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Research report

Enhancing effects of chronic lithium on memory in the rat

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Abstract

Background: In spite of recent enrichment of neurochemical and behavioural data establishing a neuroprotective role for lithium, its primary effects on cognitive functioning remain ambiguous. This study examines chronic lithium effects on spatial working memory and long-term retention.
Methods: In three discrete experiments, rats subjected to 30 daily intraperitoneal injections (2 mmol/kg) of lithium (lithium groups: serum lithium = 0.5 ± 0.4 mEq/l, 12 h post-injection) or saline (controls) were trained in 0-s delay T-maze alternation and then tested in 30-, 45- and 60-s delay alternation (Experiments 1, 2, 3, respectively). Animals from Experiment 1 were further tested in one-trial step-through passive avoidance under mild shock parameters (0.5 mA, 1 s). Retention was assessed 6 h later. Daily lithium or saline injections continued throughout behavioural testing.
Results: Lithium animals were indistinguishable from controls during 0-delay alternation baseline (Experiments 1–3, accuracy > 88%) but showed significantly higher accuracy than controls at 30- and 45-s delays (93% versus 85% and 92% versus 82%, Experiments 1 and 2, respectively). At 60-s delay (Experiment 3) this beneficial effect of lithium was no longer apparent (lithium and control accuracy = 78%). In Experiment 4, the shock used did not support 6-h passive avoidance retention in controls, whereas lithium animals showed significant step-through latency increases.
Conclusions: Chronic lithium enhanced spatial working memory and promoted long-term retention of a weak aversive contingency. The results suggest that lithium may have potential as a cognitive enhancer.

Keywords: Lithium; Working memory; Passive avoidance retention; T-maze alternation; Rat

1. Introduction

The mood-stabilizing agent lithium is the drug of choice in the treatment of and prophylaxis against both mania and depression in bipolar disorder [1–5]. In addition to its established role as a mood stabiliser, a plethora of recent findings attribute a neuroprotective [6–11] and an antiapoptotic [12,13] role to lithium.

The neuroprotective effect of lithium, which has been associated with long-term administration of therapeutic levels of the substance [9] raises expectations regarding its potential as a prophylactic agent against cognitive decline. However, early clinical reports linked lithium treatment to cognitive blurring and memory deficits (for review see [14]). More recent

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neuropsychological testing has yielded ambiguous results, associating lithium treatment with subjective complaints but not with actual impairments in terms of performance accuracy [15]. There have been several studies which tested the effects of lithium treatment on different types of memory, in psychiatric (mainly bipolar) patients [16–21], in bipolar patients compared to healthy volunteers [22–25] and in normal subjects [26–29]. The latter studies have the advantage of isolating the neuropsychological effects of lithium from those of bipolar disease processes.

In terms of lithium effects on short-term verbal memory performance, several studies report that lithium treatment caused deficits in immediate recall [16–18,20,22–25,28,29] while only three studies failed to replicate this finding [19,21,26].

In most studies investigating lithium effects on long-term verbal memory lithium was found to have a negative impact on delayed recall tasks [16,17,20,23–25,28]. Nevertheless, according to Pachet and Wisniewski [15] who reviewed these studies, the trend toward verbal memory impairment in the lithium-treated population was relatively weak and replications are needed to confirm it.

In contrast to its reported effects on verbal memory, no significant effects of lithium emerge in the area of visual memory. The immediate form of visual memory tasks was reported unimpaired by lithium administration in most relevant studies [18,21,23,25]. A single study [16] reported transient impairments in visual memory which dissipated following discontinuation of lithium. With respect to delayed recall in visual memory tasks, one study [18] reported no lithium-associated decrease in performance, whereas a later study [16] found reversible lithium-induced deficits.

The animal literature on the cognitive effects of lithium presents similar inconsistencies. Older studies suggest that lithium induces cognitive deficits, which they attribute to a narrowing of attentional filtering onto high salience stimuli. Hines and Poling [30] reported hindered acquisition of passive avoidance with no effect on active avoidance after lithium pretreatment. Hines [31,32] observed deficits in the acquisition of position discrimination and compromised shock-induced activity suppression in the open field. Cappeliez and Moore [33] and Cappeliez et al. [34] reported increased attention to high salience cues and impaired latent inhibition in lithium-treated rats.

Recent animal studies on the effects of lithium in various memory tasks are sparse. A transient deficit in spatial reference but not working memory was observed in the hole board task after chronic lithium [35]. The authors attributed this deficit to the suppressive effect of lithium on the basal expression of the immediate-early gene Nurr1 (implicated in neuronal plasticity) in the hippocampus. However, Vasconcellos et al. [36], investigating the effects of chronic lithium treatment on reference and working memory in a chronic stress model, reported no effect of lithium on reference memory in the water maze. Furthermore, they showed that the reference memory deficit induced by chronic stress was attenuated by lithium treatment. In the same study, neither stress nor lithium had any effect on working memory. The only recent study suggesting that chronic lithium impairs spatial working and reference memory used spontaneous alternation in a plus maze in black molly fish [37].

In summary, recent human studies suggest that chronic lithium causes subtle negative effects on psychomotor speed and verbal memory but no impairment on visuospatial skills, attention or concentration [15]. Animal studies suggest some behavioural deficits in active avoidance and visually cued discrimination learning, while spatial learning and memory appear to be transiently if at all impaired, or even protected by lithium pretreatment [36]. These recent findings are more in line than older studies with the biochemical literature which establishes a neuroprotective role for chronic lithium treatment. They are also in line with some early findings of our laboratory, which suggested a beneficial effect of chronic lithium on working memory in the rat [38], thus raising the possibility that lithium may act as a cognitive enhancer. This hypothesis was further investigated in the series of experiments reported here. These experiments assessed the effects of chronic lithium, at doses sustaining lithium plasma levels within the human clinical range, on spatial working memory and long-term retention.

2. Materials and methods

Experiments 1 and 4 were carried out in the Experimental Psychology laboratory, Institute of Psychiatry, University of London [38] while Experiments 2 and 3 were conducted in the Experimental Psychology laboratory, Department of Psychiatry, University of Athens Medical School. For this reason Experiments 1–3, all of which involve delayed alternation differing in delay length only (30-, 45- and 60-s, respectively) were carried out as discrete procedures rather than as a repeated-measures alternation procedure with varying delays. For the same reason the reader will note differences in rat strains and lithium suppliers used. Given the consistency of our findings, these procedural differences, as well as the fact that Experiment 2 constitutes a replication of our basic finding reported in Experiment 1, strengthen our results.

2.1. Subjects

Rat strains and group *n*'s for Experiments 1–3 are shown in Table 1. Experiment 1 included 14 naïve adult male Sprague–Dawley rats (Harlan Olac Ltd., Bicester). These same animals were then tested in Experiment 4. They were housed four per cage under a 14–10 h light cycle (lights on at 06.00), at 22–24 °C and maintained on Grain Harvesters Ltd. Rat and Mouse Diet. Experiments 2 and 3 each included 23 naïve adult male Wistar rats (Pasteur Institute of Athens). A separate group of 24 animals (from the litters of Experiments 2 and 3) were used for biochemical assessment of serum lithium levels after acute and chronic lithium administration. The total of 70 animals was housed in triads under a 12 h light cycle (lights on at 07.00), at 24–260 °C and maintained on Mucedola s.r.l 4RF18 Standard Diet.

All subjects were habituated to their respective animal rooms for at least 3 weeks, on ad libitum food. Ad libitum water was available throughout the course of the experiments. A week before the onset of behavioural training animals were placed on a 23-h food deprivation schedule, feeding for an hour after behavioural training. Having noted some weight loss in lithium chloride (LiCl)-treated animals compared to saline controls during LiCl pre-treatment we resorted in housing LiCl animals together, monitoring their weight daily and allowing extra feeding time to cages showing undue weight loss. As a result LiCl and saline controls' weights were comparable at the onset of behavioural training, ranging between 260 and 320 g (Experiments 1 and 4), 280–320 g (Experiment 2) and 250–310 g (Experiment 3). Physiological saline was available ad libitum in all home cages, so LiCl animals could replenish NaCl stores. Under these conditions animals remained in good health throughout the experiments.