Available online at www.sciencedirect.com
SCIENCE DIRECT®
Pharmacology, Biochemistry and Behavior 75 (2003) 341–347
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Thermal dehydration-induced thirst in lithium-treated rats

Christopher C. Barney*, Dorothy M. Kurylo, Justin L. Grobe

Department of Biology, Hope College, 35 East 12th Street, Holland, MI 49423, USA

Received 21 December 2002; received in revised form 14 April 2003; accepted 15 April 2003

Abstract

Lithium is used as the primary treatment for bipolar disorder but has the common side effects of diuresis and thirst. In the present study, the effects of lithium on water balance responses of male Sprague–Dawley rats to thermal dehydration were examined. Rats ate either unadulterated food or food containing 2 g/kg lithium carbonate for 10 days. Then the control and lithium-treated rats were exposed to either 25 or 37.5 °C without food or water for 4 h. The rats were then allowed access to water for 3 h at 25 °C or were anesthetized and blood samples were taken. Lithium treatment caused an initial decrease in food intake, a decrease in body weight, and an increase in urine output. Heat exposure caused similar increases in evaporative water loss in control and lithium-treated rats. Heat exposure led to changes in blood indicators of body water status indicative of dehydration, whereas lithium had no effects on blood indicators of body water status. Water intake was increased by both heat exposure and by lithium treatment with the lithium-treated rats being more responsive to the thirst-inducing effects of thermal dehydration. Lithium treatment does not appear to impair water balance responses to heat exposure.

Keywords: Body weight; Dehydration; Evaporative water loss; Food intake; Heat exposure; Lithium; Polyuria; Rehydration; Thirst; Urine output; Water intake

1. Introduction

Lithium is widely used as the primary treatment of bipolar disorder (McIntyre et al., 2001). The mechanism of action of lithium is yet unclear. Lithium has been shown to alter neurotransmitter release, signal transduction, enzyme activity, and gene and protein expression (as reviewed in Shaldubina et al., 2001), activities that may have a therapeutic effect. As with most psychotropic drugs, lithium has several side effects. Of these, increased urine production and thirst appear to be the most common (Gitlin et al., 1989; Schou and Vestergaard, 1988). These effects also occur following lithium treatment in individuals not suffering from mental illness (Bech et al., 1979) and in experimental animals, particularly rats (Galla et al., 1975; Thomsen, 1970; Zilberman et al., 1979). The primary effect of lithium on water balance appears to be of renal origin.

In rats, lithium increases vasopressin production and plasma vasopressin concentration (Anai et al., 1997) while the renal response to vasopressin is blunted (Carney et al., 1996; Galla et al., 1975; Hochman and Gutman, 1974; Thomsen, 1970) perhaps due to increases in parathyroid hormone levels (Carney et al., 1996). Thus, the increased urine output is related to lithium-induced alterations in kidney function. Lithium treatment reduces the component of renal sodium reabsorption that is sensitive to amiloride (Thomsen et al., 1999). In addition, the mechanism of polyuria induced by lithium appears to involve alterations in the expression of renal aquaporins. Lithium treatment caused reductions in expression of AQP2 and AQP3 (Kwon et al., 2000; Marples et al., 1995) without changing AQP1 and AQP4 (Kwon et al., 2000). The increased water intake caused by lithium treatment appears to be primarily a response to alterations in kidney function (Gutman et al., 1971; Marples et al., 1995) but may also involve a more direct effect of lithium on thirst (Christensen, 1983; Hochman and Gutman, 1974; Penney and Hampton, 1990; Smith and Amdisen, 1983; Smith and Balagura, 1972).

Lithium-induced changes in water balance may place individuals treated with lithium at risk under conditions of increased water loss, such as heat exposure. The similarities between lithium intoxication and heat illness have been noted (Granoff and Davis, 1978) and lithium has been considered as a risk factor for heat stroke (Epstein et al., 1997). During exposure to the heat, endotherms increase

* Corresponding author. Tel.: +1-616-3395-7710; fax: +1-616-395-7125.
E-mail address: barney@hope.edu (C.C. Barney).

0091-3057/03/$ – see front matter © 2003 Elsevier Science Inc. All rights reserved.
doi:10.1016/S0091-3057(03)00092-3

evaporative water loss for cooling purposes and become thermally dehydrated if water is not available. Rats exposed to hot environments increase saliva spreading and evaporative water loss when dry heat loss is unable to maintain core temperature (Barney and West, 1990; Hainsworth, 1968). This leads to dehydration and increased water intake when water becomes available (Barney and West, 1990; Hainsworth et al., 1968; Nose et al., 1985). In the study reported here, we were interested in determining if lithium would alter the water balance responses to heat exposure and if lithium and thermal dehydration would have interacting effects on thirst.

2. Methods

Male Sprague–Dawley rats obtained from Harlan Sprague–Dawley (Indianapolis, IN) initially weighing from 310 to 423 g were used for these experiments. The rats were housed singly in hanging stainless steel cages in an animal room kept at 23 ± 2 °C and illuminated from 6:00 a.m. to 6:00 p.m. Rats were allowed Purina rat chow (pellets or powdered) and water ad libitum except during the exposure and drink periods. The experiments were approved by the Hope College Animal Care and Use Committee.

2.1. Experiment 1—effects of lithium treatment on thirst responses to heat exposure

Thirty-six rats randomly divided into four groups of nine rats each were used for this experiment. Rats were weighed and then switched from pelleted to powdered food. The two groups of control rats received unadulterated food and the two groups of lithium-treated rats received food containing Li_2CO_3 at a concentration of 2 g Li_2CO_3/kg food. The food was placed in a glass bowl within a metal pan so that spilled food was collected. Twenty-four-hour food intakes and body weights were determined every 3 days. On the 10th day of lithium treatment, the heat exposure–drink experiment was conducted.

The rats in the four groups were weighed and placed in modified (Barney and West, 1990) Nalgene metabolism cages. The rats in the control-25 °C and the lithium-25 °C groups were placed in an environmental chamber kept at 25 ± 0.5 °C, and the rats in the control-37.5 °C and the lithium-37.5 °C groups were placed in an environmental chamber kept at 37.5 ± 0.5 °C. Rats were left in the chambers without access to food or water for 4 h. The cages were then removed from the chambers and the rats were reweighed and placed in standard Nalgene metabolism cages in the 25 °C chamber. Water bottles were provided and water intake and urine output were measured at 1-h intervals for 3 h. Evaporative water loss during the exposure period was estimated by subtracting urine and fecal losses from the change in body weight over the 4-h period. Percent rehydration was determined by dividing the water intake during the drink period by the evaporative and urinary water losses during the exposure period plus the urine loss during the drink period and then multiplying by 100%.

2.2. Experiment 2—effect of lithium treatment of blood indicators of body water status following heat exposure

Thirty-six additional rats were randomly divided into four groups for this experiment. The experiment was carried out in the same way as Experiment 1 except food intake was not measured and body weights were only determined at the beginning and the end of the lithium-treatment period. Fifteen minutes after the end of the exposure period, the rats were anesthetized with methoxyflurane and a 3-ml blood sample was taken using cardiac puncture and a syringe containing 200 units of sodium heparin. The blood was placed in a chilled centrifuge tube and triplicate measures of hematocrit, hemoglobin concentration, plasma osmolality, and plasma protein, sodium, and potassium concentrations were determined as previously described (Barney et al., 1995). In addition, plasma lithium was determined in triplicate in the blood samples from the lithium-treated rats using a Varian SpectrAA atomic absorption spectrophotometer. Due to technical problems, a blood sample was not obtained from one control-37.5 °C rat and the hemoglobin determination was not performed on the blood sample from one lithium-37.5 °C rat.

2.3. Statistical analysis

The software package SYSTAT 10 was used for statistical analysis. The data are expressed as means ± S.E.M. Two-way analysis of variance (ANOVA) and three-way ANOVA with repeated measures were used for inferential statistics with significance set at the 95% confidence level.

3. Results

3.1. Experiment 1—effects of lithium treatment on thirst responses to heat exposure

Initially, rats receiving Li_2CO_3 in their food reduced food intake to less than 50% of the rats receiving the unaltered food (Fig. 1, top). Food intake increased in the lithium-treated rats over the next 9 days so that by the 10th day of treatment, they were eating the same amount as the control rats. Three-way ANOVA with repeated measures of the food intake data showed significant main effects of lithium treatment [$F(1,32) = 117.14$, $P < .0001$] and time [$F(3,96) = 26.42$, $P < .0001$] and a significant interaction between lithium treatment and time [$F(3,96) = 39.68$, $P < .0001$]; but as expected, since the heat exposure had not yet taken place, there was no significant main effect of temperature nor any other significant interactions. Based on the food intake and the concentration of Li_2CO_3 in the

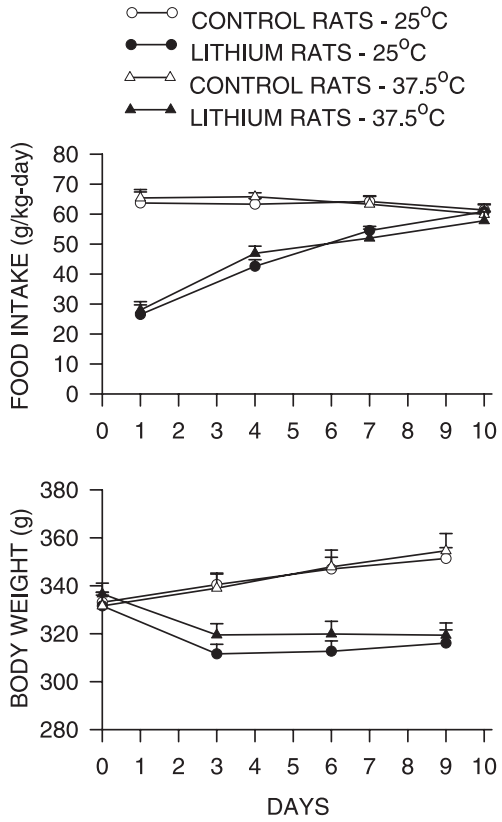

Fig. 1. Mean ± S.E.M. food intake (top) and body weight (bottom) of control rats later exposed to 25 °C, control rats later exposed to 37.5 °C, lithium-treated rats later exposed to 25 °C, and lithium-treated rats later exposed to 37.5 °C during the 10-day treatment period. $N = 9$ for each condition.

food, intake of lithium increased from approximately 1.5 mM/kg/day on Day 1 to 3.3 mM/kg/day on Day 10.

The reduction in food intake of the lithium-treated rats was associated with a decrease in body weight (Fig. 1, bottom). Whereas the control rats gained weight steadily, the lithium-treated rats lost an average of 19 g by the third day of treatment and then showed little change in body weight during the remaining days of treatment. Three-way ANOVA with repeated measures of the body weight data showed significant main effects of lithium treatment [$F(1,32) = 19.68$, $P < .0001$] and time [$F(3,96) = 16.51$, $P < .0001$] and a significant interaction between lithium treatment and time [$F(3,96) = 114.1$, $P < .0001$]; but again as expected, there was no significant main effect of temperature nor any other significant interactions.

Both the control and lithium-treated rats tolerated the heat exposure as no rats from either group died, and all rats were able to drink water during the first hour following removal from the heat. Exposure to 37.5 °C for 4 h increased evaporative water loss in both groups about 5.5-fold (Fig. 2, top). The lithium-treated rats had lower evaporative water losses than the control rats at both 25 and 37.5 °C. Two-way ANOVA of the evaporative water loss data showed significant main effects of lithium treatment [$F(1,32) = 6.78$, $P < .05$] and of temperature [$F(1,32) = 1318.86$, $P < .0001$] but no significant interaction between lithium treatment and temperature. Lithium treatment increased urine output at both environmental temperatures (Fig. 2, bottom) with two-way ANOVA of the urine output data during the exposure period showing a significant main effect of lithium treatment [$F(1,32) = 8.49$, $P < .01$] but no significant main effect of temperature nor significant interaction between lithium treatment and temperature.

Following exposure to 25 or 37.5 °C for 4 h, the control and lithium-treated rats were allowed access to water for 3 h. Water intake, urine output, and percent rehydration during that period are shown in Fig. 3. Water intake was greater in the rats exposed to 37.5 °C than in the rats exposed to 25 °C and greater in the lithium-treated rats than in the control rats (Fig. 3, top). Three-way ANOVA with repeated measures of the water intake data showed significant main effects of lithium treatment [$F(1,32) = 8.13$, $P < .01$], temperature [$F(1,32) = 56.56$, $P < .0001$], and time [$F(2,64) = 68.68$, $P < .0001$] and significant interactions between lithium treatment and time [$F(2,64) = 6.57$, $P < .01$], temperature and time [$F(2,64) = 14.37$, $P < .001$], and among lithium treatment, temperature, and time [$F(2,64) = 4.56$, $P < .05$] but no significant interaction between lithium treatment and temperature.

Urine output (Fig. 3, middle) was increased by lithium treatment and showed a trend of being decreased following exposure to 37.5 °C. Three-way ANOVA with repeated measures for the urine output during the drink

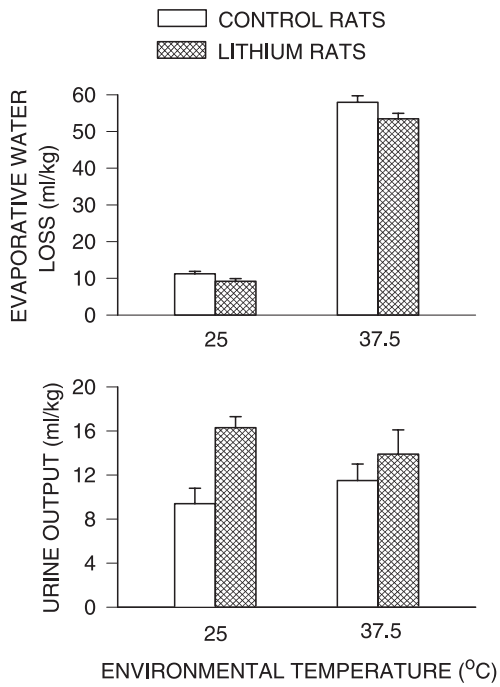

Fig. 2. Mean evaporative water loss (top) and urine output (bottom) of control and lithium-treated rats during 4 h of exposure to either 25 or 37.5 °C. One S.E.M. is set off at each bar. $N = 9$ for each condition.

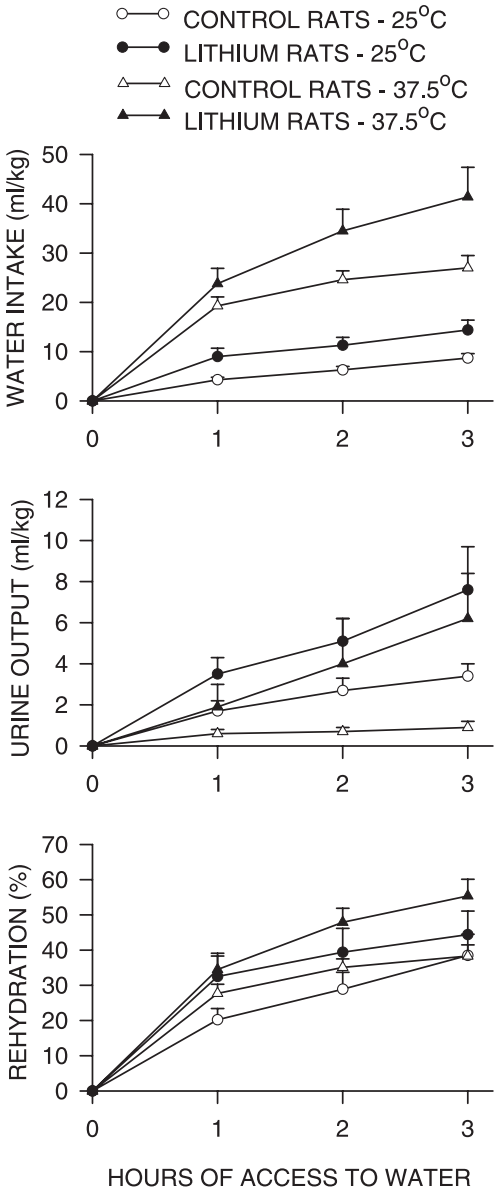

Fig. 3. Mean ± S.E.M. water intake (top), urine output (middle), and percent rehydration (bottom) of control and lithium-treated rats previously exposed to either 25 or 37.5 °C for 4 h during 3 h of access to water at 25 °C. $N = 9$ for each condition.

period data showed significant main effects of lithium treatment [$F(1,32) = 6.34$, $P < .05$] and time [$F(2,64) = 12.54$, $P < .0001$] and a significant interaction between lithium treatment and time [$F(2,64) = 4.76$, $P < .05$] but no other significant main effects nor interactions.

Although the rats had free access to water during the drink period, all four groups showed rehydration levels less than 60%. The lithium-37.5 °C group showed a higher level of rehydration than did the other three groups. Three-way ANOVA with repeated measures of the percent rehydration data showed significant main effects of lithium treatment [$F(1,32) = 5.45$, $P < .05$] and time [$F(2,64) = 107$, $P < .0001$] and a significant interaction among lithium treatment, temperature, and time [$F(2,64) = 7.64$, $P < .005$] but no other significant main effects nor interactions.

3.2. Experiment 2—effect of lithium treatment of blood indicators of body water status following heat exposure

In this experiment, the body weights at the beginning of the treatment period were 379 ± 8 g for the control-25 °C group, 384 ± 8 g for the control-37.5 °C group, 372 ± 6 g for the lithium-25 °C group, and 383 ± 7 g for the lithium-37.5 °C group. At the end of the treatment period, the body weights were 406 ± 8 g for the control-25 °C group, 408 ± 10 g for the control-37.5 °C group, 364 ± 5 g for the lithium-25 °C group, and 371 ± 6 g for the lithium-37.5 °C group. Three-way ANOVA with repeated measures of the body weight data showed significant main effects of lithium treatment [$F(1,32) = 8.99$, $P < .01$] and time [$F(3,96) = 15.68$, $P < .0005$] and a significant interaction between lithium treatment and time [$F(1,32) = 88.85$, $P < .0001$]; but as expected, there was no significant main effect of temperature nor any other significant interactions. Plasma lithium concentration of the lithium-25 °C rats was 0.72 ± 0.14 mM/l and lithium concentration of the lithium-37.5 °C rats was 0.68 ± 0.12 mM/l. There was no significant effect of heat exposure on plasma lithium concentration.

Exposure to 37.5 °C for 4 h in both the control and the lithium-treated groups led to changes in blood indicators of body water status that were indicative of dehydration (Table 1). Lithium treatment, on the other hand, was without effect on these variables. Two-way ANOVA indicated that there were no significant main effects of lithium treatment on hematocrit, hemoglobin concentration, plasma osmolality, or plasma concentrations of protein, sodium, or potassium and there were significant main effects of temperature on hemoglobin concentration [$F(1,30) = 4.89$, $P < .05$], plasma

Table 1
Effect of lithium treatment and heat exposure on blood indicators of body water status

Group	Hematocrit	Hemoglobin concentration (g/100 ml)	Plasma protein concentration (g/100 ml)	Plasma osmolality (mosM/kg)	Plasma sodium concentration (mM/l)	Plasma potassium concentration (mM/l)
Control-25 °C	43.7 ± 0.8	12.0 ± 0.3	5.5 ± 0.1	289 ± 2	140.7 ± 0.7	4.6 ± 0.1
Lithium-25 °C	44.2 ± 0.9	12.2 ± 0.2	5.6 ± 0.1	286 ± 2	139.1 ± 1.5	4.3 ± 0.1
Control-37.5 °C	44.4 ± 1.0	12.4 ± 0.3	6.1 ± 0.1	297 ± 1	146.9 ± 1.6	4.0 ± 0.25
Lithium-37.5 °C	45.7 ± 0.5	13.0 ± 0.1	6.2 ± 0.1	295 ± 2	147.9 ± 1.3	3.7 ± 0.1

Mean ± S.E.M. data are shown.

osmolality [$F(1,31)=21.20$, $P<.0001$], and plasma concentrations of protein [$F(1,31)=45.32$, $P<.0001$], sodium [$F(1,31)=32.39$, $P<.0001$], and potassium [$F(1,31)=15.06$, $P<.005$] but not on hematocrit. Importantly, there were no significant interactions between lithium treatment and temperature on any of these variables.

4. Discussion

Heat exposure in the absence of water places endotherms at risk of dehydration and heat stroke as body water is lost for evaporative cooling in order to regulate body temperature. The loss of water leads to thermal dehydration and thirst. In rats, thermal dehydration-induced thirst is primarily cellular rather than volemic in nature (Barney, 1997; Barney and West, 1990; Nose et al., 1985). Lithium treatment in both humans and rats leads to increases in urine output (Galla et al., 1975; Thomsen, 1970; Zilberman et al., 1979) and thirst (Christensen, 1983; Galla et al., 1975; Gitlin et al., 1989; Gutman et al., 1971; Marples et al., 1995; Schou and Vestergaard, 1988; Smith and Amdisen, 1983; Smith and Balagura, 1972). The thirst appears to be primarily a result of the increased urinary water loss (Gutman et al., 1971; Marples et al., 1995). Lithium treatment therefore has the potential of being a risk factor that might increase dehydration during heat exposure and the likelihood of heat stroke (Epstein et al., 1997; Granoff and Davis, 1978). However, the current study demonstrates that lithium treatment in rats does not interfere with evaporative cooling during heat exposure nor does it increase the dehydrating effects of heat exposure. In fact, following heat exposure, lithium-treated rats exhibited higher water intakes and levels of rehydration than did the control rats.

Providing lithium carbonate at 2 g Li_2CO_3/kg food to the rats led to plasma lithium levels that were similar to those in previous studies with rats (Anai et al., 1997; Christensen, 1974; Kwon et al., 2000) and to those shown to be therapeutic in humans (McIntyre et al., 2001), although the range of effective but safe lithium concentration is narrow. The addition of lithium carbonate to the diet also led to an initial decrease in food intake and subsequent loss of body weight. Food intake returned to normal levels by the 10th day of treatment, and body weight stabilized after by the 6th day of treatment. Previous studies have demonstrated similar findings (Balment et al., 1977; Smith and Amdisen, 1983) including a return of food intake to normal after prolonged lithium treatment (Balment et al., 1977). Food intake and body weight were also reduced when lithium was injected intraperitoneally (Opitz and Schäfer, 1976). Lithium also reduced body weight when infused into the cerebral ventricles (Smith and Amdisen, 1983). Lithium injections reduced gastric motility along with decreasing food intake (McCann et al., 1989), and lithium-induced reductions in food intake may involve activation of glucagon-like peptide-1 receptors (Rinaman, 1999; Seeley et al., 2000).

As in previous experiments with rats (Galla et al., 1975; Thomsen, 1970; Zilberman et al., 1979), lithium treatment increased urine output. This was observed during both the exposure and drink periods. The primary effect of lithium on water balance appears to be altered kidney function and the subsequent increased loss of water in the urine. The control rats showed a slight increase in urine output during heat exposure as previously described (Barney and West, 1990), and the lithium-treated rats showed a slight decrease in urine output during heat exposure. Water deprivation of lithium-treated rats also led to a decrease in urine output (Christensen, 1974). Although lithium treatment reduced evaporative water loss at both 25 and 37.5 °C compared to control rats, the increase in evaporative water loss with heat exposure was similar in both groups, as indicated by the lack of statistical interaction between lithium and temperature. It appears that as long as lithium-treated rats and, by extension, people have free access to water prior to heat exposure, evaporative heat losses are not impaired.

Water intake following the exposure period was increased by both heat exposure and by lithium treatment. In addition, there was an interaction between exposure temperature and lithium treatment on drinking over time. By 3 h of access to water, the lithium-37.5 °C rats showed a greater increase in water intake over the controls than did the lithium-25 °C rats. The mechanisms by which lithium increases water intake have not been determined. The increased water intake appears to be closely related to the increased urine output caused by lithium. It is interesting to note, however, that blood analyses generally have failed to show that lithium-treated rats are dehydrated (Balment et al., 1977; Carney et al., 1996; Galla et al., 1975; Kwon et al., 2000; Thomsen, 1970), and thus the normal physiological signals for drinking (hypovolemia and hyperosmolality) appear to be missing. Perhaps the stimulation of water intake caused by increased urinary water losses in lithium-treated rats is so precise that the physiological signals for the increased water intake are undetectable. In the current study, lithium was also without effect on measures of volemic signals to drink (hematocrit and hemoglobin and plasma protein concentration) or measures of osmotic signals to drink (plasma osmolality and plasma sodium concentration) in either control or thermally dehydrated rats. Thus, lithium treatment does not intensify the dehydrating effects of heat exposure. It should be noted, however, that hematocrit, hemoglobin, and plasma protein concentration are only indirect measures of plasma volume. It is possible that lithium-induced alterations in these variables themselves may have occurred, masking any effect of lithium on plasma volume. The fact that the changes would all need to be in the same direction and of the same general magnitude make this unlikely but more direct measurements of plasma volume in lithium-treated rats would be useful in this regard.

Lithium appears to also have effects on water intake that are independent of its effects on urine output. Lithium has been reported to increase water intake soon after injection

prior to increasing urine output (Smith and Balagura, 1972) and to increase water intake in Brattleboro rats that lack vasopressin and already have high urine volumes (Christensen, 1983; Hochman and Gutman, 1974). In addition, central administration of lithium to rats caused water intake to increase (Smith and Amdisen, 1983). After central administration of lithium, plasma lithium concentrations were below those needed to alter water intake when lithium was given in the diet (Smith and Amdisen, 1983). Lithium may be acting to alter some system involved in the control of water intake such as the formation of the dipsogenic hormone, angiotensin II. Lithium has been reported to increase (Balment et al., 1977; Gutman et al., 1971; Gutman et al., 1973; Mailman, 1983), decrease (Gutman et al., 1973), and has no effect (Kierkegaard-Hansen, 1974) on plasma renin activity, an indirect measure of angiotensin levels, and to slightly increase angiotensin II levels (Mailman, 1983) in rats. Another possibility is that lithium alters central responsiveness to thirst stimuli since lithium-treated rats drink more water than control rats at the same plasma osmolality and sodium concentrations (Balment et al., 1977; Galla et al., 1975; Kwon et al., 2000). This idea is supported by the results of the current study. Exposure to 37.5 °C for 4 h led to similar levels of dehydration in the control and lithium-treated rats as shown by the lack of interaction between temperature and lithium on the plasma indicators of dehydration. However, the heat-exposed lithium-treated rats had a greater increase in water intake than did the heat-exposed control rats. As a result, the lithium-37.5 °C rats had a higher level of rehydration (55%) than the control-37.5 °C rats (38%). Similarly, in humans, lithium treatment increased the thirst response to the infusion of hypertonic saline (Penney and Hampton, 1990).

In summary, although lithium treatment in rats causes polyuria, water intake appears to match water losses such that dehydration does not occur. Lithium did not alter the increase in evaporative water loss due to heat exposure, and lithium-treated rats tolerated thermal dehydration in terms of survival as well as control rats. When allowed access to water, thermally dehydrated lithium-treated rats drank more and rehydrated to a greater level than the thermally dehydrated control rats. These data support the idea that lithium causes an increase in the sensitivity of rats to thirst-inducing stimuli. These data also suggest that unless toxic plasma levels of lithium occur, lithium therapy may not increase the risks associated with thermal dehydration and that individuals on lithium treatment may actually rehydrate better than nontreated individuals when water becomes available.

Acknowledgements

This work was supported by grants from the National Science Foundation REU Program (BIR-9100398 and DBI-9820571) and a student research award to D. Kurylo from the Pew Midstates Science and Mathematics Consortium. We thank Dr. Michael Seymour for valuable advice.

References

Anai H, Ueta Y, Serino R, Nomura M, Kabashima N, Shibuya I, et al. Upregulation of the expression of vasopressin gene in the paraventricular and supraoptic nuclei of the lithium-induced diabetes insipidus rat. Brain Res 1997;772:161–6.

Balment RJ, Jones IC, Henderson IW. Time course of lithium-induced alterations in renal and endocrine function in normal and Brattleboro rats with hypothalamic diabetes insipidus. Br J Pharmacol 1977;59:627–34.

Barney CC. Effects of preloads of water and saline on thermal dehydration-induced thirst. Physiol Behav 1997;61:763–9.

Barney CC, West DR. Control of water intake in thermally dehydrated rats. Physiol Behav 1990;48:387–95.

Barney CC, Vergoth C, Renkema L, Meeuwsen KW. Nycthemeral variation in thermal dehydration-induced thirst. Physiol Behav 1995;58:329–35.

Bech P, Thomsen J, Prytz S, Vendsbor PB, Zilstorff K, Rafalsen OJ. The profile and severity of lithium-induced side effects in mentally healthy subjects. Neuropsychobiology 1979;5:160–6.

Carney SL, Ray C, Gillies AHB. Mechanism of lithium-induced polyuria in the rat. Kidney Int 1996;50:377–83.

Christensen S. Effects of water deprivation in rats with polydipsia and polyuria due to long-term administration of lithium. Acta Pharm Toxicol 1974;35:201–11.

Christensen S. Effects of lithium on water intake and renal concentrating ability in rats with vasopressin-deficient diabetes insipidus (Brattleboro strain). Pflugers Arch 1983;396:106–9.

Epstein Y, Albukrek D, Kalmovitc B, Moran DS, Shapiro Y. Heat intolerance induced by antidepressants. Ann NY Acad Sci 1997;813:553–8.

Galla JN, Forrest JN, Hecht B, Kashgarian M, Hayslett JP. Effect of lithium on water and electrolyte metabolism. Yale J Biol Med 1975;48:305–14.

Gitlin MJ, Cochran SD, Jamison KR. Maintenance lithium treatment: side effects and compliance. J Clin Psychiatry 1989;50:127–31.

Granoff AL, Davis JM. Heat illness syndrome and lithium intoxication. J Clin Psychiatry 1978;39:103–7.

Gutman Y, Benzakein F, Livneh P. Polydipsia induced by isoprenaline and by lithium: relation to kidneys and renin. Eur J Pharmacol 1971;16:380–4.

Gutman Y, Tamir N, Benzakein F. Effect of lithium on plasma renin activity. Eur J Pharmacol 1973;24:347–51.

Hainsworth FR. Evaporative water loss from rats in the heat. Am J Physiol 1968;214:979–82.

Hainsworth FR, Stricker EM, Epstein AN. Water metabolism of rats in the heat: dehydration and drinking. Am J Physiol 1968;214:983–9.

Hochman S, Gutman Y. Lithium: ADH antagonism and ADH independent action in rats with diabetes insipidus. Eur J Pharmacol 1974;28:100–7.

Kierkegaard-Hansen A. The effect of lithium on blood pressure and on plasma renin substrate and renin in rats. Acta Pharm Toxicol 1974;35:370–8.

Kwon T-H, Laursen UH, Marples D, Maunsbach AB, Knepper MA, Frøkiær J, et al. Altered expression of renal AQPs and Na^+ transporters in rats with lithium-induced NDI. Am J Physiol Renal Physiol 2000;279:F552–64.

Mailman RB. Lithium-induced polydipsia: dependence on nigrostriatal dopamine pathway and relationship to changes in the renin-angiotensin system. Psychopharmacology 1983;80:143–9.

Marples D, Christensen S, Christensen EI, Ottosen PD, Nielsen S. Lithium-induced downregulation of aquaporin-2 water channel expression in rat kidney medulla. J Clin Invest 1995;95:1838–45.

McCann MJ, Verbalis JG, Stricker EM. LiCl and CCK inhibit gastric

emptying and feeding and stimulate OT secretion in rats. Am J Physiol, Regul Integr Comp Physiol 1989;256:R463–8.
McIntyre RS, Mancini DA, Parikh S, Kennedy SH. Lithium revisited. Can J Psychiatry 2001;46:322–7.
Nose H, Yawata T, Morimoto T. Osmotic factors in restitution from thermal dehydration in rats. Am J Physiol, Regul Integr Comp Physiol 1985; 249:R166–71.
Opitz K, Schäfer G. The effect of lithium on food intake in rats. Int Pharmacopsychiatry 1976;11:197–205.
Penney MD, Hampton D. The effect of lithium therapy on arginine vasopressin secretion and thirst in man. Clin Biochem 1990;23:233–6.
Rinaman L. A functional role for central glucagon-like peptide-1 receptors in lithium chloride-induced anorexia. Am J Physiol, Regul Integr Comp Physiol 1999;277:R1537–40.
Schou M, Vestergaard P. Prospective studies on a lithium cohort: 2. Renal function. Water and electrolyte metabolism. Acta Psychiatr Scand 1988; 78:427–33.
Seeley RJ, Blake K, Rushing PA, Benoit S, Eng J, Woods SC, et al. The role of CNS glucagon-like peptide-1 (7-36) amide receptors in mediating the visceral illness effects of lithium chloride. J Neurosci 2000; 20:1616–21.
Shaldubina A, Agam G, Belmaker RH. The mechanism of lithium action: state of the art, ten years later. Prog Neuropsychopharmacol Biol Psychiatry 2001;25:855–66.
Smith DF, Amdisen A. Central effects of lithium in rats: lithium levels, body weight, and water intake. Acta Pharm Toxicol 1983;52:81–5.
Smith DF, Balagura S. Sodium appetite in rats given lithium. Life Sci 1972; 11:1021–9.
Thomsen K. Lithium-induced polyuria in rats. Int Pharmacopsychiatry 1970;5:233–41.
Thomsen K, Bak M, Shirley DG. Chronic lithium treatment inhibits amiloride-sensitive sodium transport in the rat distal nephron. J Pharmacol Exp Ther 1999;289:443–7.
Zilberman Y, Kapitulnik J, Feuerstein G, Lichtenberg D. Effects of prolonged lithium treatment on the water consumption and lithium content of rats. Pharmacol Res Commun 1979;11:467–74.