

Effect of Lithium on Water and Electrolyte Metabolism

JOHN N. GALLA, JOHN N. FORREST, BARRY HECHT,
MICHAEL KASHGARIAN, and JOHN P. HAYSLETT¹
(with the technical assistance of Trudy Klein-Robbenhaar and Joan Pantalena)

*The Departments of Medicine, Pediatrics, and Pathology,
Yale School of Medicine, New Haven, Connecticut*

Received May 3, 1975

Studies were performed in the rat to determine the effect of lithium on electrolyte transport in distal portions of the nephron since steep corticomedullary gradient for lithium has been demonstrated and ionic competition and/or substitution of lithium for sodium and potassium may play a role in inhibition of vasopressin-induced water transport. During the intravenous infusion of LiCl, in the absence of volume expansion and at plasma levels of 2-5 mequiv/liter of Li, maximum urine concentration was inhibited. Under the same conditions lithium administration impaired potassium secretion and urinary acidification and resulted in a natriuresis. These results indicate that lithium affects electrolyte transport in the same nephron segments in which the action of vasopressin is inhibited.

In addition, evidence is provided that suggests that during the chronic administration of LiCl, the sustained increase in oral intake of water and urinary flow rate results from an increase in thirst as well as reduced renal concentrating ability.

The complex array of lithium-induced biological effects on water and electrolyte transport has received increasing attention since introduction of lithium to treat psychiatric disorders in man. It is now well established that lithium can produce a reversible nephrogenic diabetes insipidus syndrome in man (1) and experimental animals (2) as well as block vasopressin-induced water transport in physiological models *in vitro* (1, 3). Interest in lithium has also included its effect on renal electrolyte transport *in vivo* (4, 5), on electrolyte movement in ion-substitution experiments *in vitro* (6, 7), and recently the possible usefulness of lithium as a marker for proximal tubular reabsorption (8).

The present experiments were designed to examine the effect of lithium on electrolyte transport in distal portions of the nephron, since lithium is concentrated in the hypertonic renal medulla (2, 9), and lithium-induced alterations in electrolyte concentration and movement may play a role in the inhibition of the action of vasopressin on water transport (10). Since previous studies have suggested that lithium may also increase urinary flow rate through a central action (11), an experimental model was developed so that possible changes in electrolyte transport could be studied under conditions known to include inhibition of vasopressin on water transport.

METHODS

Studies were performed in male Sprague-Dawley rats (Charles River Breeding Laboratories, Wilmington, Massachusetts) with an initial weight of 125-200 g. To evaluate the effect of lithium on renal concentrating ability and on the reabsorption and secretion of electrolytes, experiments were performed during chronic lithium

¹Address correspondence to John P. Hayslett, M. D., Department of Medicine, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510.

treatment and in acute studies in which previously treated and untreated animals were infused intravenously with lithium.

CHRONIC EXPERIMENTS

Experimental animals were injected intraperitoneally (IP) with LiCl (0.3 M) in a dose of 4 mequiv/kg body weight per day, fed normal Purina Chow, and given tap water to drink. Control rats were given 4 mequiv/kg body weight per day of NaCl (0.3 M) IP, fed normal Purina Chow, and given a 5% glucose solution to drink in order to produce a comparable diuresis. Fluid intake was estimated daily from the change in weight of the water bottle.

In order to determine whether urinary flow rate changed or remained constant during the 24-hr period after the single daily injection of LiCl, six experimental animals were placed in metabolic cages on the seventh day of chronic treatment while food and water were provided ad lib. Urine volume was measured during the intervals 0–6, 6–12, and 12–24 hr following the IP injection of LiCl.

The concentration of lithium in the plasma of rats on chronic treatment was measured on the seventh day in six animals during the 24-hr interval after the single daily injection of LiCl. Blood samples were obtained from the orbital plexus during ether anesthesia.

Plasma osmolality was determined in eight experimental and eight control animals on the seventh day of chronic treatment 24 hr after the last single daily injection. In addition, plasma osmolality was determined in eight normal nondiuretic rats and in 12 animals with hereditary neurogenic diabetes insipidus (Brattleboro strain) and on ad lib. diet of Purina Chow and tap water.

To determine maximum urinary concentration ability in rats on chronic lithium treatment, studies were performed in six experimental and seven control animals. On the seventh day of treatment and 24 hr after the last single daily injection of either LiCl or NaCl, anesthesia was induced with Inactin (100 mg/kg body weight) (Promonta, Hamburg, Germany), and the urine was immediately aspirated from the bladder for determination of the baseline urine osmolality. Thereafter, a tracheostomy was performed, and polyethylene tubing (PE 50) was secured into one jugular vein and the bladder. Aqueous vasopressin (Pitressin: Park, Davis & Co., Detroit, Michigan) in a concentration of 3 mU/ml of 0.15 M NaCl was infused intravenously at a rate of 1.2 ml/hr. This dose of aqueous vasopressin (60 μ U/min) has previously been shown to produce maximal urinary concentration in rats with hereditary neurogenic diabetes insipidus (12). Urine was collected under oil for determination of osmolality during six consecutive 30-min intervals after initiating the infusion. Plasma lithium concentration was measured at the termination of the study.

ACUTE EXPERIMENTS

Maximum Urinary Concentration

These experiments were performed to determine maximum urine concentration during the acute infusion of lithium chloride in the absence of volume expansion and while plasma levels of lithium were relatively constant. Animals were anesthetized and surgically prepared as in the previous group of experiments (chronic experiments). In experimental animals, following the placement of catheters, lithium was administered intravenously in a primary dose of 0.5 ml of 0.3 M LiCl, and a maintenance infusion of 3 mU/ml of aqueous vasopressin in 0.15 M LiCl was begun at

the rate of 1.2 ml/hr. This dose of LiCl was calculated to result in a concentration of lithium of 3–5 mequiv/liter in the plasma since the expected volume of distribution was 40% of body weight and urinary fractional excretion of lithium was 30% (4).² Control animals received a similar primary dose of 0.3 M NaCl and maintenance infusion of aqueous vasopressin in 0.15 M NaCl. Urine was collected under oil for osmolality from both experimental and control animals during six sequential 30-min periods, and plasma lithium concentration was determined at the termination of the last collection period. Two groups of animals were studied. Group I included five experimental rats on chronic LiCl treatment and five control animals receiving daily injections of NaCl and drinking 5% glucose solution. The acute experiment was performed on the seventh day of chronic treatment and 24 hr after the last single daily injection.

Group II included 12 previously untreated normal animals. One-half of this group were designated as experimental and were infused with LiCl, whereas the remaining animals served as controls and were infused with NaCl.

Effect of Lithium on Sodium and Potassium Excretion

Following induction of anesthesia, untreated normal rats were given either LiCl (seven animals) or NaCl (five animals) in a manner employed in acute experiments to determine maximum urinary concentration. In order to estimate glomerular filtration rate, methoxy-inulin-H³ (New England Nuclear) was given in a prime of 10 μ C (0.1 ml) and a sustaining dose of 10 μ C/hr in 0.15 M NaCl at 0.6 ml/hr. After 30 min of equilibration, three 30-min urine collection periods were performed. Tail blood was obtained at the midpoint of each collection period to determine plasma inulin concentration. Urine samples were examined for inulin, sodium, and potassium concentration. An aortic blood sample was taken at the end of the last urine collection to determine plasma lithium.

Effect of Lithium on Maximum Urinary Acidification

Anesthesia was induced in previously untreated rats, and LiCl (six animals) and NaCl (six animals) were administered acutely as in the previous group of experiments. Thirty minutes after starting the sustaining infusion of 0.15 M LiCl or NaCl, an acute load of NH₄Cl was given in a dose of 8 mM/kg by gastric lavage. Bladder urine was collected under oil before and during a 2-hr interval following the NH₄Cl load for determination of Ph. A sample of aortic blood was obtained anaerobically at the termination of the last urine collection to measure blood pH.

Effect of Lithium on Renal Excretion of Potassium

Following induction of anesthesia in previously untreated animals, LiCl (eight animals) and NaCl (eight animals) were administered acutely as in the previous group of experiments. In addition to the usual sustaining infusion of 0.15 M LiCl or NaCl, NaCl (0.15 M) was infused at 0.6 ml/hr through a second intravenous catheter while two 30-min urine collection periods were performed to determine the control rate of potassium excretion, expressed as μ equiv min⁻¹ 100 g⁻¹ body wt. Then KCl, in a concentration of 1 M, was substituted for NaCl in both groups of animals and infused at 0.6 ml/hr. During infusion of KCl, three 30-min collection periods were performed. The interval 60–90 min after beginning KCl was taken as the period of maximum

²For comparison, the concentrations of lithium in plasma of patients receiving therapeutic doses of lithium are generally 0.5–1.5 mequiv/liter (1).

excretion, and an arterial blood sample was obtained at 90 min to determine the plasma potassium and lithium concentration.

The determination of sodium and potassium in plasma and urine samples was performed by flame photometry, utilizing a lithium internal standard. Lithium was measured by atomic absorption spectrophotometry, and the concentration of inulin was counted by a liquid scintillation counter (New England Nuclear). The pH of urine and blood samples was measured on a Radiometer pH meter, and osmolality on an Advanced Instrument Osmometer. The unpaired Student's *t* test was utilized in comparing results from different groups whenever applicable. Values are expressed as mean \pm SEM.

RESULTS

Chronic administration of LiCl, achieved by a single daily intraperitoneal injection, caused an increase in fluid intake, beginning on the first day of lithium administration, in all animals treated. By the seventh day of chronic lithium administration, water intake averaged 50 ± 7 ml/100 g body wt per day as compared to a mean of 16 ± 1 in normal nondiuretic rats drinking tap water ($p < 0.001$). Although lithium was given as a bolus once per day, the urine flow rate, and presumably the oral intake of water, remained relatively constant during the succeeding 24 hr. When Urine flow rate was determined during consecutive time periods in six animals on the seventh day of chronic treatment, shown in Fig. 1a, the average urine flow rates were 50 ± 7 μ l/min during the first 6 hr after injection of 4 mequiv/kg LiCl, 66 ± 13 μ l/min 6-12 hr after injection, and 55 ± 5 μ l/min 12-24 hr after injection. It seems likely that urinary flow rate remained elevated throughout the last collection period (12-24 hr) since the urine osmolality from the bladder aspirate at 24 hr was 482 ± 148 mosm/kg H₂O, as compared to 1209 ± 217 mosm/kg H₂O in normal rats drinking tap water. It was of interest that after a week of lithium injections, the polydipsia and sustained polyuria observed in all chronically treated animals were not associated with chronically elevated plasma levels of lithium. As shown in Fig. 1b, plasma lithium rose to a level of 3.6 ± 0.9 mequiv/liter 1 hr after the seventh daily injection and fell exponentially during the subsequent 23 hr. The

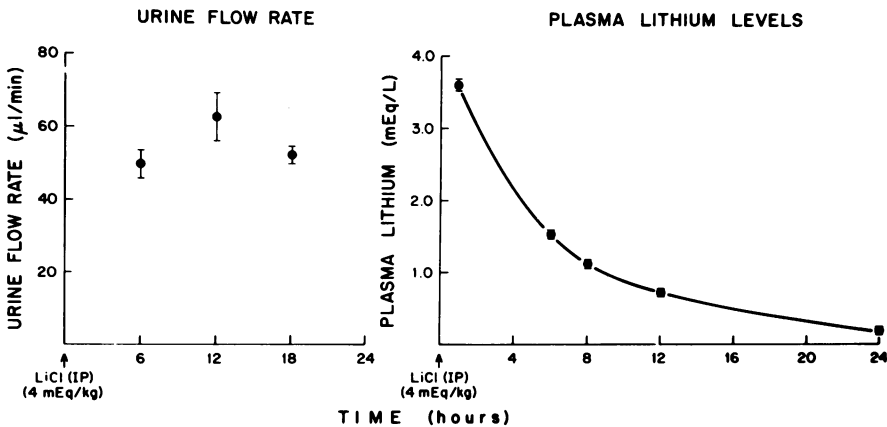


FIG. 1. (a) Urine flow rate (μ l/min) on the seventh day of chronic lithium treatment during periods 0-6, 6-12, and 12-24 hr following injection of LiCl. Values represent the mean \pm SEM. (b) Plasma lithium concentration in rats on chronic lithium treatment during seventh day of treatment. Values represent the mean \pm SEM.

TABLE 1
Plasma Osmolality in Normal Nondiuretic Rats and Experimental Groups with Polydipsia^a

	Intake (ml/100 g body wt)	Plasma osmolality (mosm/kg HOH)
Normal nondiuretic (8) ^b	16	282.1
	±1	± 2.4
5% G/W polyuria (8)	35	279.9
	±3	± 2.0
LiCl polyuria (8)	50	280.8
	±7	± 2.1
Neurogenic DI polyuria (12)	66	305.1 ^c
	±4	± 2.9

^a Values represent mean ± SE.

^b Number of animals studied is shown in parentheses.

^c Indicates a $p < 0.001$ as compared to normal nondiuretic animals.

24-hr plasma lithium values in rats treated by daily intraperitoneal injection were similar to those reported by Schou (13) in animals on a moderate intake of dietary sodium and given 3 mequiv/kg per day of lithium.

In order to determine whether polydipsia and sustained high rates of urine flow in rats on chronic LiCl treatment were associated with evidence of chronic dehydration, due to obligatory urinary losses of water, plasma osmolality was measured in polydipsic rats on LiCl and compared to other groups of animals with polydipsia resulting from other causes. As shown in Table 1, the plasma osmolality in rats on chronic LiCl treatment and an oral intake of water of 50 ± 7 ml/100 g BW per day was 280.8 ± 2.1 mosm/kg H₂O. This value was not significantly different statistically from the plasma osmolality found in normal nondiuretic rats (282.1 ± 2.4) with an intake of 16 ± 1 ml/100 g body wt nor the level found in rats with primary polydipsia, drinking a 5% glucose solution (279.9 ± 2.0). In contrast, the plasma osmolality in rats with hereditary neurogenic diabetes insipidus and impaired urinary concentration was significantly elevated to 305.1 ± 2.9 mosm/kg H₂O ($p < 0.001$). The water intake of this group was not significantly different from the intake of LiCl treated animals.

Despite the sustained water diuresis in rats on chronic lithium treatment, there was no evidence of impaired concentrating ability 24 hr after the last daily injection. Immediately after the induction of anesthesia, urine was aspirated from the bladder to determine baseline osmolality. Baseline osmolality of urine (U₀) from rats on chronic LiCl treatment, 24 hr after the last intraperitoneal injection, was 482.4 ± 148.2 mosm/kg H₂O, a value that was not significantly different from 606.3 ± 151.0 found in control rats given injections of NaCl and a 5% glucose solution to drink. During the infusion of aqueous vasopressin, urine osmolality, in mosm/kg H₂O, increased in both experimental (E) and control (C) animals to a similar extent in each of the six 30-min collection periods (U₁, 1418 ± 169 C vs 1329 ± 46 E; U₂, 1578 ± 182 C vs 1406 ± 58 E; U₃, 1729 ± 231 C vs 1361 ± 76E; U₄, 1742 ± 240 C vs 1419 ± 115 E; U₅, 1933 ± 416 C vs 1516 ± 101 E; U₆, 1912 ± 356 C vs 1555 ± 77 E).

The urine osmolality values for periods U₀ and U₆ are shown in Fig. 2 (designated as chronic Li, plasma Li < 0.5 mequiv/liter). Urine flow rate was also similar in both groups and averaged 6.2 ± 0.8 μl/min control and 5.7 ± 0.8 experimental

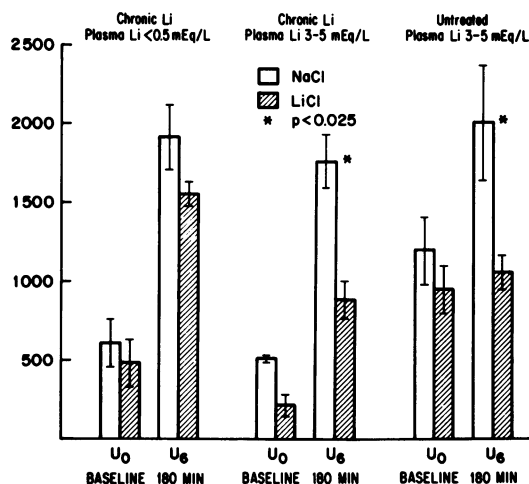


FIG. 2. Borderline urine osmolality (U_0) and urine osmolality 150–180 min (U_6) after beginning infusion of aqueous vasopressin (60 mU/min) are shown from three different groups of experiments. In the left panel (chronic Li, plasma Li < 0.5 mequiv/liter), experimental animals (hatched bars) were given daily injections of LiCl for 7 days and are compared to control rats (clear bars) given daily injections of NaCl and a 5% glucose solution to drink. In the middle panel (chronic Li, plasma Li 3–5 mequiv/liter), rats on chronic LiCl or NaCl treatment for 7 days were infused intravenously with LiCl or NaCl, respectively, during the infusion of aqueous vasopressin (Group I). In the right panel (untreated, plasma Li 3–5 mequiv/liter), untreated animals were infused with either LiCl (hatched bars) or NaCl (clear bars) during the infusion of vasopressin (Group II). The symbol * indicates a $p < 0.025$ when control and experimental values are compared. Values represent mean \pm SEM.

during period U_6 . The average plasma lithium concentration was 0.22 ± 0.08 mequiv/liter, and fluid intake was similar in both groups during the 24-hr interval preceding the study (42.3 ± 6.8 ml 100 g body wt day⁻¹, control vs 46.7 ± 5.8 experimental).

Acute Experiments

In contrast to animals studied during chronic treatment when plasma lithium levels averaged less than 0.5 mequiv/liter, there was a blunted response to vasopressin and reduced concentrating ability during the acute infusion of LiCl. This effect was seen in both animals on chronic lithium treatment and in previously untreated animals and occurred independently of the baseline urine osmolality. During period U_6 , urine osmolality rose to a level of 1800–2000 mosm/kg H₂O in Group I and Group II control rats, whereas urine osmolality failed to increase above 1200 mosm/kg in either experimental group during the intravenous infusion of LiCl as shown in Fig. 2. The plasma lithium concentration in experimental rats was 3.8 ± 0.22 mequiv/liter in Group I and 4.6 ± 0.4 in Group II.

To determine the effect of lithium on tubular transport of electrolytes, studies were performed during the acute infusion of lithium since impaired water movement was clearly demonstrated under this experimental condition. Acute lithium administration resulted in an increase in sodium and potassium excretion, as shown in Table 2. $U_{Na}V$ was 1.02 ± 0.15 μ equiv min⁻¹ 100 g body wt⁻¹ and U_kV was 1.37 ± 0.07 μ equiv min⁻¹ 100 g body wt⁻¹ in experimental rats, as compared to control values of 0.11 ± 0.03 ($p < 0.001$) and 0.72 ± 0.12 ($p < 0.001$), respectively. Although the infusion of lithium resulted in an increase in filtered sodium, it seems likely that so-

TABLE 2
Effect of Sustained Infusion of Lithium on Renal Function^a

Group	Cin ($\mu\text{l}/\text{min}$)	Cin ($\mu\text{l}/\text{min}^{-1}$ 100 g^{-1})	V ($\mu\text{l}/\text{min}^{-1}$ 100 g^{-1})	$U_{\text{Na}}V$ ($\mu\text{equiv min}^{-1}$ 100 g^{-1})	$U_{\text{K}}V$ ($\mu\text{equiv min}^{-1}$ 100 g^{-1})
NaCl (5) ^b	1929 \pm 14	1056 \pm 8	1.9 \pm 0.2	0.11 \pm 0.03	0.72 \pm 0.12
LiCl (7)	2955 \pm 23 ^c	1565 \pm 13 ^c	6.1 \pm 0.8 ^c	1.02 \pm 0.15 ^c	1.37 \pm 0.07 ^c

^a Values represent mean \pm SE.

^b The number of animals studied is shown in parentheses.

^c Denotes $p < 0.001$ as compared to NaCl group.

dium reabsorption was reduced by the direct action of lithium since fractional sodium excretion was 0.53 ± 0.08 in experimental animals and 0.10 ± 0.05 in controls ($p < 0.001$). Plasma lithium concentration was 4.3 ± 0.4 mequiv/liter in the experimental group.

The administration of lithium also resulted in impaired urinary acidification. In these experiments, a moderately severe metabolic acidosis (blood pH: 7.23 ± 0.06 experimental and 7.32 ± 0.01 control) resulted from the administration of NH_4Cl . As shown in Fig. 3, urine pH was reduced from the baseline value of 6.66 ± 0.19 in control rats to 5.51 ± 0.05 . In contrast, there was little change in urine pH during acidosis in lithium-treated animals. The baseline urine pH of 7.39 ± 0.18 was decreased to a minimum value of 6.83 ± 0.09 . The difference in urine pH between lithium-treated and nontreated groups was highly significant in all time intervals examined during acidosis ($p < 0.001$).

Since potassium secretion is a function of the distal portion of the nephron (14), along with urinary concentration and the establishment of a minimal urine pH, it was of interest to determine the effect of lithium on potassium secretion during acute potassium loading. As shown in Table 3, the constant infusion of lithium markedly reduced excretory rates of potassium during acute potassium loading. During 60–90 min after initiating the infusion of $1M$ KCl , plasma potassium rose to 6.6 ± 0.3 mequiv/liter both in controls and in experimental animals. In response to acute potassium loading, $U_{\text{K}}V$ increased from 0.68 ± 0.08 mequiv min^{-1} 100 g body wt^{-1} to 3.58 ± 0.13 in control animals. In lithium treated rats, the rise in potassium excretion was severely blunted. $U_{\text{K}}V$ rose from 0.99 ± 0.08 mequiv min^{-1} 100 g body wt^{-1} to 1.47 ± 0.23 . At the termination of the study, plasma lithium was 2.3 ± 0.1 in experimental animals.

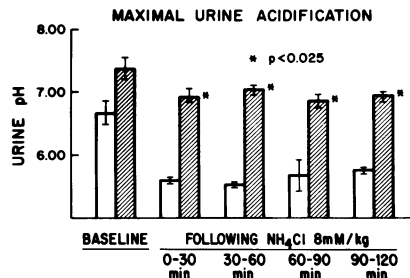


FIG. 3. Urine pH before (baseline) and following administration of NH_4Cl , 8 mM/kg in rats during infusion of NaCl (clear bars) and LiCl (hatched bars). Values represent the mean \pm SEM.

TABLE 3
Effect of Lithium on Maximal Potassium Excretion^a

	NaCl group U _K V (μequiv min ⁻¹ 100 g ⁻¹) (8) ^c	LiCl group U _K V (μequiv min ⁻¹ 100 g ⁻¹) (8)
Control period	0.68 ±0.08	0.99 ±0.08
Potassium loading ^b	3.58 ±0.13	1.47 ^d ±0.23
Δ change (μequiv min ⁻¹ 100 g ⁻¹)	2.89 ±0.11	0.48 ^d ±0.25

^a Values represent mean ± SE.

^b The potassium loading period was clearance period 60–90 min after beginning infusion of 1 M KCl.

^c Number of animals studied is shown in parentheses.

^d Indicates $p < 0.025$ as compared to NaCl group.

DISCUSSION

Lithium-induced diabetes insipidus is well established and has been shown to occur in some patients on chronic lithium therapy (1, 15) and in experimental animals during both acute (16) and chronic administration (2, 9). Although the mechanism of this effect is unclear, it seems likely that lithium acts directly on vasopressin-sensitive cells to inhibit activation of adenylyl cyclase (1, 3) or to block the action of cAMP (2). In addition to the effect of lithium in inhibiting the action of vasopressin, it has been suggested that lithium may cause diuresis in the intact organism through a central effect. Evidence to support this possibility is provided by the observation that rats injected with LiCl consistently drink more water than animals given NaCl, even when animals with a similar degree of volume contraction are compared (11).

The present study provides additional evidence to support a central effect of lithium. All rats injected with LiCl developed an increase in water intake and urine flow rate that was sustained when LiCl was administered in a bolus once daily. There was no evidence, however, of dehydration in rats on chronic LiCl treatment after plasma lithium levels had fallen to a low value. When compared to normal nondiuretic rats or animals with glucose-stimulated primary polydipsia, there was no difference in plasma osmolality. In contrast, there was clear evidence of dehydration in rats with hereditary neurogenic diabetes insipidus with a water intake comparable to that of LiCl-treated animals. Moreover, when maximum concentrating ability was directly examined 24 hr after the last LiCl injection, while urine flow rate was still elevated, there was no evidence that the action of vasopressin was impaired. Evidence was provided to show that urine flow rate was elevated at the time that concentrating ability was measured by the low urine osmolality of aspirated bladder urine and the finding that flow rate was unchanged 12–24 hr after injection of LiCl, as compared to the first 6 hr following injection. Previous studies (2) have demonstrated that the action of vasopressin is impaired when tested within the first 12 hr after intraperitoneal injection in rats on chronic treatment. Taken together, these data suggest that the increased water intake and urinary flow rate in animals on chronic lithium treatment result from a direct effect in the central nervous system as well as inhibition of the peripheral action of vasopressin.

Although these experiments were not designed to identify the mechanism of the central action of lithium, it seems likely that lithium stimulates thirst rather than inhibits the production or release of vasopressin. Previous studies (17) have shown

that preincubation of the neurohypophysis in media containing lithium does not impair the release of vasopressin. Furthermore, Myron Miller (personal communication) has found that urinary ADH excretion increases appropriately after dehydration of rats on chronic lithium treatment and that ADH content decreases normally in pituitary tissue in lithium-treated animals in response to the stimulus of dehydration. Further evidence for a central stimulatory action of lithium to increase thirst has been provided by recent studies of N. Berliner and J. N. Forrest (unpublished). Despite the intense stimulation of thirst usually present in rats with neurogenic diabetes insipidus, administration of LiCl, in a dose of 1.5 mequiv kg⁻¹ day⁻¹, caused a 44% increase in fluid intake.

Since it was of interest to evaluate the effect of lithium on renal electrolyte transport under conditions of known vasopressin inhibition, studies on the renal handling of sodium, potassium, and acid were performed during the intravenous infusion of LiCl to achieve plasma levels of 2–5 mequiv/liter. In the present study the action of vasopressin was clearly impaired under this experimental condition. In addition to blocking water transport, lithium infusion resulted in a modest but significant reduction in sodium reabsorption, a fall in the rate of potassium secretion during acute potassium loading, and impaired urinary acidification. Since potassium secretion and production of high tubular fluid concentrations of hydrogen ion are special properties of the distal portions in the nephron, it seems likely that lithium inhibits electrolyte secretion in the same tubular segments in which the action of vasopressin is blocked. The tubule site(s) in which lithium reduces sodium reabsorption cannot be determined from this study. It seems likely, however, that sodium reabsorption was reduced in the distal portions of the nephron. Recent studies (18) have demonstrated that the mechanism that controls the absorption of sodium in the distal tubule and collecting duct has a powerful influence on absolute urinary excretion, even under conditions of increased distal delivery.

It has recently been suggested that lithium may influence transepithelial electrolyte movement through a partial substitution of lithium for other ions, especially sodium and potassium (10). Evidence is available showing that Na⁺ and Li⁺ share a common transport mechanism in toad urinary bladder (6) and frog skin (7). Although Na⁺ and Li⁺ share the same pathway for cell entry, Li⁺ accumulates in the cell at the expense of K⁺ and may increase to values 10 times the outside concentration (7). It is possible, therefore, that cellular accumulation of lithium may alter the critical microenvironment of the cell required for optimal potassium and hydrogen ion secretion and possibly for the optimal action of hormones such as vasopressin. Medullary portions of the collecting duct would be expected to be influenced especially by this mechanism because of the steep corticopapillary gradient for lithium. In respect to the question of the tubular sites involved in the reabsorption of filtered lithium, it seems apparent that direct analysis of lithium concentrations at the level of individual nephron segments will be a necessity. The usefulness of clearance techniques to estimate the site(s) of lithium transport is mitigated by the significant direct effect of lithium on the tubular transport of other electrolytes.

ACKNOWLEDGMENTS

This work was supported by USPHS Grants AMO7369, HL13647, AM18061, and TIAM5015 and the American Heart Association. Dr. Hayslett is an Established Investigator of the American Heart Association, and Dr. Kashgarian is the recipient of Research Career Development Award HE13683.

REFERENCES

1. Singer, I., Rotenberg, D., and Puschett, J. B. Lithium-induced nephrogenic diabetes insipidus: in vivo and in vitro studies. *J. Clin. Invest.* **51**, 1081–1091 (1972).
2. Forrest, J. N., Cohen, A. D., Torretti, J., Himmelhock, J. M., and Epstein, F. H. On the mechanism of lithium induced diabetes insipidus in man and the rat. *J. Clin. Invest.* **53**, 1115–1123 (1974).
3. Singer, I. and Franko, E. A. Lithium-induced ADH resistance in toad urinary bladders. *Kidney Int.* **3**, 151–159 (1973).
4. Foulks, J., Mudge, G. H., and Gilman, A. Renal excretion of cation in the dog during infusion of isotonic solutions of lithium chloride. *Amer. J. Physiol.* **168**, 642–649 (1952).
5. Homer, L. D., and Solomon, S. Stop-flow studies on renal handling of lithium ions in the dog. *Amer. J. Physiol.* **203**, 897–900 (1962).
6. Herrera, F. C., Egea, R., and Herrera, A. M. Movement of lithium across toad urinary bladder. *Amer. J. Physiol.* **220**, 1501–1508 (1971).
7. Leblanc, G. The mechanism of lithium accumulation in the isolated frog skin epithelium. *Pfluegers Arch.* **337**, 1–18 (1972).
8. Steele, T. H., and Dudgeon, K. L. Reabsorption of lithium and phosphate by the rat kidney: Role of the parathyroids. *Kidney Int.* **5**, 196–203 (1974).
9. Thomsen, K. Lithium-induced polyuria in rats. *Int. Pharmacopsychiatr.* **5**, 233–241 (1970).
10. Singer, I., and Rotenberg, D. Mechanisms of lithium action. *N. Engl. J. Med.* **289**, 254–260 (1973).
11. Smith, D. F., Balagura, S., and Lubran, N. Antidotal thirst and lithium excretion in rats with hypothalamic lesions. *Physiol. Behav.* **6**, 209–213 (1971).
12. Jamison, R. L., Buerkert, J., and Lacy, F. A micropuncture study of collecting tubule function in rats with hereditary diabetes insipidus. *J. Clin. Invest.* **50**, 2444–2452. (1971).
13. Schou, N. Lithium studies. I. Toxicity. *Acta Pharmacol. Toxicol.* **15**, 70–84 (1958).
14. Mello-Aires, N. de, Giebisch, G., and Malnic, G. Kinetics of potassium transport across single distal tubules of rat kidney. *J. Physiol. (London)* **232**, 47–70 (1973).
15. Lee, R. V., Jampol, L. M., and Brown, W. V. Nephrogenic diabetes insipidus and lithium intoxication—complications of lithium carbonate therapy. *N. Engl. J. Med.* **284**, 93–94 (1971).
16. Harris, C. A., and Jenner, F. A. Some aspects of the inhibition of the action of antidiuretic hormone by lithium ions in the rat kidney and bladder of the toad *Bufo marinus*. *Brit. J. Pharmacol.* **44**, 223–232 (1972).
17. Torp-Pedersen, C., and Thorn, N. A. Acute effects of lithium on the action and release of antidiuretic hormone in rats. *Acta Endocrinol.* **73**, 665–671 (1973).
18. Stein, J. H., Osgood, R. W., Boonjarern, S., and Ferris, T. F. A comparison of the segmental analysis of sodium reabsorption during Ringer's and hyperoncotic albumin infusion in the rat. *J. Clin. Invest.* **52**, 2313–2323 (1973).