Available online at www.sciencedirect.com

SCIENCE DIRECT

European Journal of Pharmacology 515 (2005) 117 – 127

www.elsevier.com/locate/ejphar

Dose response effects of lithium chloride on conditioned place aversions and locomotor activity in rats

Christine M. Tenk*, Martin Kavaliers, Klaus-Peter Ossenkopp

Neuroscience Program and Department of Psychology, Social Science Centre, University of Western Ontario, 1100 Richmond St., London, Ontario, Canada N6A 5C2

Received 18 November 2004; received in revised form 14 February 2005; accepted 8 April 2005

Abstract

The present study examined the multi-variable locomotor activity effects of lithium chloride (LiCl) treatment in male rats. Of interest was a determination of which variables might show a dose–response relationship in LiCl-induced conditioned place aversions. Automated open-fields were partitioned into two chambers distinct in tactile and visual cues. A control group [$n=8$] received saline (NaCl; 0.15 M) paired with both chambers while three LiCl groups (0.15 M; 32 mg/kg [$n=7$], 95 mg/kg [$n=7$], 127 mg/kg [$n=7$]) received LiCl paired with the normally preferred chamber and saline paired with the non-preferred chamber. During extinction trials, rats were allowed to choose between the two chambers to provide an index of conditioned place aversions. Locomotor activity and its distribution within the chambers were also assessed during both conditioning and extinction trials. Dose-dependent decreases occurred in all measures of locomotor activity following LiCl administration during conditioning. During extinction trials, place aversions developed in animals conditioned with LiCl. LiCl-treated rats spent significantly less time in the LiCl-paired chamber relative to controls but not in a dose-dependent manner. Animals that had been conditioned with 95 or 127 but not 32 mg/kg LiCl, displayed significantly more vertical activity in the LiCl-paired chamber than controls during extinction trials. These findings indicate that, in addition to producing dose-dependent unconditioned effects on locomotor activity, LiCl also produces dose-dependent conditioned effects on vertical activity. These conditioned rearing response effects provide a valid measure of the conditioned avoidance response that provides evidence for dose-dependent LiCl-induced conditioned place aversions.

Keywords: Lithium chloride; Place conditioning; Biased conditioning apparatus; Nausea; Toxin; Long-Evans rat; Open-field

1. Introduction

Lithium chloride (LiCl) is a toxin that induces vomiting in species with an emetic reflex, including some primates, dogs, cats, and ferrets (Borison, 1989). Furthermore, LiCl produces symptoms consistent with visceral illness in species that do not vomit, such as rats and mice (Ossenkopp and Eckel, 1995; Parker, 2003). For example, LiCl administration causes a reduction in food intake (e.g., Curtis et al., 1994), decreases sodium consumption following sodium depletion (e.g., Chavez et al., 1995), and induces conditioned taste aversions to flavors paired with administration of the toxin (e.g., Eckel and Ossenkopp, 1996; Ossenkopp et al., 2003; Parker, 1982; Zalaquett and Parker, 1989; Nachman and Ashe, 1973; Nachman, 1970). In addition to producing conditioned taste aversions, LiCl also causes conditioned place aversions to environments previously paired with toxin administration (e.g., Frisch et al., 1995; Miller et al., 2000; Parker, 1992; Turenne et al., 1996; White and Carr, 1985).

LiCl-induced conditioned place aversions have been found following the pairing of specific environmental cues and a range of doses of the toxin. For example, Khroyan et al. (1995) demonstrated that rats spent significantly less time in a chamber paired with administration of 127 mg/kg LiCl than in a chamber paired with saline injections. Similarly, rats spent significantly less time in a chamber

* Corresponding author. Tel.: +1 519 661 2111x81214; fax: +1 519 661 3961.

E-mail address: ctenk@uwo.ca (C.M. Tenk).

0014-2999/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2005.04.007

when it was paired with injections of 62 mg/kg (White and Carr, 1985) or 75 mg/kg LiCl (Parker and McDonald, 2000) relative to a saline-paired chamber. It also was demonstrated that injections of 50 mg/kg LiCl significantly reduced the amount of time spent in the drug-paired context (Turenne et al., 1996) as did doses of 40 and 20 mg/kg LiCl (Miller et al., 2000). However, administration of 10 mg/kg LiCl did not produce a significant decrease in the time spent in the toxin-paired chamber (Miller et al., 1999, 2000).

Despite much research on dose-related effects of LiCl-induced conditioned place aversion, no clear dose-dependent effects of LiCl on the strength of the conditioned avoidance response were found in these previous studies when time spent in the drug-paired chamber was used as the measure of aversion. Some studies demonstrated that increasing doses of LiCl decreased the amount of time spent in the toxin-paired chamber in a dose-related manner (Miller et al., 1999, 2000), while others indicated that no dose-dependent relationship exists (White and Carr, 1985).

It is known that LiCl administration tends to suppress locomotor activity in rats (e.g., Johnson, 1972, 1975; Ladowsky and Ossenkopp, 1986; Meachum and Bernstein, 1992; Parker et al., 1984). For example, injections of 95 mg/kg LiCl have been shown to significantly reduce ambulation in an open-field (Smith, 1981) and treatment with 64 mg/kg LiCl causes significant decreases in three measures of locomotor activity (Smith, 1983). However, few studies have examined the effects of LiCl on locomotor activity during both the conditioning and test (extinction) trials in the place aversion procedure. A detailed analysis of locomotor activity throughout the place conditioning procedure could provide additional indices of LiCl-induced conditioned place aversion and clarify a putative dose–response relationship.

Measuring activity during conditioning trials allows for the examination of the unconditioned (direct) effects of the toxin while measures of activity obtained during test (extinction) trials allow for the assessment of conditioned locomotor effects of the toxin. Conditioned effects are those effects that are elicited in an environment previously paired with toxin administration. One such study examining unconditioned and conditioned responses, observed that, during conditioning, the duration and frequency of rearing exhibited by rats decreased, along with crossings over gridlines within the chamber, following administration of 127 mg/kg LiCl (Parker et al., 1984). During test trials, these rats conditioned with 127 mg/kg LiCl displayed an increase in rearing duration and “limb flicks” (rapid shaking of the forepaws). In addition, Meachum and Bernstein (1992) recorded decreased grooming during conditioning in rats administered 127 mg/kg LiCl. During the test trial, these rats exhibited an increase in “freezing” behaviour as well as decreased grooming.

The purpose of the present study was to examine activity variables for additional evidence of a dose–response relationship in LiCl-induced conditioned place aversion using a new, automated, two-chamber place conditioning apparatus that allowed for multi-variable assessments of locomotor activity. Locomotor activity was measured during both conditioning and extinction trials allowing for an examination of both the unconditioned and conditioned effects of LiCl.

2. Materials and methods

2.1. Subjects

The subjects were 29 male Long-Evans rats (Charles River, Canada) weighing between 290 and 350 g at the start of the experiment. The rats were housed in pairs in standard polypropylene cages ($45 \times 22 \times 20$ cm) in a temperature-controlled colony room (20 ± 1 °C) maintained on a 12:12 h light:dark cycle (lights on at 07:00) with ad libitum access to both food (Prolab RMH3000 lab chow) and tap water. All testing took place during the light phase of the light:dark cycle. All procedures were approved by the University of Western Ontario Animal Care Committee and were in accordance with the Canadian Council of Animal Care (CCAC) Guidelines.

2.2. Drug

Lithium chloride (Fisher Scientific, Toronto, ON) was dissolved in distilled water to a molarity of 0.15 M. Doses of LiCl were achieved by manipulating the volume of the 0.15 M solution and were administered at 32, 95 and 127 mg/kg intraperitoneally (i.p.). These doses of LiCl were chosen on the basis of past research demonstrating LiCl induced-conditioned place aversions with doses ranging from 20 mg/kg to 127 mg/kg (Khroyan et al., 1995; Miller et al., 2000; Parker, 2003). Isotonic (0.9%, 0.15 M NaCl; i.p.) saline was used both as the 0 mg/kg LiCl salt solution, administered at 5 ml/kg and as a control injection for LiCl, administered in the same volume as LiCl.

2.3. Apparatus

The two chamber, place-conditioning apparatus consisted of eight, modified Versamax Animal Activity Monitors (Accuscan Model RXYZCM-16, Columbus, OH). Each monitor consisted of a clear Plexiglas open-field ($40 \times 40 \times 30.5$ cm) covered by a Plexiglas lid with air holes. Infrared photobeams were located 2.54 cm apart and 5.7 cm above the floor along the perimeter of the box (16 beams per side). Two additional banks of 16 photobeams were located on opposite sides of the box, 2.54 cm apart and 16.4 cm above the floor. Beams breaks in lower and upper banks correspond to movements in the horizontal or vertical plane, respectively (Ossenkopp and Kavaliers, 1996). All activity monitors were connected to a Versamax data analyzer (Accuscan Model DCM-8, Columbus, OH), which then transmitted data to an IBM Pentium II computer for