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TIME COURSE OF LITHIUM-INDUCED ALTERATIONS IN RENAL AND ENDOCRINE FUNCTION IN NORMAL AND BRATTLEBORO RATS WITH HYPOTHALAMIC DIABETES INSIPIDUS

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1 A lithium chloride (1.1 g/kg) supplemented diet was given to Long Evans (LE) and Brattleboro (DI) rats to investigate its actions in the presence (LE) and absence (DI) of vasopressin.

2 During the first 24 h, Li-supplemented LE rats displayed an initial water deficit (drinking less than renal output), increased plasma antidiuretic (ADH) titres and slightly increased plasma renin activities (PRA) and plasma osmolarities. Such changes were qualitatively similar to those seen in rats fed a normal diet, but deprived of water for 24 hours. After 12 days, the Li-supplemented rats had elevated plasma ADH titres, but reduced pituitary oxytocic and antidiuretic activities.

3 The urinary losses of Na, K and Cl exceeded dietary intakes in LE rats on the introduction of the Li-supplement, and the urinary osmolarity fell by 50%. Electrolyte balances were gradually re-established, although drinking and urine production increased in parallel to reach twice the control values by day 12 of the supplement.

4 Aldosterone and corticosterone secretory rates and their peripheral plasma concentrations were unchanged both after 24 h and 28 days of the Li-supplement.

5 Li elicited no water deficit or saluresis in DI rats, and although the polyuria and polydipsia were exacerbated, urinary osmolarity did not change over the 12 day observation period.

6 Li increased Ca excretion in both rat types; after 12 days the PRA of DI but not LE animals was increased.

7 It is concluded that the overall renal actions of Li are tempered by vasopressin rather than adrenocorticosteroids.

Introduction

The treatment of certain psychiatric disorders with lithium (Li) salts is a well established procedure (Davis & Fann, 1971; Schou & Thomsen, 1975), but the mechanisms involved are not clear. Further there are many physiological processes affected by Li, and undesirable side effects occur including a polydipsic-polyuric syndrome (Singer & Rotenberg, 1973; Forrest, Cohen, Torreti, Himmelhoch & Epstein, 1974). Thus Li influences water and electrolyte metabolism (Forrest *et al.*, 1974) possibly by interfering with vasopressin action (Harris & Jenner, 1972), the renin-angiotensin system (Gutman, Tamir & Benzakein, 1973) and/or with adrenocortical function (Murphy, Goodwin & Bunney, 1969; Hendler, 1975). In addition Li may have direct actions on a variety of renal tubular mechanisms which secondarily influence physiological regulation (Hecht, Galla, Forrest, Kashgarian & Hayslett, 1974; Roscoe, Goldstein, Halperin, Wilson & Stinebaugh, 1976).

The present studies (reported in preliminary form by Balment, Henderson & Chester Jones, 1976b) examine the actions of Li on vasopressin, adrenocortical function and the renin-angiotensin system using intact rats and rats lacking endogenous vasopressin, as a result of an inherited defect in vasopressin synthesis (Sawyer, Valtin & Sokol, 1964). The latter rats have been previously shown to have exacerbated polydipsia and polyuria when given Li (Thomsen & Schou, 1973).

Methods

Animals

Male and female Long Evans (LE) and Brattleboro (DI) rats, weighing between 160 and 300 g and bred in the Department of Zoology, University of Sheffield, were used.

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Experimental protocols

(i) Groups of 5 rats (male Long Evans and female Brattleboro) were individually adapted to all glass metabolism cages (Jencons Metabowl, Hemel Hempstead) for 10 days, after which daily intakes and urinary excretions of water and electrolytes (Na, K, Ca, Mg, Cl) were measured for 3 consecutive days during which the animals were provided with a normal laboratory chow. A Li-supplemented diet was then substituted and measurements continued daily for a further 12 days. The animals were then anaesthetized with ether, and blood (5–8 ml) was collected from the abdominal aorta into heparinized syringes (in less than 1 minute). Pituitary glands were removed, and like the blood plasma stored at −20° until assay.

(ii) A group of 5 Long Evans male rats were given the Li-supplement for 24 h only and then killed (as in (i) above), to assess more exactly the initial events in the response to lithium. The plasma electrolytes, plasma renin activities, plasma ADH titre and pituitary neurohypophysial peptide stores of these rats were compared with those of normal rats and those of rats killed after 24 h water deprivation, both fed the normal diets.

(iii) Adrenal venous blood was collected from male Long Evans rats 24 h and 28 days after receiving the Li supplement. Appropriate control rats were also studied. Under pentobarbitone anaesthesia (Nembutal, Abbott, 60 mg/kg body wt., i.p.) the left adrenal vein was catheterized (26 g hypodermic needle attached to PE 50 catheter) directly and blood was collected for 10 to 15 minutes. Plasma was stored at −20°C until analysis.

Analytical methods and hormone assays

Pituitary oxytocic activity was assayed on the rat isolated uterus (Holton, 1948), plasma and pituitary antidiuretic activities on the ethanol anaesthetized, water diuretic rat (Dicker, 1953), and plasma renin activity measured indirectly by radio-immunoassay of generated angiotensin I (Stockigt, Collins & Biglieri, 1971). These methods have been previously described for this laboratory (Balment, Henderson & Oliver, 1975; Balment, Chester Jones, Henderson & Oliver, 1976a). Aldosterone and corticosterone in adrenal venous and peripheral arterial blood plasmas were assayed by radioimmunoassays (Mayes, Furayama, Kem & Nugent, 1970; Gross, Ruder, Brown & Lipsett, 1972 respectively). Electrolyte concentrations in plasma and urine were determined by flame emission and absorption spectrophotometry (Pye Unicam SP90A) and their osmolarities on a Fiske Osmometer (Quincy, Mass.).

Analysis of data

The analysis of 24 h water and electrolyte balances has been previously described (Balment *et al.*, 1976a). The balance refers to

$$\frac{\text{urinary loss}}{\text{dietary intake}} \times 100\%$$

so that values in excess of 100% indicate that the animal is excreting more than its dietary intake. In experiment (i) the values observed under the Li regime were compared with the three day control period by paired t tests; each animal thus served as its own control. Other comparisons were made using Student's t tests, and values are presented as means ± s.e. mean.

Diets

The laboratory diet (B.P., R & M No. 1; B.P. Nutrition (UK) Ltd., Witham, Essex) contained (in mEq/g) 0.119 Na, 0.213 K, 0.277 Ca, 0.145 Mg and 0.182 Cl. The Li-supplemented diet was prepared by incorporating 1.06 g LiCl into each kg of the standard diet as follows: the R & M No. 1 pellets were made into a slurry with distilled water, and 500 ml of a LiCl solution dissolved therein. The mixture was then dried and made into cubes. Control diets were prepared similarly but LiCl was not added. Distilled water to drink and the foods were provided *ad libitum*. The Li-supplement provided on average 0.2 mEq Li per 100 g body wt. daily and gave, after 10 to 12 days, mean plasma Li concentrations of 0.5 mEq/litre.

The following abbreviations are used. ADH = antidiuretic hormone; DI = rats with Diabetes Insipidus; LE = Long Evans rats; Li-supplemented = Lithium supplemented diet; PRA = Plasma renin activity.

Results

Balance studies (Table 1, Figures 1 and 2)

Plasma composition was largely unaffected in either group of rats on the Li supplement; the only significant change was the mild hypokalaemia of the LE rats ($P < 0.001$) after 12 days. The plasma Li concentrations achieved were similar in the two types of rat.

Food intakes fell transitorily during the first 24 h but normal rates were gradually re-established. Growth continued normally in DI rats, but little weight gain occurred in LE rats during the 12 day observation period. In DI rats an increased drinking rate was detectable during the first 24 h ($P < 0.05$), while no such change occurred in normal rats. However, both types of rat increased their rates of urine production (DI, $P < 0.05$; LE, $P < 0.02$). LE rats were thus in an initial water deficit when Li was added to the diet, and indeed the mean plasma osmolarity increased during this period (Table 1). Figure 1 shows

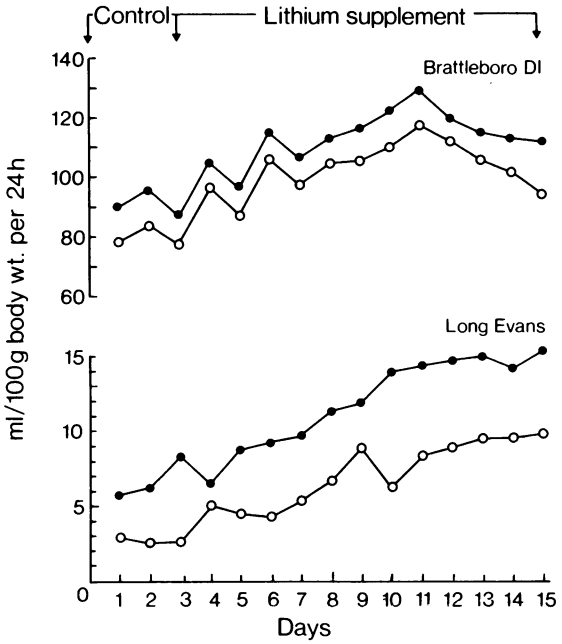

Figure 1 Effects of a lithium supplemented diet on urine production (○) and drinking (●) rates (ml/100 g body wt. per 24 h) by Long Evans and Brattleboro (DI) rats. A three day control period with normal diet provided, was followed by 12 days with a lithium supplement. Each point is the mean value from 5 rats.

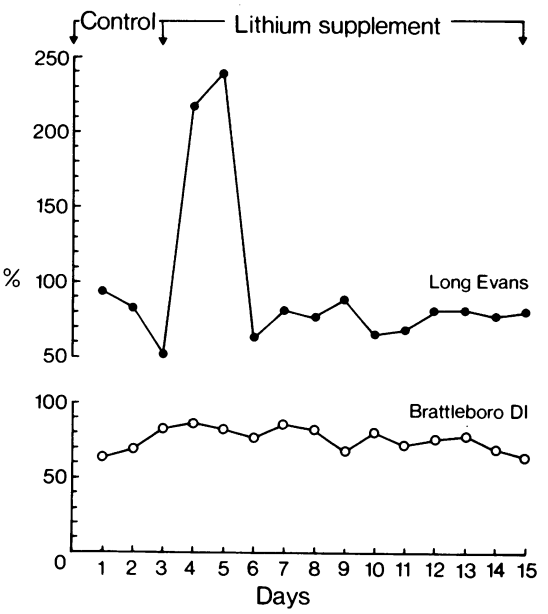

Figure 2 Effects of a lithium supplemented diet on sodium balance

$$\frac{\text{urinary loss}}{\text{dietary intake}} \times 100\%$$

of Long Evans (●) and Brattleboro (DI) (○) rats. A three day control period with normal diet provided, was followed by 12 days with a lithium supplement. Each point is the mean value from 5 rats.

the sequential changes in water metabolism of the DI and LE rats; except for the somewhat aberrant increase in drinking on control day 3 and the initial 24 h response in LE, parallel changes in intake and output are seen.

In the presence of diabetes insipidus, Li had no effect on urinary osmolarity and solute excretion (Table 1), while in normal rats urine became more dilute and solute excretion increased ($P<0.01$ for both). These changes were associated with little change in the osmotically free water excretion of normal rats, but in DI rats a 25% increase occurred.

Table 1 (part 2) gives electrolyte balances and plasma concentrations of rats 24 h and 12 days after Li supplement. In DI rats the proportion of dietary electrolyte appearing in the urine remained stable throughout the 15 day study (Figure 2; Table 1) except that relatively more K ($P<0.05$, for 3 of the 12 day Li-regime), Ca ($P<0.05$ for 10 days) and Cl ($P<0.05$ for 4 days) appeared in the urine. The time courses of these changes did not follow a clearly decipherable pattern. However, in no instance did the renal loss exceed the dietary intake of individual electrolytes.

In contrast, in LE rats Li affected electrolyte balances. Initially, the Li-supplement produced severe negative balances for Na ($P<0.05$), K (NS) and Cl ($P<0.02$): Figure 2, for Na, typifies the time course. In excess of 200% of the dietary intake of these electrolytes appeared in the urine during this initial period. Thereafter balances gradually returned to more normal, pre-Li levels except for Cl which remained elevated for 6 days ($P<0.05$). Ca excretory patterns were not changed in LE rats, although there was slight retention of Mg ($P<0.05$ for 2 days).

Li-responses at 24 h compared with water deprivation (Table 2)

Plasma Li concentrations in animals given Li for 24 h averaged 0.09 mEq/litre, and during this period LE rats displayed an acute water deficit (see above). This phase of the response was in many respects qualitatively similar to that of rats deprived of water for 24 h, but fed a normal diet. Thus plasma osmolarity ($P<0.001$ dehydrated rats), plasma renin activity ($P<0.001$, dehydrated rats) and plasma antidiuretic titre ($P<0.001$ for both dehydrated and Li rats) were all elevated compared with control animals. Plasma K concentrations were reduced ($P<0.01$,

Table 1 Twenty-four hour water and electrolyte balances in Long Evans and Brattleboro DI rats on normal and Li supplemented diet for 24 h or 12 days

Part 1		*Long Evans male*			*Brattleboro DI female*	
Group	*Control*	*24 h Lithium*	*12 day Lithium*	*Control*	*24 h Lithium*	*12 day Lithium*
Food intake (g/100 g body wt.)	6.0 ± 0.9	2.2 ± 1.0	6.8 ± 0.7	8.9 ± 0.3	7.7 ± 0.7	9.7 ± 0.7
Water intake (ml/100 g body wt.)	6.8 ± 0.6	6.6 ± 0.9	15.3 ± 2.3	90.7 ± 5.9	104.1 ± 8.4	111.0 ± 2.9
Urine output (ml/100 g body wt.)	2.7 ± 0.5	5.0 ± 0.4	9.8 ± 2.1	80.8 ± 4.3	96.1 ± 7.6	98.3 ± 3.4
Urinary osmolarity (mOsm/litre)	1843.0 ± 181.6	755.0 ± 154.0	935.8 ± 202.0	144.6 ± 10.8	139.2 ± 9.7	140.4 ± 6.9
Free water clearance (C_{H_2O}) ml/100 g body wt.)	−12.4 ± 1.6	−6.9 ± 2.1	−15.7 ± 3.4	+42.8 ± 4.8	+52.9 ± 6.5	+53.2 ± 2.7
Solute excretion (mOsm/100 g body wt.)	4.6 ± 0.6	3.7 ± 0.6	7.8 ± 0.6	11.4 ± 0.6	13.2 ± 0.4	13.8 ± 0.9
Part 2		*Long Evans Male*			*Brattleboro DI female*	
Group	*Control*	*24 h Lithium*	*12 day Lithium*	*Control*	*24 h Lithium*	*12 day Lithium*
Electrolyte balances (%)						
Sodium	76.1 ± 11.8	215.8 ± 36.9	79.8 ± 3.4	71.5 ± 4.8	85.4 ± 6.3	63.4 ± 4.7
Potassium	75.3 ± 15.2	265.8 ± 88.1	80.1 ± 4.5	70.7 ± 4.4	86.1 ± 4.9	70.4 ± 5.0
Calcium	1.07 ± 0.42	2.77 ± 0.89	3.61 ± 1.19	5.79 ± 0.89	9.45 ± 0.73	10.13 ± 1.81
Magnesium	12.33 ± 2.41	6.31 ± 4.10	9.27 ± 0.95	6.99 ± 3.40	7.24 ± 2.25	8.05 ± 4.23
Chloride	63.7 ± 5.5	185.5 ± 30.3	94.8 ± 6.0	71.9 ± 3.6	85.9 ± 5.0	73.5 ± 7.9
Plasma concentrations						
Sodium mEq/litre	149.1 ± 2.0	145.8 ± 0.8*	146.5 ± 0.6	142.6 ± 2.5	—	143.8 ± 1.4
Potassium mEq/litre	4.76 ± 0.1	4.36 ± 0.27*	4.07 ± 0.02	3.88 ± 0.15	—	3.96 ± 0.15
Lithium mEq/litre	0.00	0.09 ± 0.01*	0.46 ± 0.01	0.00	—	0.48 ± 0.02
Osmolarity mOsm/litre	305.9 ± 0.8	313.3 ± 3.9*	305.5 ± 2.4	309.8 ± 1.6	—	308.3 ± 0.8

5 animals in each group. Values are mean ± s.e. mean.
* Values are also given in Table 2.

Table 2 Plasma antidiuretic (ADH) and renin (PRA) activities, electrolyte concentrations and osmolarity in normal, 24 h dehydrated and 24 h Li-supplemented male Long Evans rats

Group	*Sodium (mEq/litre)*	*Potassium (mEq/litre)*	*Lithium (mEq/litre)*	*Osmolarity (mOsm/litre)*	*PRA (ng equiv angiotensin I/ml)*	*Plasma ADH (μu/ml)*
Controls $n=5$	146.1 ± 0.8	4.74 ± 0.19	0.00	307.4 ± 1.5	309.3 ± 13.0	133.6 ± 3.8
24 h Lithium $n=5$	145.8 ± 0.8	4.36 ± 0.27	0.09 ± 0.01	313.3 ± 3.9	350.0 ± 43.7	366.8 ± 12.7
24 h dehydrated $n=4$	150.6 ± 2.4	3.92 ± 0.07	0.00	320.0 ± 4.1	466.8 ± 49.0	833.7 ± 39.0

Values are means ± s.e. mean.

Table 3 Adrenocortical function in normal and Li-supplemented male Long Evans rats

Group		*Corticosterone*		*Aldosterone*	
	Paired adrenal weight	*Concentration*	*Secretory rate*	*Concentration*	*Secretory rate*
	(mg/100 g body wt.)	(μg/100 ml plasma)	(μg min^{-1} 100 g^{-1} body wt.)	(μg/100 ml plasma)	(ng min^{-1} 100 g^{-1} body wt.)
Control	12.2 ±0.8 (5)	875.4 ±98.4 (13)	0.17 ±0.02 (13)	3.40 ±0.93 (9)	0.55 ±0.15 (9)
24 h lithium	—	780.0 ±74.7 (10)	0.16 ±0.02 (10)	3.14 ±0.19 (5)	0.44 ±0.16 (5)
28 day lithium	13.7 ±0.5 (5)	791.1 ±72.1 (9)	0.18 ±0.02 (9)	1.88 ±0.56 (4)	0.43 ±0.12 (4)

Li supplements were provided for 24 h and 28 days before collection of adrenal venous blood. Means ± s.e. mean. Number of animals given in parentheses.

dehydrated rats), and Na concentrations were elevated in the dehydrated group.

Adrenocortical function (Table 3)

Control rat peripheral plasma aldosterone, 38.0 ± 4.4 ng/100 ml, and corticosterone, 12.4 ± 3.1 μg/100 ml, concentrations were similar to those of rats fed Li for 12 days (37.2 ± 2.4 ng aldosterone/100 ml; 9.4 ± 0.6 μg corticosterone/100 ml).

No differences in paired adrenal weights were noted. The concentrations of corticosterone in adrenal venous plasma, the adrenal venous flow and hence its secretory rates were similar in control, 24 h Li and 28 day Li rats (Table 3). Aldosterone was measured in only five 24 h and four 28 day Li rats. In the former group the concentration ranged from 2.6 to 3.6 μg % and from 1.0 to 3.5 μg % in the latter. The secretory rate of aldosterone was not apparently modified by Li (Table 3).

Plasma renin activity, pituitary oxytocic and pituitary antidiuretic activities at 12 days

The PRA, after an initial increase in LE rats, had returned to normal values at 12 days (269.2 ± 28.8 ng angiotensin I equiv/ml). In the DI rats, however, PRA after 12 days was significantly higher in Li rats (356.1 ± 28.4 ng equiv/ml) than in controls (155.6 ± 26.5; $P < 0.001$).

In LE rats, the acute increase (24 h) in antidiuretic titre after Li was sustained to reach 976.4 ± 62.6 μu/ml ($P < 0.001$ compared with untreated controls) after 12 days. There were reduced pituitary antidiuretic and oxytocic activities in Li rats: pituitary antidiuretic activity (in mu/gland) was 706 ± 46.4 in control and 138.8 ± 8.1 in Li rats, while oxytocic activity (mu/gland) was 739.9 ± 18.5 in control and 454.0 ± 37.8 in Li rats ($P < 0.001$ for both).

Discussion

The polyuric-polydipsic actions of lithium salts are among the important side effects of their application to affective disorders in man (Singer & Rotenberg, 1973; Forrest *et al.*, 1974). In the present studies Li was added to the dried diet, and, apart from the day 1 reduction in food intake, produced a regime akin to the clinical one. This contrasts with other studies in which intraperitoneal or intragastric routes of administration, both stressful procedures, were employed (Baer, Kassir & Fieve, 1970; Martinez-Maldonado, Stavroulaki-Tsapara, Tsaparas, Suki & Eknoyan, 1975) and in which Li was added to the drinking water (Ellman & Gan, 1973). In the latter case, there are obvious difficulties regarding the quantities given, since the induced polydipsia causes the animal to increase its Li load.

The availability of animals precluded the use of a single sex of animals throughout the present study but the Brattleboro DI rats provided a unique opportunity to study the effects of Li in the absence of vasopressin (ADH). In our experience the maintenance of rats in metabolism cages for periods in excess of 2 weeks, after an initial 10 day adaptation period, has no adverse effects on the daily water and electrolyte metabolism (Balment *et al.*, 1976a). The effects of Li were thus assessed from a 3 day control period after adaptation, and a period of Li supplement. Each animal served as its own control and so minimized inter-animal variations.

Many of the sequelae of Li administration have nephrogenic origins. The sensitivity to exogenous vasopressin is diminished (Forrest *et al.*, 1974), while the blockade of endogenous hormone (Harris & Jenner, 1972) may itself provoke the increased water turnover and the reduction in urinary osmolarity of the LE rats. The ion may have direct neural actions which impinge upon the hypothalamo-neurohypophysial system. For example, Li is accumulated in the pituitary gland (Wittrig, Woods & Anthony, 1970) and can deplete the hypothalamo-neurohypophysial system of neurosecretory material (Ellman & Gan, 1973; Hochman & Gutman, 1974). Li may thus interfere with the synthesis, storage and/or release of vasopressin. Indeed Li causes release of vasopressin *in vitro* (Torp-Pedersen & Thorn, 1973). These effects may be associated with, or perhaps be essential components of, the Li actions on CNS sodium fluxes (Baker, 1971). In the present studies significant changes in plasma and pituitary ADH occurred. The plasma values are somewhat high, probably reflecting the method of blood collection (Forsling, Martin, Sturdy & Burton, 1973). Qualitatively, however, LE rats given Li display increased plasma and decreased pituitary ADH compared with control animals. The immediate (within 24 h) increase in plasma antidiuretic titres, and the overall 7-fold increment after 12 days, may be compared with the clinical observation that nephrogenic diabetes insipidus and high plasma vasopressin titres may exist in patients given Li (Padfield, Morton, Lidop & Timbury, 1975).

It is perhaps significant that pituitary oxytocic stores are also depleted by Li and this suggests a general over-stimulation of the hypothalamo-neurohypophysial system. An analogous situation exists in the normal DI rat in which failure to synthesize vasopressin occurs alongside relatively smaller amounts of oxytocin within the pituitary (Balment *et al.*, 1975).

Interference with vasopressin physiology cannot explain the effects of Li on DI rats observed in the present studies and by Thomsen & Schou (1973) and

Hochman & Gutman (1974). Rather, Li may act directly upon thirst mechanisms (Smith & Balagura, 1972), so that the polyuria is secondary (Smith, Balagura & Lubrau, 1970). Thus in the DI rat, Li produces a primary polydipsia, while in LE rats polyuria may be induced perhaps in combination with a central neural action on water intake.

Li may indeed act upon vasopressin-independent aspects of fluid balance, by, for example influencing proximal tubular cation transport (Hecht *et al.*, 1974; Martinez-Maldonado *et al.*, 1975). In the present studies LE rats displayed an initial water deficit resulting from failure to increase drinking in the face of increased renal losses, and elevated plasma vasopressin titres. Concurrently the renal losses of Na, K and Cl exceeded the dietary intakes, features noted in other studies (Tupin, Schlagenhauf & Creson, 1968; Murphy *et al.*, 1969; Baer *et al.*, 1970; Martinez-Maldonado *et al.*, 1975). Neither the fluid nor the electrolyte imbalances occurred in DI rats fed Li. The initial response to Li may thus depend upon vasopressin, although in both LE and DI rats given long term Li, relatively greater percentages of dietary intakes, particularly Cl, appeared in the urine. An additional feature in both LE and DI rats is that the urinary Ca excretion increased, contrasting with the findings of Tupin *et al.* (1968).

Available data are equivocal as to whether Li alters the activity of either the renin-angiotensin system (Gutman *et al.*, 1973; Padfield *et al.*, 1975) or the adrenal cortex (Murphy *et al.*, 1969; Hendler, 1975). Such is perhaps surprising in view of the markedly altered Na and water balances. Adrenocortical function in LE rats was not apparently changed by Li, even after 28 days and the differences in PRA were not statistically significant. The PRA's of DI rats were, however, considerably elevated 12 days after beginning the Li-supplement, but it is premature to speculate on the possible mechanisms involved.

Li thus affects fluid and electrolyte balances in the absence of vasopressin. In the presence of vasopressin the character of the response differs. It is suggested that Li has primary, perhaps direct, actions on neural processes governing thirst, and on renal electrolyte and water transport systems. The inhibition of vasopressin action, both renally and extrarenally must clearly temper the overall Li effect. Vasopressin rather than adrenocorticosteroids modulate the action of Li on the kidney.

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