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Neurobehavioral effects of lithium in the rat: Investigation of the effect/concentration relationships and the contribution of the poisoning pattern

Anne-Sophie Hanak[a,b,c], Lucie Chevillard[a,b,c], Rodolphe Lebeau[a,b,c], Patricia Risède[a,b,c], Jean-Louis Laplanche[a,b,c], Nadia Benturquia[a,b,c], Bruno Mégarbane[a,b,c,d,*]

[a] Inserm, UMR-S1144, Paris, France
[b] Paris-Descartes University, Paris, France
[c] Paris-Diderot University, Paris, France
[d] Assistance Publique - Hôpitaux de Paris, Lariboisière Hospital, Department of Medical and Toxicological Critical Care, Paris, France

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ABSTRACT

Severity of lithium poisoning depends on the ingested dose, previous treatment duration and renal function. No animal study has investigated neurobehavioral differences in relation to the lithium poisoning pattern observed in humans, while differences in lithium pharmacokinetics have been reported in lithium-pretreated rats mimicking chronic poisonings with enhanced brain accumulation in rats with renal failure. Our objectives were: 1)-to investigate lithium-related effects in overdose on locomotor activity, anxiety-like behavior, spatial recognition memory and anhedonia in the rat; 2)-to model the relationships between lithium-induced effects on locomotion and plasma, erythrocyte, cerebrospinal fluid and brain concentrations previously obtained according to the poisoning pattern. Open-field, elevated plus-maze, Y-maze and sucrose consumption tests were used. In acutely lithium-poisoned rats, we observed horizontal ($p < 0.001$) and vertical hypolocomotion ($p < 0.0001$), increased anxiety-like behavior ($p < 0.05$) and impaired memory ($p < 0.01$) but no altered hedonic status. Horizontal ($p < 0.01$) and vertical ($p < 0.001$) hypolocomotion peaked more markedly 24 h after lithium injection and was more prolonged in acute-on-chronically vs. acutely lithium-poisoned rats. Hypolocomotion in chronically lithium-poisoned rats with impaired renal function did not differ from acutely poisoned rats 24 h after the last injection. Interestingly, hypolocomotion/concentration relationships best fitted a sigmoidal E_{max} model in acute poisoning and a linear regression model linked to brain lithium in acute-on-chronic poisoning. In conclusion, lithium overdose alters rat behavior and consistently induces hypolocomotion which is more marked and prolonged in repeatedly lithium-treated rats. Our data suggest that differences between poisoning patterns regarding lithium-induced hypolocomotion are better explained by the duration of lithium exposure than by its brain accumulation.

1. Introduction

Lithium (Li) is the cornerstone of bipolar disorder treatment (Geddes and Miklowitz, 2013). However, due to its narrow therapeutic index, significant neurocognitive and behavioral adverse effects often occur, resulting in psychomotor slowing, apraxia, dysarthria and impaired memory (Pachet and Wisniewski, 2003). Neurotoxicity is usually reversible with the adjustment of the Li dosage regimen but syndromes of irreversible lithium-effectuated neurotoxicity (SILENT) have been reported (Adityanjee et al., 2005). When considering Li overdose, three patterns are described depending on the ingested dose, the duration of exposure and the renal function, i.e. acute, acute-on-chronic and chronic poisoning characterized by discrepancies between toxicity features and the plasma Li concentration (Jaeger et al., 1993; Vodovar et al., 2016).

To investigate Li neuropharmacokinetics, we developed three Sprague-Dawley rat models mimicking the different Li poisoning patterns observed in humans (Hanak et al., 2015). In comparison to acute exposure, we showed significant brain Li accumulation after prolonged exposure, enhanced in the presence of renal failure. However, whether the observed differences in the blood and brain Li kinetics between the three rat models resulted in differences in neurobehavioral effects remained to be determined.

In rodents, Li is responsible for significant behavioral effects

Abbreviations: CSF, cerebrospinal fluid; EPM, elevated plus-maze; Li, lithium; NAC, *nucleus accumbens*; OPF, open field; TTRT, two-trial recognition task

* Corresponding author at: Assistance Publique - Hôpitaux de Paris, Lariboisière Hospital, Department of Medical and Toxicological Critical Care, Paris, France.
E-mail address: bruno-megarbane@wanadoo.fr (B. Mégarbane).

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investigated after acute and repeated administration (O'Donnell and Gould, 2007). Variably altered horizontal locomotor activity (Johnson, 1972a; Mukherjee et al., 1977; Smith, 1976; Smith and Smith, 1973; Tenk et al., 2005; Tomasiewicz et al., 2006), reduced rearing (Gray et al., 1976; Johnson, 1972b; Johnson and Wormington, 1972; Smith, 1975, 1983; Wolthuis et al., 1975), decreased exploratory and anxiety-like behaviors (Katz, 1980; Youngs et al., 2006) and anhedonic effects (Flaisher-Grinberg et al., 2009; Pezzato et al., 2015) were observed. Regarding Li-induced cognitive alterations, conflicting data were reported with hindered, unaffected or enhanced effects on learning and memory (Nocjar et al., 2007; Tsaltas et al., 2007, 2009).

To date, no study has investigated Li-related effects on rat behavior according to the poisoning pattern. One study showed that the peak depressant effects on motor activity induced by a single Li injection in the rat occur at the Li peak in the brain (Mukherjee et al., 1977). In another rat study, various Li dosage regimens leading however to similar plasma Li concentrations resulted in distinct behavioral responses, suggesting different patterns of Li distribution in the brain (Lima et al., 2008). Since we observed variable Li accumulation in the rat brain in relation to the poisoning pattern (Hanak et al., 2015), we hypothesized that variable neurobehavioral manifestations could be observed in each poisoning pattern, explained by the amount of accumulated Li. Thus, we designed an experimental study in Sprague-Dawley rats: 1)- to investigate the effects of Li overdose on locomotor activity, anxiety-like behavior, spatial recognition memory and anhedonia; and 2)- to compare the relationships between the effects on locomotion and plasma, erythrocyte, cerebrospinal fluid (CSF) and frontal cortex Li concentrations according to the poisoning pattern we previously measured.

2. Materials and methods

Experiments were carried out within the ethical guidelines established by the National Institutes of Health and the French Ministry of Agriculture. Protocols were approved by the Paris-Descartes University ethics committee for animal experimentation.

2.1. Animals

We used 7-week-old male Sprague-Dawley rats (Janvier, France), weighing 250–300 g at the start of the experiment. Animals (3/cage) were housed for 7 days before the experiment in an environment maintained at 20 ± 1 °C with controlled humidity and light-dark cycle. Food and water were provided *ad libitum*. To avoid the novelty effect, rats received standard 5 min-handling procedure on three different days prior to the experiment.

2.2. Chemicals and drugs

Lithium carbonate (Li_2CO_3) and potassium dichromate ($K_2Cr_2O_7$) purchased from Sigma-Aldrich (Saint-Quentin Fallavier, France) were diluted at 50 and 15 mg/ml in saline, respectively. Li_2CO_3 was diluted in water to obtain an 800 mg/l-solution. Hypertonic sodium bicarbonate (8.4% $NaHCO_3$) was supplied by B. Braun Medical S.A. (Diegem, Belgium).

2.3. Behavioral measurements

2.3.1. Locomotor activity

2.3.1.1. Open field (OPF) test. The OPF consisted of an enclosed white Plexiglas chamber open at the top, divided into four equal-sized areas (50 × 50 × 35 cm) and maintained under low illumination (10 lx). Twenty-four hours prior to the experiment, rats received one habituation session for 5 min. At the experiment time, one rat was placed in each area and recorded during 15 min. The chamber was fitted with an infrared floor connected to a miniature overhead infrared video-camera and a PC that used automated video-tracking software (ViewPoint®, Videotrack, Lyon, France) to determine rat horizontal locomotor activity (travelled distance) and inactivity time. Vertical locomotor activity (rearing) was recorded using an ethological keyboard.

2.3.2. Anxiety-like behavior

2.3.2.1. OPF test. The previous chamber was used with intensified brightness (180 lux). The central (26 × 26 cm) and peripheral outer (remaining) areas were defined as described (Lad et al., 2010). The number of entries and time spent in each area were tracked during 5 min using ViewPoint® software.

2.3.2.2. Elevated plus-maze (EPM) test. The EPM consisted of black Plexiglas boards forming a central platform (10 × 10 cm) surrounded by two opposed highly illuminated (180 lux) open arms (50 × 10 cm) and two opposed faintly illuminated (10 lux) enclosed arms (50 × 10 cm with 45 cm-high walls). The maze was placed 50 cm above an infrared floor. At the experiment time, each rat was placed in the central platform facing the open arm away from the experimenter. Rat behavior was recorded by a miniature overhead infrared video-camera over a 5 min-period as previously described (Walf and Frye, 2007). The number of entries and time spent in each arm were tracked using Viewpoint® software.

2.3.3. Spatial recognition memory

2.3.3.1. Two-trial recognition task (TTRT) test. The Y-maze consisted of three black Plexiglas arms (40 × 15 × 35 cm) intersecting at 120°-angles, open at the top and maintained under dim illumination (50 lux). Rat movement and location were recorded by a video-monitoring system allowing manual data scoring. The protocol consisted of two trials (Dellu et al., 1992). Trial-1 (acquisition phase): A guillotine-door closed one randomly chosen arm of the Y-maze. The rat was placed in one open arm, its head pointing away from the maze center and was allowed to visit the two open arms for 5 min. Trial-2 (evaluation of memory performance): The door was removed 20 min later and the rat placed in the same initial arm with free access to the three arms for 5 min. During this trial, the number of entries and time spent in each arm were recorded to evaluate whether the rat discriminated the novel arm and visited it for longer and/or more often than the two familiar arms. An arm visit was considered when the rat moved all four paws into the arm.

2.3.3.2. Spontaneous alternation test. The same Y-maze and recording system were used. Twenty-four hours prior to the experiment, rats received one habituation session lasting 5 min. At the experiment time, the rat was placed at the end of one arm and allowed to freely explore the maze. The sequence of arm entries was recorded over a 10 min-period. The number of spontaneous alternations was determined. An alternation occurred if the rat successively entered the three different arms. The percentage of spontaneous alternations was calculated as follows: [number of alternations/(total number of arm visits − 1)] × 100.

2.3.4. Anhedonia

2.3.4.1. Sucrose consumption test. Single-housed rats were left free to choose between two bottles, one with 1%-sucrose solution and another with tap water, during 48 h (Flaisher-Grinberg et al., 2009). To prevent any effect of side-preference in drinking behavior, the bottle position was switched after 24 h. No previous food or water deprivation was applied before the test. Water and sucrose consumption was determined by weighing the bottles and sucrose preference calculated as follows: