Kidney International, Vol. 50 (1996), pp. 377–383

Mechanism of lithium-induced polyuria in the rat

SHANE L. CARNEY, CHERYL RAY, and ALASTAIR H.B. GILLIES

Faculty of Medicine and Health Sciences, University of Newcastle, Newcastle, New South Wales, Australia

Mechanism of lithium-induced polyuria in the rat. While many studies have demonstrated a nephrogenic diabetes insipidus syndrome (NDI) with prolonged lithium (Li) treatment, experiments in the isolated rat papillary collecting duct have suggested that the defect may be due to a circulating factor that inhibits the action of arginine vasopressin (AVP). Since Li-treatment can produce a form of hyperparathyroidism and parathyroid hormone (PTH) can act as a partial agonist to AVP, *in vivo* and *in vitro* studies were performed on rats made polyuric by daily intraperitoneal (i.p.) Li (4 mmol/kg) treatment. Li-treatment for three weeks produced an increase in PTH (194 ± 20 compared with 118 ± 18 pg/ml in control rats; $P < 0.01$) as well as an increase in the plasma calcium concentration (2.38 ± 0.05 compared with 2.25 ± 0.04 mmol/liter; $P < 0.05$). Clearance studies were performed on water loaded Li-treated and control rats, and the defect in urine concentration was only observed with a low physiological concentration of AVP (10 mU/kg body wt over 5 min). Maximal urine osmolality was 328 ± 31 compared with 613 ± 81 mOsm/kg ($P < 0.05$) in controls. There was no detectable difference with a prolonged maximal physiological AVP concentration (10 mU bolus and 50 mU/kg body wt per hr) and papillary solute concentrations were unchanged. When Li-treated rats had been parathyroidectomized (PTX), a significant difference in urine concentration with the low AVP concentration could not be demonstrated when compared to non-PTX control rats. In the isolated papillary collecting duct preparation a medium was used that contained fresh plasma from Li-treated or control rats, both intact and PTX. Experiments using plasma from Li-treated intact rats produced only a 25.4 ± 5.1% increase in diffusional water permeability with the addition of AVP (200 μU/ml) compared to 52.6 ± 9.0% in control rats ($P < 0.01$). However, when plasma from Li-treated PTX rats was used, the AVP induced increase in water permeability (54.7 ± 11.2%) was not significantly different from that observed in PTX control rats. These studies show that the NDI-like defect in Li-treatment is small and easily overcome by higher concentrations of AVP and suggests that the concentration defect is at least in part due to increased circulating levels of PTH acting as a partial agonist to AVP and thereby inhibiting its hydroosmotic action.

It is accepted that the diabetes-insipidus-like syndrome induced by prolonged lithium (Li) administration is due to a resistance of the collecting duct cells to the antidiuretic action of vasopressin (AVP) [1]. However, a series of experiments in the isolated rat papillary collecting duct did not support this hypothesis [2]. AVP induced increases in water permeability were not reduced by the presence of bath Li concentrations similar to that found in papillary tissue and urine of polyuric Li-treated rats [3, 4]. Furthermore, the addition of Li to the perfusate as well as the bath in papillary collecting ducts from Li-treated polyuric rats also failed to demonstrate any inhibitory effect of Li on AVP action. Bentley and Wasserman [5] were also unable to demonstrate any effect of Li on AVP induced osmotic water transport in the toad bladder, although other studies using this model, which is not analogous to the mammalian collecting duct, have demonstrated inhibitory effects of Li on AVP stimulated water flow [6–8]. However, *in vivo* micropuncture studies in Li-treated rats have also failed to demonstrate a depressant action of Li on AVP induced distal water reabsorption [9, 10]. Clearly there are significant contradictions in the available experimental data.

There are two ways to reconcile an apparent paradox in the rat where clearance studies support a nephrogenic diabetes insipidus-like syndrome, yet *in vivo* and *in vitro* micropuncture studies do not. One possibility is that Li interferes with the ability of the kidney to produce a maximal corticopapillary concentration gradient. Unfortunately, measurements of this gradient have again produced conflicting results, with reports of normal [3, 11, 12] and reduced [4, 7, 13] papillary solute concentrations with Li-treatment. Since these experiments were performed comparing polyuric Li animals with non-polyuric controls, comparing solute gradients during comparable water diuresis in both groups would be more appropriate.

Another possibility is that Li-treatment produces a circulating factor that inhibits the response of the collecting duct to AVP or inhibits the release of a facilitatory factor to AVP. Such a possibility is supported by *in vitro* studies [14, 15] where plasma from Li-treated rats was added to the bath and compared with artificial medium. Evidence that Li-treatment produces a form of primary hyperparathyroidism [16–19], combined with evidence that parathyroid hormone (PTH) can act as a partial agonist to AVP *in vivo* and *in vitro* [20, 21] suggested that PTH could be a cause of the nephrogenic diabetes insipidus (NDI) syndrome. Consequently, the effect of high and low physiological concentrations of AVP on urine concentration in chronic Li-treated and control animals was evaluated, both in the presence and absence of their parathyroid glands. Both Li-treated and control animals were studied in a comparable diuretic state. Papillary solute concentrations were also measured. In addition, the effect of AVP on isolated papillary collecting duct water permeability was studied using a medium composed of plasma from parathyroidectomized (PTX) or intact Li-treated and control rats.

Methods

Experiments were conducted on adult male and female Wistar rats weighing between 250 and 300 g housed in an air-conditioned room (21° to 23°C). One group of rats was fed a normal laboratory diet and allowed water *ad libitum* (control group) while another

Received for publication December 3, 1990
and in revised form January 23, 1996
Accepted for publication March 3, 1996

group was, in addition, treated with daily i.p. injections of LiCl (4 mmol/kg body wt) for at least 21 days to produce a marked polyuria [3]. In the unanesthetized rat, such a protocol produces a urine output of approximately 42 compared to 3 ml/100 g body wt/day [19]. On the day of the clearance or micropuncture studies, Li-treated rats were given their daily i.p. injection one hour before anesthesia or decapitation while control rats were given an equimolar injection of NaCl.

In vivo clearance studies

All rats were anesthetized with Inactin (100 mg/kg i.p.) and placed on a heated table to maintain body temperature at 37°C. Following tracheotomy, animals were infused via a jugular vein catheter (PE50) with a 75 mmol NaCl and 1.75% dextrose solution at a rate of 6% body wt over a 20 minutes period. This rate was then reduced to a rate of 12 ml/hr for a further 60 minutes. A 15-minute urine collection was then performed and a midpoint blood sample collected. AVP was then administered via the jugular catheter as a bolus injection of 10 mU/kg body wt and continued at a rate of 50 mU/kg body wt/hr (maximal AVP concentration) or as a bolus dose of 10 mU/kg body wt over five minutes without continued infusion (low AVP concentration). The former concentration has been demonstrated to produce a maximal antidiuretic effect in this preparation [21], while the latter and smaller dose has been employed in an earlier published study that showed an inhibitory effect of Li on water transport [3]. Three more 15-minute urine collections were then performed as well as midpoint blood samples between the first and second as well as the second and third urine collections.

In some Li-treated and control rats, PTX was also performed immediately after tracheotomy by identification of both glands under stereomicroscopic vision, splitting the fascial covering and avulsing both glands with forceps. This cleanly removed both glands but was followed by electrocautery of the resulting cavities in the thyroid gland. To ensure degradation of any residual PTH, clearance experiments were commenced 120, not 60, minutes later.

In an additional series of experiments, papillae were removed from both anesthetized control and Li-treated diuretic rats immediately before the administration of AVP and the papillary solute concentration was measured by the method of Gardner and Vierling [22].

In vitro micropuncture studies

Normal rats were given 10 ml water i.p. and decapitated one hour later. Renal papillae were rapidly isolated and incubated for one hour at 37°C before experimentation in a modified Krebs-Ringer solution (NaCl 150, K_2HPO_4 2.5, $MgSO_4$ 1.2, $CaCl_2$ 1, urea 200, dextrose 5.5 mmol and calf serum 5% by volume and vigorously bubbled with 95% O_2 with pH adjusted to 7.4). Papillae were then set up in a bath for micropuncture as previously described [23]. The bath contained a 1 to 1 mixture of a modification of the above Krebs-Ringer solution (NaCl 160, KCl 5, $MgCl_2$ 2, urea 400 mmol) and plasma taken from intact or PTX Li-treated and untreated rats. Half of these rats had been anesthetized the evening before the experiments with sodium pentothal and had their parathyroid glands removed while the others had sham operations. The next morning all animals were anesthetized, blood collected from the abdominal aorta, placed in heparinized tubes and centrifuged, and the plasma mixed with the artificial solution for immediate use in the micropuncture studies.

Table 1. Plasma parameters in lithium-treated and control rats

	Control (N = 8)	Li-treated (N = 8)	P value[a]
PTH *pg/mL*	108 ± 18	194 ± 20	0.01
Plasma Ca *mm/liter*	2.25 ± 0.04	2.38 ± 0.05	0.05
UF Ca *mm/liter*	1.36 ± 0.04	1.49 ± 0.04	0.05
Plasma Li *mm/liter*	—	1.21 ± 0.09	—
Hematocrit %	40 ± 1	39 ± 1	NS

Abbreviation is: UF, ultrafilterable.
[a] Statistical significance Li vs. control

Experiments were then performed to determine the diffusional water permeability of superficial papillary collecting ducts before and after the addition a maximal concentration of AVP (200 μU/ml) for this preparation [24]. Collecting ducts were punctured and perfused using a perfusion solution (NaCl 150, K_2HPO_4 2.5, $MgSO_4$ 1.2, $CaCl_2$ 1.0, urea 200 mmol) having the same osmolarity as the medium and containing tritiated water. Table 1 demonstrates the concentrations of solutes in the perfusion solution and final medium. The same collecting ducts were then punctured at a distal site and duplicate collections made. AVP was then added and distal collections were repeated. The micropuncturist was unaware of the origin of the medium used. The diffusional water permeability was calculated from the formula [25] $P = Vi/A \times Ln (C_i/C_o)$ where V_i is the perfusion rate (30 nl/min), A is the luminal surface area, C_i the isotope counts in the perfusate and C_o the isotope counts in the collected samples.

Analysis

[^{51}Cr]EDTA levels for the measurement of glomerular filtration rate were counted on a gamma counter (Packard Instrument Co.). The mean arterial pressure was monitored using a pressure transducer (Gould-Stratham) and a polygraph (Grass). Sodium, potassium and lithium concentrations were measured on a flame photometer (Corning); calcium and magnesium were measured by an atomic absorption spectrophotometer (Varian), and phosphate by a colorimetric method [26]. Plasma calcium and magnesium ultrafiltrates were obtained using ultrafiltration cones (Amicon). Urine and plasma osmolalities were measured on a micro-osmometer (Wescor Advance Instruments), and tritiated water radioactivity was determined in a liquid scintillation spectrometer (Packard Instrument Co.). Plasma PTH concentrations were performed using a radioimmunoassay [27].

Materials

Arginine vasopressin (350 U/mg) was purchased from Sigma Co., and bovine serum albumin from Commonwealth Serum Laboratories.

Analysis

All results are expressed as means ± SEM. Statistical analysis was performed using an analysis of variance and a t-test adapted for multiple comparisons [28].

Table 2. Clearance data and papillary tissue analysis from control and lithium treated anesthetized rats during a water diuresis induced by a 0.75 mmol NaCl and 1.75% dextrose solution

	Control ($N = 7$)	Lithium-treated ($N = 7$)	P value*
Urine flow *μl/min*	164 ± 18	155 ± 16	NS
U_{Osm} *(mOsm/kg H_2O*	114 ± 6	116 ± 7	NS
P_{Osm} *mOsm/kg H_2O*	289 ± 7	282 ± 4	NS
C_{Osm} *mOsml/kg/min*	65 ± 5	64 ± 4	NS
C_{H_2O} *μl/min*	99 ± 6	92 ± 5	NS
GFR *ml/min*	2.8 ± 0.2	2.6 ± 0.3	NS
P_{Li} *mmol/liter*	—	1.2 ± 0.2	—
Water content *% tissue wet wt*	87 ± 1	88 ± 1	NS
Na^+ content *mmol/kg H_2O*	167 ± 11	157 ± 10	NS
K^+ content *mmol/kg H_2O*	47 ± 2	50 ± 4	NS
Li^+ content *mmol/kg H_2O*	—	8 ± 1	—
Total solutes *mmol/kg H_2O*	2730 ± 237	2736 ± 259	NS

Abbreviations are: GFR, glomerular filtration rate; U, urine; P, plasma; C, clearance; C_{H_2O}, free water clearance.

[a] Values $P > 0.05$ were considered nonsignificant (NS).

Results

Effect of chronic Li-treatment on calcium metabolism

Li-treated rats had a significantly elevated PTH concentration when compared to non-treated animals (194 ± 20 compared to 118 ± 18 pg/ml; $P < 0.01$), while the plasma total and ionized calcium concentrations were elevated: 2.38 ± 0.05 and 1.49 ± 0.04 compared to 2.25 ± 0.04 and 1.36 ± 0.04 mmol/liter ($P < 0.05$) in eight Li-treated and eight control rats killed two hours after the morning i.p. injection, respectively (Table 1). In the Li-group the Li concentration was 1.21 ± 0.09 mmol/liter.

Clearance studies

Water diuretic control and Li-treated rats failed to demonstrate any significant difference in glomerular filtration rate, urine flow, and solute and water excretion (Table 2). Also, the papillary solute concentrations measured were not significantly different. When a maximal concentration of AVP (10 mU/kg stat and 50 mU/kg/hr) was infused into water diuretic anesthetized Li-treated rats, no significant difference in urine flow or osmolality was observed when the response was compared to the control group (Table 3). AVP produced a prompt and significant increase in urine osmolality in both groups: 1020 ± 107 compared with 924 ± 115 mOsm/kg, respectively, during the final collection period. However, with the administration of a low concentration of AVP (10 mU/kg infused for only 5 min), the previously described inhibitory effect of Li-treatment in this preparation was noted. While this concentration of AVP still produced a reduction in urine flow and an increase in urine osmolality in the Li-treated group, this effect was significantly less than in the control group in the first two but not the final collection period.

In a further series of experiments using the low concentration brief AVP infusion protocol (10 mU/kg over 5 min), the effects of prior PTX was compared in control and Li-treated animals. Again, in the intact groups, Li-treatment inhibited the action of AVP (Fig. 1). However, PTX abolished this inhibitory effect and urine osmolality and flow was not significantly different in the control and Li-treated rats. Parathyroid glands were also larger in the Li-treated animals on microscopy and weight. Weight ratio between Li-treated and control rats was 1.41.

Micropuncture studies

The increase in the diffusional water permeability in perfused superficial collecting ducts of control intact rats with a maximal concentration of AVP (200 μU/ml) was 52.6 ± 9.0% ($P < 0.01$) the diffusional water permeability increasing from 4.68 ± 0.19 to 7.14 ± 0.55 μm/sec (Fig. 2). Plasma from PTX rats did not significantly alter the increase produced by AVP (51.3 ± 11.8%). However, the increase in water permeability with AVP was significantly depressed in medium composed of plasma from intact Li-treated rats with only a 25.4 ± 5.1% rise. However, when the medium used was from plasma of PTX Li-treated rats, the water permeability response was much greater (54.7 ± 11.2%): 4.75 ± 0.35 μm/sec pre-AVP and 7.35 ± 0.51 μm/sec post-AVP. This increase was not significantly different from control PTX rats. The relative concentrations of electrolytes in the bathing medium as well as perfusate for this series of experiments is detailed in Table 4. In particular, the mean calcium concentration in the Li medium was not significantly different from that measured in the control group.

Discussion

A water diuretic model was chosen to inhibit endogenous AVP release and dextrose was used because increasing plasma concentrations do not stimulate AVP release [29]. Because of the chosen experimental model, the animals required anesthesia, however, Shirley, Zearde and Walter [30] have demonstrated that renal function and electrolyte transport in inactin anesthetized rats is similar to that measured in unstressed conscious rats. Acute PTX was used to minimise receptor changes from hypocalcemia. Concentrations of AVP used were based on previous studies in this model [21]; however, because of our inability to detect any inhibitory effect of Li-treatment on AVP action in the intact animal (several AVP concentrations were used although the results are not presented), we finally followed the original protocol of Forrest et al [3] where a relatively low physiological concentration of AVP was administered as a bolus rather than a prolonged infusion. In these experiments, Li-treatment produced a form of hyperparathyroidism with a 65% increase in the plasma PTH concentration at the time of testing, similar to that previously observed in human and rat [16, 17]. The previously described NDI syndrome was again demonstrated in anesthetized Li-treated rats [3, 6]; however, this inhibitory effect of Li-treatment on AVP action in the collecting duct was only apparent with a low AVP concentration infused over a short time period (low) and was easily overcome with a higher (maximal) and sustained concentration. Thus, the NDI syndrome has been confirmed *in vivo*. Such a syndrome is unlikely to be due to a reduced papillary solute concentration gradient since water loaded polyuric control rats had a similar gradient when compared with Li treated rats.

Removal of the parathyroid glands appeared to reverse the concentration defect in the Li rats, and this reversal was also demonstrated in the isolated papillary collecting duct where an artificial medium and plasma mix from PTX Li-treated rats allowed a normal diffusional water permeability response to AVP. These results therefore support the proposition that an increased plasma concentration of PTH is the circulating factor that inhibits

Table 3. Comparison between a constant maximal infusion and a brief minimal infusion of AVP in control and lithium treated anesthetized rats

	Pre-AVP		Post-AVP					
			Collection 1		Collection 2		Collection 3	
	Control	Li	Control	Li	Control	Li	Control	Li
Maximal AVP								
10 mU/kg stat + 50 mU/kg/hr	(12)[a]	(11)	(12)	(11)	(12)	(11)	(12)	(11)
Urine flow *μl/min*	163 ± 22	149 ± 7	56 ± 28	61 ± 16	45 ± 11	38 ± 9	38 ± 15	29 ± 7
U_{Osm} *mOsm/kg* H_2O	109 ± 7	108 ± 5	496 ± 71	414 ± 50	738 ± 98	696 ± 81	924 ± 115	1020 ± 107
Minimal AVP								
10 mU/kg over 5 min	(8)	(8)	(8)	(8)	(8)	(8)	(8)	(8)
Urine flow *μl/min*	154 ± 18	149 ± 21	39 ± 6	58 ± 7[b]	82 ± 18	129 ± 17[b]	161 ± 23	183 ± 15
U_{Osm} *mOsm/kg* H_2O	110 ± 7	112 ± 7	411 ± 28	328 ± 31[b]	613 ± 81	231 ± 53[b]	315 ± 57	137 ± 18

[a] Numbers in parenthesis denotes number of rats in group; [b] $P < 0.05$

the action of AVP. Thus PTH acts as a partial agonist to AVP, having a weak AVP-like action on water transport at high concentrations yet inhibiting the effect of low concentrations of AVP. This inhibitory effect can be overcome by higher concentrations of dDAVP, as has been demonstrated *in vitro* [20] and *in vivo* [21]. Christensen [31] has also demonstrated in rats that higher doses of AVP can overcome the NDI effect of Li-treatment, thus supporting our proposition. These experiments therefore offer an explanation for the apparent paradox where *in vivo* experiments have demonstrated a defect in concentration [3, 6], while *in vitro* experiments in artificial medium have not [2]. In support of such an hypothesis, calcitonin, another polypeptide hormone with similar distal tubule transport functions to PTH has also been found to act as a partial agonist to AVP both *in vivo* and *in vitro* and over a similar concentration range [32, 33]. In another target tissue, PTH has been found to inhibit AVP induced vascular smooth muscle contraction [34], further supporting an interaction of these related polypeptide hormones.

It is difficult to compare the concentrations of hormone necessary to produce such a specificity 'spill over' effect in *in vivo* and *in vitro* conditions. In the isolated collecting duct, 50 ng/ml of PTH in the medium produced a 20% increase in diffusional water permeability, and a 10% increase at 5 ng/ml was not significant [20]. The level of PTH measured in our Li-treated rats was 0.194 ng/ml. Nevertheless, in other comparisons of *in vivo* and *in vitro* systems, for example, using AVP, hormone concentrations required to produce an *in vitro* physiological effect are often 10 to 100 times higher than that required in *in vivo* systems [24]. In a recent study, 2 μg/kg body wt rat PTH [1–34]/hr infused into adult rats which is a maximal phosphaturic concentration in the model used, produced a sudden although brief (30 to 40 min) 35% fall in urine excretion [21]. These observations lend support to the proposition that the effect of PTH on AVP receptors can occur at high physiological rather than pharmacological concentrations of hormone.

Another possible explanation for the role of Li-induced hyperparathyroidism in inhibiting the action of AVP is the hypercalcemia produced by Li-treatment. In the *in vivo* studies, a small but significant increase in plasma calcium was measured. However, in the *in vitro* studies where a mixture of plasma and artificial medium was used, these differences were very small and not statistically significant. Therefore it seems most unlikely that calcium could be the elusive circulating factor. In a recent review [34] it was suggested that hypercalcemia was unlikely to impair the hydroosmotic action of AVP. Other workers have in fact demonstrated such a defect [35] but only at very high calcium concentrations, and such a defect could not be overcome by higher concentrations of AVP.

The observation in many studies of a corresponding inhibition of the adenylate cyclase-cAMP system has always supported the assumption that Li-treatment produces a NDI syndrome. However, several workers have failed to demonstrate a close association between this system and the corresponding physiological event, both in AVP-induced water transport [2, 24] and in other systems [36–38]. More recently Anger et al [39] couldn't demonstrate any inhibitory effect of Li on cAMP generation in cultured rat inner medullary collecting tubule cells with 5 mM Li, a concentration that would reasonably be expected within the medulla. However, very high concentrations of 10 mM or more acutely inhibited cAMP generation while prolonged exposure enhanced cAMP formation. To further underline our lack of understanding of the effect of Li on this complex system, even in studies where Li was found to inhibit the generation of cAMP, the proposed sites of action were contradictory [3, 6, 40].

An inhibitory effect of Li on proximal tubule function [10] could theoretically inhibit urine concentration and could partly explain the contradictory *in vivo* and *in vitro* data. However, this is unlikely to be important since there is clearly a defect in AVP action and

Table 4. Solute concentrations in final medium derived from normal control or lithium treated rats and in the artificial collecting duct perfusate

	Li medium ($N = 12$)[a]	Control medium ($N = 13$)	Perfusate
Na *mmol/liter*	147 ± 3	148 ± 2	150
K *mmol/liter*	4.90 ± 0.3	5.0 ± 0.5	5.0
Cl *mmol/liter*	142 ± 6	140 ± 5	152
Ca *mmol/liter*	1.19 ± 0.09	1.14 ± 0.07	1.0
Mg *mmol/liter*	1.29 ± 0.08	1.26 ± 0.08	1.20
Li *mmol/liter*	0.61 ± 0.5	—	—
PO_4 *mmol/liter*	0.69 ± 0.10	0.78 ± 0.08	2.50
Urea *mmol/liter*	202 ± 15	203 ± 18	200
Osmolality *mOsm/kg*	519 ± 42	520 ± 31	513
[b] (Ca mmol/liter)	(0.96 ± 0.11)	(0.92 ± 0.12)	

[a] Denotes number of experiments where solutes measured
[b] Final calcium concentration in the medium made with plasma from PTX rats

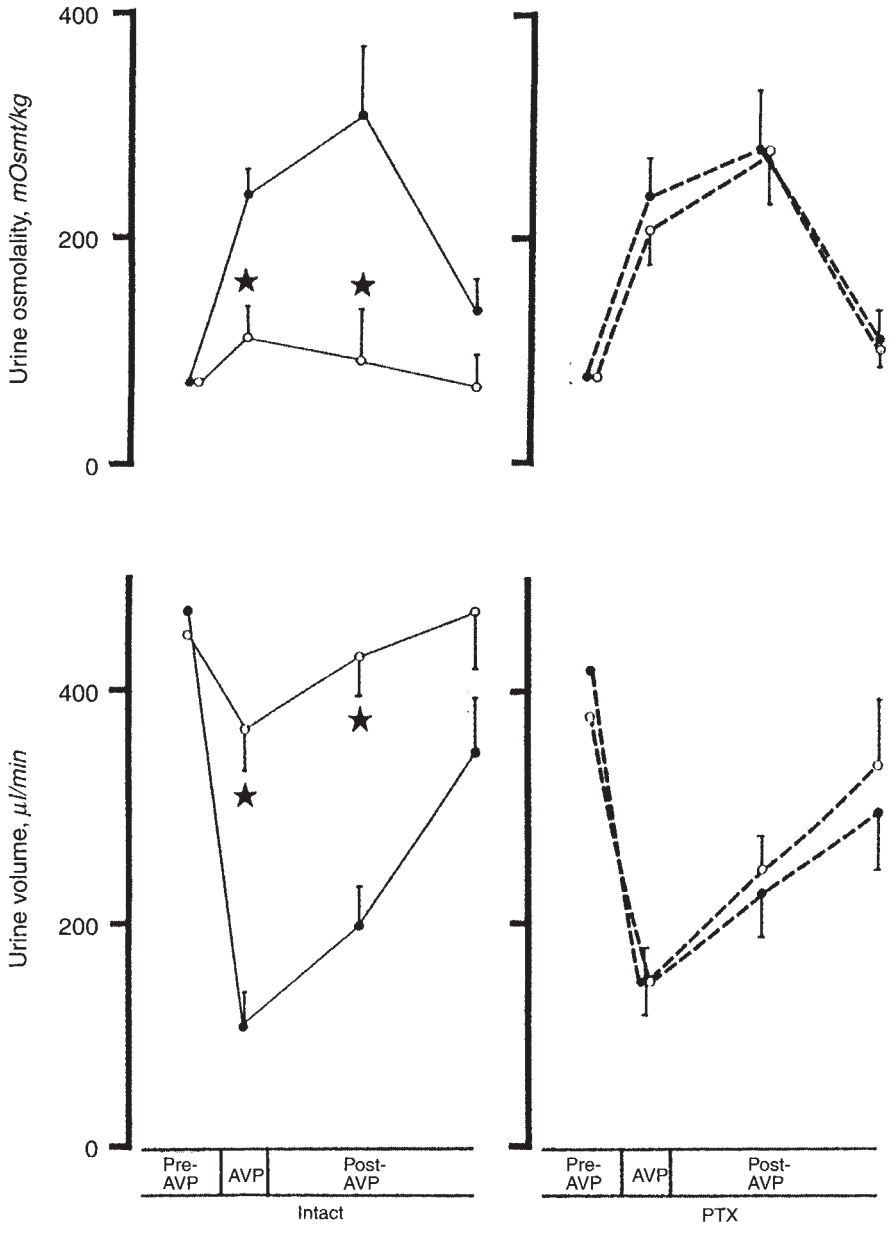

Fig. 1. *Changes in urine osmolality (upper panel) and urine volume (lower panel) with time in control (●) and Li-treated (○) intact and PTX anesthetized rats using the minimal AVP concentration (10 mU/kg body wt over 5 min).* Each point denotes mean ± SEM of between 9 and 18 samples. *Denotes value significantly ($P < 0.01$) different from control (t-test).

this can be overcome with modest concentrations of AVP in the *in vivo* situation.

A recent study has demonstrated that Li-treatment down regulates aquaporin-2 water channel expression in rat renal medulla [41]. While such an observation appears to support the notion that Li does directly alter tubule water transport, an alternative explanation also fits many of the experimental observations. Since Li-treatment produces a central form of polydipsia and is therefore responsible for at least part of the 670% increase in urine output measured in these rats, a fall in circulating AVP would be expected, although this was not measured. Such a reduction would be a powerful stimulus for reduced aquaporin expression. If Li toxicity was the stimulus for a fall in aquaporin expression, why would concomitant thirsting markedly increase aquaporin expression? Again, this may have been due to an increase in circulating AVP. Certainly the plasma osmolality was significantly higher in rats treated with Li for 34 days with thirsting for two days compared with animals not thirsted but treated for 35 days with Li (397 ± 8 compared with 314 ± 5 mOsm/kg H_2O). Concomitant dDAVP also produced a partial response and supports our results.

In summary, these studies suggest that Li-treatment does produce a modest form of NDI and that this defect is at least in part due to a state of hyperparathyroidism whereby excessive circulating levels of PTH act as a partial agonist to the hydroosmotic action of AVP. This inhibitory effect is easily overcome by higher but physiological doses of AVP. While the clinical situation of patients with marked polyuria might suggest that the defect in

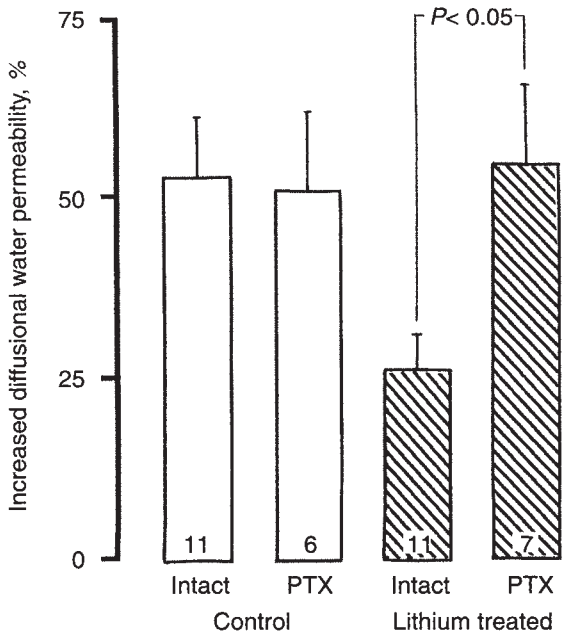

Fig. 2. *Percentage increase in diffusional water permeability with AVP (200 μU/ml) in isolated rat papillary collecting duct.* Medium composed of plasma from control (□) or Li-treated (▨) intact or PTX rats. Each bar denotes mean ± SEM of total number of samples, denoted at the bottom of the bars.

water metabolism during Li-treatment is more severe than suggested by the above results, there is good evidence that Li-treatment increases water intake in rats with hereditary diabetes insipidus presumably by some central effect [42, 43]. This could be the main cause of the observed polyuria. For example, an evaluation of patients with chronic psychiatric illness and water intoxication not taking Li concluded that this common problem was associated with unexplained defects in urine dilution, osmoregulation of water intake as well as the secretion of AVP [44]. Also, it would be predicted that the administration of AVP to a water diuretic subject would produce a suboptimal response due to a reduction in the papillary solute gradient [45]. Thus excessive water drinking combined with mild hyperparathyroidism would appear to be the major basis for the NDI defect induced by Li-treatment in rats and probably humans. While acute and long-term Li-treatment has been demonstrated to impair the hydroosmotic response to AVP in rabbit cortical collecting tubules [46, 47], species differences may be important here since with chronic Li administration, polyuria does not occur in the rabbit and defects in urine concentration are not detected [47]. Differential effects of Li on sodium channels in the cortical collecting tubule may be another confounding variable when the cortical tubule is compared to the papillary collecting duct. While these experiments did not detect a direct effect of Li on water transport, it is possible that such an effect does occur but was too small to be detected.

Acknowledgment

Professor S. Posen, Royal North Shore Hospital, Sydney kindly performed PTH measurements for this study.

Reprint requests to Dr. Shane L. Carney, Department of Medicine, John Hunter Hospital, Locked Bag #1, Hunter Region Mail Centre 2310, New South Wales, Australia.

References

1. GODINICH MJ, BATLLE DC: Renal tubular effects of lithium. *Kidney Int* 37(Suppl 28):S52–S57, 1990
2. CARNEY S, RAYSON B, MORGAN T: The effect of lithium on the permeability response induced in the collecting duct by antidiuretic hormone. *Pflügers Arch* 366:19–23, 1976
3. FORREST JNJ, COHEN AD, TORRETTI J, HIMMELHOCH M, EPSTEIN FH: On the mechanism of lithium-induced diabetes insipidus in man and the rat. *J Clin Invest* 53:1115–1123, 1974
4. CHRISTENSEN S, KUSANO E, YUSUFI ANK, MURAYAMA N, DOUSA TP: Pathogenesis of nephrogenic diabetes insipidus due to chronic administration of lithium in rats. *J Clin Invest* 75:1869–1879, 1985
5. BENTLEY PJ, WASSERMAN A: The effects of lithium on the permeability of an epithelial membrane, the toad urinary bladder. *Biochim Biophys Acta* 266:285–292, 1972
6. SINGER IM, ROTENBERG D, PUSCHETT JB: Lithium-induced nephrogenic diabetes insipidus: In vivo and in vitro studies. *J Clin Invest* 51:1081–1091, 1972
7. HARRIS CA, JENNER FA: Some aspects of the action of antidiuretic hormone by lithium in the rat kidney and bladder of the toad Bufo marinus. *Brit Pharmacol* 44:223–232, 1972
8. FERNANDEZ-RIPOLLET E, LEFURGEY A, HARDY MA, TISHER CC: Structural and functional response of toad urinary bladder to LiCl. *Kidney Int* 24:719–730, 1983
9. CARNEY SL, WONG NLM, DIRKS JH: Effect of lithium treatment on rat renal tubule function: Evidence against impaired antidiuretic hormone action. *Nephron* 25:293–298, 1980
10. HECHT B, KASHGARIAN M, FORREST JN JR, HAYSLETT P: Micropuncture study on the effects of lithium on proximal and distal tubule function in rat kidney. *Pflügers Arch* 377:69–74, 1978
11. ANGRIST BM, GERSHON S, LEVITAN SJ, BLUMBERG AC: Lithium induced diabetes insipidus-like syndrome. *Comp Psych* 11:141–146, 1970
12. SOLOMON S: Action of alkali metals on papillary-cortical Na gradient of dog kidney. *Proc Soc Exp Biol Med* 125:1183–1186, 1967
13. JENNER FA, MACNEIL S: The effects of lithium ions on the antidiuretic action of vasopressin in the rat. *Brit J Pharmacol* 55:527–534, 1975
14. MYERS JB, MORGAN TO, CARNEY SL, RAY C: Effects of lithium on the kidney. *Kidney Int* 18:601–608, 1980
15. RAY C, MORGAN T, CARNEY S: The mechanism of polyuria in rats pretreated with lithium: Studies by in vitro microperfusion. *Clin Exp Pharmacol Physiol* 10:153–160, 1983
16. CHRISTIANSEN C, BAASTRUP PC, TRANSBOL I: Lithium-induced primary hyperparathyroidism. *Calcif Tissue Res* 22(Suppl):341–343, 1977
17. MCEACHRON DL, KRIPKE DF, EAVES M, LENHARD L, PAULINAC D, DEFTOS D: The interaction of lithium and time-of-day on calcium, magnesium, parathyroid hormone, and calcitonin in rats. *Psych Res* 7:121–131, 1980
18. SHEN FJ, SHERRARD DJ: Lithium-induced primary hyperparathyroidism: An alteration of the 'setpoint'. *Ann Intern Med* 96:63–65, 1982
19. THOMPSON L, MORGAN T, CARNEY S: Lithium administration and urinary electrolyte excretion in the rat. *Miner Electrol Metab* 10:122–126, 1984
20. CARNEY SL, DIRKS JH: Effect of parathyroid and antidiuretic hormone on water and calcium permeability in the rat collecting duct. *Miner Electrol Metab* 14:142–145, 1988
21. CARNEY SL, GILLIES AHB: Acute effect of parathyroid hormone on urine concentration in the rat. *Clin Sci* 88:197–201, 1995
22. GARDNER KD, VIERLING JM: Solids, water and solutes in papillary region of rat kidney. *Am J Physiol* 217:58–64, 1969
23. MORGAN R, SAKAI F, BERLINER RW: In vitro permeability of medullary collecting ducts to water and urea. *Am J Physiol* 214:574–581, 1968
24. RAYSON BMR, CARNEY S, GARDNER G, MORGAN T: The interrelationships between antidiuretic hormone, adenylcyclase, tissue cyclic

AMP and diffusional water permeability. *Clin Exp Pharmacol Physiol* 1:23–30, 1976
25. GRANTHAM JJ, BURG MB: Effect of vasopressin and cyclic AVP on permeability of isolated collecting tubules. *Am J Physiol* 211:255–259, 1966
26. CHEN PS JR, TORIBARA TG, WARNER H: Microdetermination of phosphorus. *Ann Chem* 28:1756–1758, 1956
27. KLEEREKOPER M, INGHAM JP, MCCARTHY SW, POSEN S: Parathyroid hormone assay in primary hyperparathyroidism: Experience with a radioimmunoassay based on commercially available reagents. *Clin Chem* 20:369–375, 1974
28. WALLENSTEIN S, ZUCKER CL, FLEISS JL: Some statistical methods useful in circulation research. *Circ Res* 47:1–9, 1980
29. ZERBE RL, ROBERTS GL: Osmoregulation of thirst and vasosuppression secretion in human subjects. Effect of various solutes. *Am J Physiol* 244:E607–E614, 1983
30. SHIRLEY DG, ZEARDE T, WALTER SJ: Renal function in normal and potassium depleted rats before and after preparation for micropuncture experimentation. *Pflügers Arch* 416:74–79, 1990
31. CHRISTENSEN S: DDAVP (1-desamino-8-arginine-vasopressin) treatment of lithium-induced polyuria in the rat. *Scand J Clin Lab Invest* 40:151–157, 1980
32. CARNEY S, MORGAN T, RAY C, THOMPSON L: Effect of calcitonin on urine concentration in the rat. *Am J Physiol* 244:F432–F435, 1983
33. DE ROUFFIGNAC C, ELALOUF JM: Effects of calcitonin on the renal concentrating mechanism. *Am J Physiol* 245:F506–F511, 1983
34. GOLDFARB S, AGUS ZS: Mechanism of the polyuria of hypercalcemia. *Am J Nephrol* 4:69–76, 1984
35. CARNEY S, RAYSON B, MORGAN T: A study in vitro of the concentrating defect associated with hyperkalemia and hypercalcemia. *Pflügers Arch* 366:11–17, 1976
36. GREENGARD P: Phosphorylated proteins as physiological effectors: Protein phosphorylation may be a final common pathway for many biological regulatory agents. *Science* 199:146–152, 1978
37. COLE AJ, EBER SL, POELLING RE, THORNE PK, FORTE LR: A dual mechanism for regulation of kidney phosphate transport by parathyroid hormone. *Am J Physiol* 253:E221–E227, 1987
38. ANDO Y, TABEI K, FURUYA H, ASANO Y: Glucagon stimulates chloride transport independently of cyclic AMP in the rat medullary TAL. *Kidney Int* 36:760–767, 1989
39. ANGER MS, SHANLEY P, MANSOUR J, BERL T: Effects of lithium on cAMP generation in cultured rat inner medullary collecting tubule cells. *Kidney Int* 37:1211–1218, 1990
40. MARTINEZ-MALDONADA M, STRAVROULAKI-TSAPAR A, TSAPARAS N, SUKI WN, EKNOYAN G: Renal effects of lithium administration in rats: Alterations in water and electrolyte metabolism and the response to vasopressin and cyclic adenosine monophosphate during prolonged administration. *J Lab Clin Med* 86:445–461, 1975
41. MARPLES D, CHRISTENSEN S, CHRISTENSEN EI, OTTOSEN PD, NIELSEN S: Lithium-induced down regulation of aquaporin-2 water channel expression in rat kidney medulla. *J Clin Invest* 95:1838–1845, 1995
42. HOCHMAN S, GUTMAN Y: Lithium: ADH antagonism and ADH independent action in rats with diabetes insipidus. *Eur J Pharmacol* 28:100–107, 1974
43. CARNEY SL, RAY C: Lithium: A cause of dipsogenic diabetes insipidus in the rat. *Lithium* 4:195–198, 1993
44. GOLDMAN MB, LUCHINS DJ, ROBERTSON GL: Mechanisms of altered water metabolism in psychotic patients with polydipsia and hyponatraemia. *N Engl J Med* 318:397–403, 1988
45. JAMISON RL: Counter current systems, in *Kidney and Urinary Tract Physiology, MTP International Review of Science, Physiology Series 1* (vol 6), edited by GUYTON AC, THURAU K, New York, Butterworths, University Park Press, 1974, pp 199–245
46. COGAN E, ABRAMOW M: Inhibition by lithium of the hydroosmotic action of vasopressin in the isolated perfused collecting tubule of the rabbit. *J Clin Invest* 77:1507–1514, 1986
47. COGAN E, NORTIER J, ABRAMOW M: Impaired hydroosmotic response to vasopressin of cortical collecting tubules from lithium-treated rabbits. *Pflügers Arch* 199:695–703, 1990