).

The development of animal models for mania, however, has proven to be more challenging. The most widely used approach has been to examine the manic-like hyper-locomotor response of animals treated with psychomotor stimulant drugs (such as amphetamine). The rationale for this approach is based upon research demonstrating that the occurrence of manic symptoms in bipolar patients is associated with higher urinary dopamine levels, that psychomotor stimulants (which commonly act as dopamine agonists) can exacerbate or even induce a manic episode in such patients, that these drugs produce behavioral effects (e.g., hyperlocomotion) in healthy subjects that resemble those observed in manic patients, and that lithium – the drug of choice for the treatment of manic episodes – reduces the increased activity produced by such drugs (see reviews by Young et al., 2011; Logan and McClung, 2016). Thus, the model would appear to have both face and predictive validity. There are, however, some limitations to the model, most notably the observation that, while acute administration of lithium reverses the hyperactivity produced by amphetamine, a regimen of chronic exposure to lithium comparable to that required in the human clinical arena, does not appear to alter amphetamine's psychomotor effects, thereby greatly reducing its translational utility (e.g., Fessler et al., 1982; Cappeliez and Moore, 1990; Young et al., 2011; Logan and McClung, 2016).

While other pharmacological models of mania have been examined with varying success (e.g., Young et al., 2011; Logan and McClung, 2016) most recently, researchers have proposed that ketamine-induced increases in rodent locomotor activity may serve as a more viable model of the hyperactivity exhibited by manic patients (Debom et al., 2016; Gazal et al., 2014, 2015; Ghedim et al., 2012). Given its recent popularity as an antidepressant and its long-standing reputation as an anesthetic (Berman et al., 2000; Dong et al., 2015; Garcia et al., 2008) ketamine might seem a non-intuitive candidate for mania induction. However, when administered daily in subanesthetic doses to rodents, it has been shown to produce a sensitized hyperlocomotor response that is reversed by the administration of lithium (Arslan et al., 2016; Debom et al., 2016; Gazal et al., 2014; Wendler et al., 2016). While such studies have provided encouraging results, the methodology employed in this work may have limited the translational utility of the model by employing a relatively short protocol for lithium exposure (3–15 days) whereas the clinical use of the drug typically requires several weeks before therapeutic effects are observed (e.g., Maj, 2003; Richardson and Macaluso, 2017). Additionally, the methods described in the literature have involved intraperitoneal administration of lithium which has the drawback of introducing an arousing and potentially stressful injection procedure for the subjects and, of course, differs from the oral administration used by human patients. Finally, the previously published studies have employed an extremely brief and highly variable measure of hyperlocomotion (i.e., typically examining rodent ambulation during a single 5-min open-field test). The current study was devised to address each of these potential issues by employing a modified version of the ketamine-model of mania in which: a) animals were exposed to a regimen of chronic lithium that more closely resembles human clinical protocol (i.e., 70 days), b) as in the human condition, the lithium was ingested orally in the animal's diet; and c) the impact of lithium on ketamine-induced hyperactivity was assessed during relatively long 30-min test sessions in automated locomotor activity chambers.

2. Methods

2.1. Subjects

Subjects were initially 20 albino male Sprague-Daley rats (Charles River Laboratory, Hollister, CA) weighing approximately 225 g at arrival. Subjects were individually housed within a temperature controlled (22 °C) vivarium maintained on a 12-hour light-dark cycle (lights on at 08:00 h). Rats initially were provided with ad libitum access to food (Purina rat chow) and water and were gently handled daily for the first 7 days after arrival. All animal procedures strictly adhered to the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* and were reviewed and approved by the University of California at Santa Barbara's Institutional Animal Care and Use Committee (IACUC).

2.2. Drugs

Lithium chloride (LiCl; Sigma-Aldrich) was dissolved in purified drinking water and then introduced to the animals through their diet. Starting one week after arrival, half of the subjects had their daily rat chow replaced with a high-incentive food – i.e., 10 g of low-sodium artificially-sweetened peanut butter (creamy style JIF® brand) with 0.5 ml of the LiCl (n = 9; one animal became ill and was excluded from the data analyses) at a dose of 2.0 mEq/kg. An additional group of animals exposed to a higher 3.0 mEq/kg dose of LiCl was originally included in the study, but this dose was found to be toxic to the animals and was therefore discontinued. To control for the resulting salty taste of the solution and its potential effects on water retention and thirst, peanut butter infused with an equimolar solution of sodium chloride (NaCl; Fisher Chemical) was provided to the remaining subjects who served as a non-lithium (salt) control group (n = 10). Subjects were weighed daily and over time provided a supplement of regular rat chow to ensure weight gain when necessary. Since human patients experience the therapeutic effects of lithium only after several weeks of administration, subjects here were maintained on these diets for 70 days. The LiCl and NaCl solutions were freshly created each week with the volume and amount of drug adjusted upwards as the animals gained weight in order to maintain the same daily dose of LiCl. Ketamine (Henry-Schein) was diluted in 0.9% sodium chloride and injected daily over the last 10 days of lithium exposure with a single dose of 25.0 mg/kg IP (in a volume of 1.0 ml/kg). The dose of lithium and the dose and treatment protocol for ketamine were based upon previous studies using this animal model (e.g. Arslan et al., 2016; Debom et al., 2016; Gazal et al., 2014, 2015; Ghedim et al., 2012; Wendler et al., 2016).

2.3. Locomotor apparatus

A group of 10 identical locomotor chambers (Kinder Scientific, San Diego, CA) was used to measure the spontaneous ambulatory activity (distance traveled per unit time) of each subject. The locomotor apparatus consisted of Plexiglass chambers (20 cm L × 40 cm W × 20 cm H) each fitted with 15 infrared photodetector-emitter pairs evenly spaced along the long axis of the chamber and 8 evenly spaced along the short axis of the chamber. Interruption of the infrared beams sent signals to a desk-top computer running custom software (Kinder Scientific) that recorded the distance traveled (cm) by each animal in real time.

2.4. Procedure

As described above, animals were exposed to their LiCl or NaCl diets for a total of 70 days. On Day 60, all subjects underwent a 30 min baseline trial to assess whether or not there were any inherent group differences in locomotor behavior prior to ketamine administration. Ketamine (25 mg/kg IP in a volume of 1.0 ml/kg) was then administered once daily over the next 10 days during which all animals

continued with their LiCl or NaCl diets. Four subjects (two each from the LiCl and the NaCl groups) served as non-ketamine controls and were injected daily during the last 10 days of the study with 1.0 ml/kg IP of 0.9% physiological saline. These non-ketamine animals were included solely to ensure that the current ketamine procedure produced the reliable increases in ambulation that others had previously reported (papers cited in the Introduction of this paper). The primary focus of the current study remained the comparison of the two ketamine-treated groups (LiCl + ketamine and NaCl + ketamine).

On Days 9 and 10 (the last two days of ketamine treatment) the ambulatory behavior of subjects was tested daily during single 30-min locomotor activity tests. The first test was conducted on the next to last day of treatment (Day 9), and began 30 min post-ketamine injection to be consistent with the methods described in the published literature. However, due to the drug's fast onset and short duration of action (e.g., Haas and Harper, 1992; Páleníček et al., 2011; Williams et al., 2004) a second locomotor test was conducted on the final day of treatment (Day 10) and initiated immediately following the IP ketamine injection to ensure that animals were tested during the peak actions of the drug. This procedure produced three groups of animals: a LiCl + ketamine group (n = 7), a NaCl + ketamine group (n = 8), and a non-ketamine control group (n = 4).

2.5. Blood plasma analyses

On the day following the conclusion of behavioral testing, all subjects were euthanized with an overdose of sodium pentobarbital and phenytoin sodium solution (Euthasol; Henry Schein, NY). Blood was then drawn by syringe directly from the heart from a subset of lithium-treated subjects (n = 9) and a smaller subset of the non-lithium NaCl subjects (n = 3) and sent to an external laboratory (Antech Diagnostics, Ventura, CA) for analysis of drug plasma levels.

3. Results

3.1. Statistical analyses

Since computation of Analyses of Variance (ANOVA) require that the scores within each sample be normally distributed, Shapiro-Wilk normality tests were computed on the total distances traveled by the LiCl and NaCl groups during the pre-ketamine baseline. Both groups passed these normality tests (W = 0.93 and 0.87 for the LiCl and NaCl groups respectively). This permitted the subsequent analysis of each test session using mixed-factor repeated measures Group × Time ANOVAs. When significant differences among the groups were identified, subsequent analysis was performed by computation of post hoc Newman-Keuls comparisons. As indicated above, the inclusion of a small non-ketamine control group was solely intended to ensure that ketamine had produced the elevation in responding that others had previously reported. The primary focus of the study was the comparison of the performance of the LiCl and NaCl groups. Consequently, when the post hoc analyses identified differences in the behavior of the LiCl and NaCl groups, this effect was re-examined by computation of an additional ANOVA that selectively compared the performance of these two groups alone (without the non-ketamine controls). In all cases, the alpha level for statistical significance was $p < 0.05$ and all analyses were computed using Prism version 6.0 (www.graphpad.com).

3.2. Locomotor test

A baseline trial conducted after 60 days of treatment, revealed that the LiCl and NaCl animals did not differ in ambulatory behavior prior to the start of ketamine treatments (see Fig. 1). A mixed two-factor (Group × Time) repeated measures ANOVA computed on the data shown in the figure produced no significant differences between the two groups ($F_{(1, 17)} = 0.5907$, $p > 0.05$) during baseline. As expected,

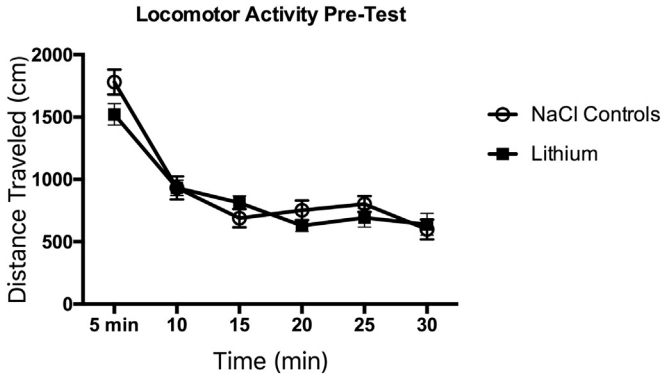

Fig. 1. Pre-ketamine Baseline — Locomotor activity (Mean ± SEM distances traveled in cm) of animals after 60 days of lithium or sodium chloride consumption prior to the start of ketamine treatments.

there was a significant effect of the repeated measures factor (i.e. a decrease in the overall locomotor behavior of subjects over Time as animals habituated to the apparatus; $F_{(5, 85)} = 76.11$, $p < 0.0001$) as well as a significant Group × Time interaction ($F_{(5, 85)} = 2.42$, $p = 0.04$). The latter result indicates that the groups behaved differently relative to each other over the course of the 30 min time period (i.e., the lithium group was observed to be less active during the first 5 min of the baseline trial).

Fig. 2 depicts the results from the two 30-min locomotor activity tests conducted on the last two days of ketamine treatment. The first test (left panel of Fig. 2) was conducted 30-min after IP ketamine injections, in line with the methods employed in previous studies. As described and explained in the Methods section above, the second locomotor test (right panel of Fig. 2), began immediately after ketamine was administered. For each test, separate two-factor (Group × Time) ANOVAs were computed on the resulting data. In Test I, the ANOVA revealed a highly significant effect of both Time ($F_{(5, 80)} = 12.64$, $p < 0.001$) and Group ($F_{(2, 16)} = 21.45$, $p < 0.001$), but no Group × Time interaction ($F_{(10,80)} = 1.65$, $p = 0.11$). Post hoc Newman-Keuls comparisons confirmed that both the LiCl + ketamine and NaCl + ketamine groups exhibited greater ambulation than control animals injected with saline in place of ketamine ($p < 0.05$). While the activity of the lithium + ketamine group appeared to be attenuated during the first 5–10 min of the session, when averaged across the entire 30-min session those two groups did not significantly differ from one another.

Differences in the behavior of the three groups became more apparent in Test II (right panel of Fig. 2). The ANOVA identified a highly significant effect of Group ($F_{(2, 16)} = 11.28$, $p < 0.001$) but, as the figure clearly illustrates, there was no main effect of Time ($F_{(5, 80)} = 1.07$, $p = 0.38$) nor a significant Group × Time interaction ($F_{(10,80)} = 0.51$, $p = 0.88$). Post hoc Newman-Keuls comparisons confirmed that both ketamine groups were more active than the non-ketamine controls, and most importantly, the lithium + ketamine group exhibited less ambulation than that of the sodium (NaCl) + ketamine group (all comparisons $p < 0.05$).

3.3. Blood serum analysis

As shown in Fig. 3, analyses of blood plasma drawn from the LiCl group identified an average of 0.47 mEq/L of lithium per subject while no drug was detected in the small sample of NaCl-treated subjects (< 0.1 mEq/L of lithium in plasma). Six of the eight animals tested exhibited blood plasma levels within the human therapeutic range (i.e., ≥ 0.4 mEq/L).

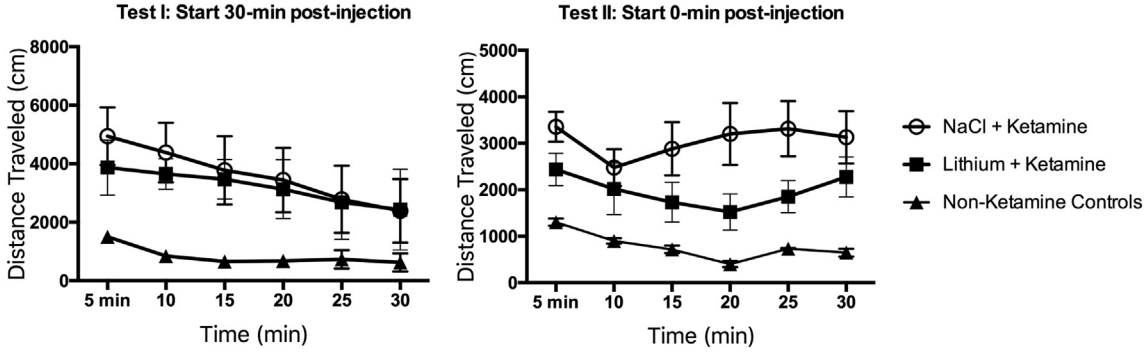

Fig. 2. Effects of lithium treatments on ketamine-induced hyperlocomotion: Test I (left panel) was conducted beginning 30-min post-ketamine injection and Test II (right panel) was conducted the next day starting immediately after ketamine injection. Data depict Mean ± SEM distance traveled (cm) during a 30-min tests in animals pretreated for 9–10 days with single daily 25 mg/kg IP injections of ketamine or saline. Lithium animals had ingested a daily dose of 2.0 mEq/kg lithium chloride delivered in their diet over 70 days; NaCl animals consumed a daily equimolar dose of sodium chloride in their diet. Non-ketamine controls consisted of two animals each from the lithium and sodium groups that received injections of saline in place of ketamine during the final 10 days of the experiment.

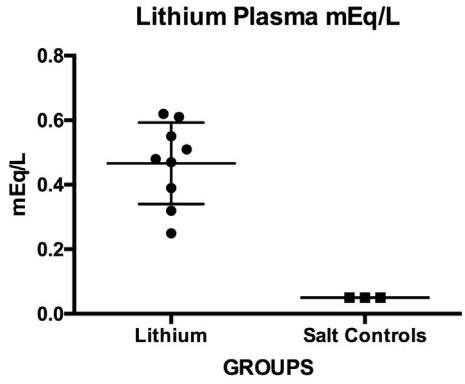

Fig. 3. Mean blood plasma levels of lithium. The figure identifies the individual data points plus the Mean (± SEM) blood plasma levels of lithium in chronic 70-day lithium-treated animals. There were no detectable levels of lithium in the blood plasma of any of the NaCl (Salt) control animals.

3.4. Weights

Animal weights upon arrival averaged 225 g for each group. While both groups increased their mean body weight over the course of the experiment, the lithium animals did so at a slower rate than did the sodium controls. By the last day of testing the mean (± SEM) of the lithium group was 302.8 ± 11.2 g compared to the sodium controls 378.6 ± 4.1 g.

4. Discussion

The current study replicates and extends the findings of researchers who have recently proposed a rodent model of manic disorder in which daily systemic treatments of sub-anesthetic doses of ketamine produce a hyperlocomotor response that is reversible by co-administration of lithium (Arslan et al., 2016; Gazal et al., 2014; Ghedim et al., 2012). Hyperactivity is, of course, a hallmark symptom of mania and recent multivariate assessments of the locomotor profiles of human subjects have revealed patterns of ambulatory behavior (i.e., time spent moving, distance traveled, consistency with which movement occurs in the same direction, time spent exploring novel objects, etc.) that are highly comparable for bipolar patients and for rodents exposed to stimulant drugs (e.g., Perry et al., 2009; Young et al., 2007, 2016). The current observation that ketamine-induced hyperactivity is significantly attenuated in animals exposed to chronic lithium, further strengthens the face validity of this methodology as a model of human manic disorder. Additionally, ketamine has been shown to alter glutamatergic function as a competitive NDMA antagonist and has been shown to potentiate oxidative stress in the brain (de Oliveira et al., 2009; Réus et al., 2017). Bipolar disorder has been linked to both glutamatergic dysfunction (Chen et al., 2010; Sanacora et al., 2008) and increases in oxidative stress (Berk et al., 2011) thereby further strengthening the rationale for employing ketamine in a model for the induction of mania in rodents.

The current results cannot easily be accounted for by some form of simple motoric or sedative actions of the lithium since the drug produced no prolonged deficits in baseline locomotor activity when examined prior to the start of ketamine injections. Similarly, while the lower weights of the lithium animals may have contributed to the drug's effects on ketamine locomotion, the absence of a significant difference in the baseline responding of the two groups suggests that weight was not a likely factor in the results. It is noteworthy that here was a short-lived reduction in baseline responding during the first 5-min of both the baseline test (Fig. 1) and the first ketamine test conducted beginning 30-min post-injection (left panel of Fig. 2), however, the statistical analyses did not detect a main effect of Group on either trial. This is consistent with the conclusion of O'Donnell and Gould (2007) who, after a comprehensive review of the rodent lithium literature concluded that: "…it has consistently been shown that therapeutic doses of lithium, which effectively alter drug-induced changes in locomotion, do not change baseline locomotion in tests with a sufficient time course (p.936)." The need for tests conducted with a "sufficient time course" is what motivated the decision to employ locomotor tests over 30-min session as opposed to the brief 5-min test sessions most often described in the literature (see references cited above). O'Donnell and Gould (2007) further concluded that for acute administration "therapeutic serum levels are achieved by doses between 1.5 and 3 mEq/kg." The chronic dosing regimen employed here was 2.0 mEq/kg and produced serum levels averaging just under 0.5 mEq/L, which represented levels in the low to moderate human therapeutic dose range of 0.4–1.2 mEq/L (Severus et al., 2008). Additionally, as in human patients, lithium was administered orally in the animals' diet, thereby adding translational value to the current methodology over the intraperitoneal injections (which add a potentially aversive daily component to the treatment regimen) previously used in prior ketamine-hyperactivity studies.

As referenced above and in the Introduction of this paper, the ketamine protocol described in the published literature employed a short 5-min test conducted beginning 30-min after the final ketamine injection. The decision to wait 30-min before testing was undoubtedly due to concerns about the potential sedative effects of ketamine immediately after injection. However, other researchers (e.g., Ma and Leung, 2007; Ward et al., 1994) have observed ketamine-induced increases in locomotor behavior when subjects were tested immediately after drug injections, which is, of course, consistent with the current findings. As demonstrated in the Fig. 2 (right panel) there was no evidence that ketamine had any sedative effect after 10 days of treatment. Of course,

it's possible that the subjects may have developed tolerance to the ketamine's sedative action or that a sensitized response developed to the locomotor activating effects of the drug – although, as indicated above, O'Donnell and Gould's (2007) review of the literature concluded otherwise when acute sub-anesthetic doses are employed. In either case, the current results confirm the utility of examining ketamine's locomotor effects starting immediately after injection and conducted over longer test sessions. Indeed, given the fast onset and short half-life of the drug (e.g., Páleníček et al., 2011; Peltoniemi et al., 2016), it seems reasonable to examine the behavioral effects of ketamine at time-points that include its peak pharmacological effects. Páleníček et al. (2011) have shown that when ketamine is injected IP in rats at doses comparable to those employed here, the behavioral (locomotor) effects of ketamine, changes in EEG, as well as increases in brain and plasma levels of the drug, all peak at 10–15 min post-injection. Additionally, these investigators observed an increase in locomotor behavior that was sustained throughout a 30-min open field test, a result consistent with that observed in the current study.

Previous descriptions of the ketamine-hyperactivity model of mania have invariably employed an open field for the measurement of ambulatory behavior. While the use of an open field has its critics (e.g., see Ennaceur, 2014) the test has the putative advantage of providing researchers with information not only about ambulation, but also about the presumed anxiety level of the subjects, as reflected in the frequency with which they cross into the “unprotected” center sections of the apparatus. So, for example, Gazal et al. (2014) have reported that lithium reverses the hyperlocomotive effects of ketamine in the open field, without altering the anxiogenic response of the animal (as measured by entries into the center of the apparatus). Hence the effects of lithium were unlikely to be accounted for by a change in the stress or anxiety level of the animals. Since lithium has long been known to reduce exploratory and investigatory (i.e., rearing) behavior in animals exposed to novel environments (e.g., Hines, 1985; Johnson, 1976, 1979; Katz, 1980; Smith, 1980), this may provide a behavioral explanation for the drug's efficacy in altering the enhanced locomotor response to ketamine as observed in an open field. However, such an interpretation is less likely to account for the current results given the small size of the locomotor chambers and their high degree of similarity to the subjects' home cages. The relevance of this distinction is important since the systems mediating lithium's effects on ambulatory behavior are likely to be different from those mediating exploratory behaviors.

In summary, the current results demonstrate the face and predictive validity of a modified version of the ketamine-hyperactivity model of mania that more closely compares to the human condition in terms of length of lithium exposure and route of drug administration. Research is currently underway in our laboratory to employ this model in the examination of the mechanisms by which lithium produces its behavioral effects.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgements

This work was supported by a Heising-Simons Foundation (USA) Science Program Grant (#2017-0496).

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