The Acute Effect of Lithium on Renal Renin and Prostaglandin E Synthesis in the Dog

JOSEPH V. NALLY, GREGORY W. RUTECKI, AND THOMAS F. FERRIS

SUMMARY Acute administration of lithium chloride (Li) to hydropenic anesthetized dogs significantly increased mean arterial pressure (MAP), plasma renin activity (PRA), and urinary prostaglandin E (UPGE) excretion with an increase in urinary volume, osmolar clearance, and sodium excretion. Solute-free water reabsorption increased during Li administration which argues against antagonism to ADH induced by increased PGE synthesis being a factor in the diuresis. The increase in renin secretion during Li administration was not caused by variation in sodium delivery to the macula densa, activation of the adrenergic nervous system, or change in renal resistance. Indomethacin, 5 mg/kg, prevented the rise in PRA and UPGE, abolished the natriuresis and diuresis, but did not prevent hypertension, whereas the angiotensin I-converting enzyme inhibitor, SQ20881, prevented both the rise in MAP and UPGE excretion. The fall in renal blood flow, rather than the inhibition of prostaglandin synthesis following indomethacin administration, probably accounted for the prevention of the natriuresis and diuresis since the converting enzyme inhibitor prevented the increase in UPGE excretion without effect on the natriuresis or diuresis. These studies demonstrate that Li increases renin and PGE synthesis. The increased renin secretion appears to be a direct effect of lithium on the juxtaglomerular apparatus, and the increase in PGE synthesis, which is secondary to angiotensin II generation, is not the cause of the diuresis or natriuresis.

The effect of lithium on renal function has received increasing attention because of its use in the treatment of manic-depressive states. Both a primary polydipsia and a concentrating defect have been described in patients receiving lithium (Forrest et al., 1974; Singer et al., 1972). In animals, a natriuresis and diuresis occur with acute infusion of Li, and in vitro studies using the toad bladder have demonstrated that lithium antagonizes the hydro-osmotic effect of ADH, as well as the aldosterone-induced increase in sodium transport (Singer and Franko, 1973; Cox and Singer, 1978). Since PGE2 is known to antagonize the hydro-osmotic effect of ADH in the isolated collecting tubule (Grantham and Orloff, 1968) and to cause a natriuresis when infused into the renal artery (Vander, 1968), we determined the acute effects of lithium chloride on urinary prostaglandin E (UPGE) excretion and renal function in the hydropenic dog. The results indicate that lithium significantly increases renal renin and PGE synthesis, but the accompanying diuresis and natriuresis are not caused by the increased PGE synthesis.

Methods

Mongrel female dogs weighing between 15 and 25 kg were deprived of food and water for 18 hours and given 5 U of pitressin tannate in oil, 24 hours before and immediately prior to the experiment. Pentobarbital, 30 mg/kg, was used for anesthesia with additional doses given for maintenance of anesthesia during the experiment. An endotracheal tube was inserted, and the dogs were ventilated with a Harvard respirator (Harvard Apparatus Co.). Catheters were placed in both ureters via a suprapubic incision and a Goodale-Lubin catheter was placed via the left femoral artery into the left ventricle for injection of radioactive microspheres labeled with either 85Sr, 141Ce, or 51Cr (3M Co.). The left renal vein was cannulated via the left femoral vein. Another catheter was inserted in the right femoral artery for pressure monitoring and blood sampling. Mean arterial blood pressure (MAP) was measured by a Statham strain gauge connected to a Hewlett-Packard polygraph. In experiments in which intra-renal infusions were carried out (group II), a 23-gauge needle was inserted into the left renal artery, and a contralateral nephrectomy was performed. A mean of three 10-minute urine collections was obtained for all control and experimental periods.
Experiments

**Group I (n = 6)—Acute Lithium Infusion**

Lithium chloride (1 m) was infused at a rate of 1 ml/min for 15 minutes prior to and during the 30-minute experimental period. MAP was recorded continuously, and collections for urine volume, GFR, urine sodium excretion, and osmolality were obtained during the control and experimental periods.

In another series of six hydropenic dogs, osmolar clearance was increased with a saline infusion, and solute-free water reabsorption (TcH2O) was compared with animals given Li.

**Group II—Studies of Renin Secretion**

(1) Ureteral obstruction—Li was infused as in group I, but both ureters were ligated 1 hour prior to the control period.

(2) Papaverine, 3 mg/min, was infused into the renal artery 5 minutes prior to and during the Li infusion.

(3) Propranolol (d-Inderal, Ayerst), 2.2 µg/kg per min, was infused into the renal artery 30 minutes before and during the Li infusion.

(4) Phenoxycbenzamine (Smith, Kline & French), 10 µg/kg per min, into the renal artery was begun 90 minutes before and maintained during Li infusion.

(5) Renal denervation—Li was infused after dissecting and applying 10% phenol in alcohol to the renal artery.

**Group III—Effect of Prostaglandin Inhibition**

Indomethacin, 5 mg/kg, was given iv 45 minutes prior to beginning Li infusion.

**Group IV—Effect of Angiotensin I Blockage**

The angiotensin I-converting enzyme inhibitor (SQ20881, Squibb), 2 mg/kg, was given iv 30 minutes prior to Li infusion.

Plasma renin activity (PRA) was measured by the method of Haber et al. (1969) after incubation for 3 hours at pH 5.5. Urinary PGE was determined by modification of an immunoassay previously described for plasma (Venuto et al., 1975). One milliliter of urine was collected and stored at -6°C until time for assay. The sample was thawed and adjusted to pH 3 with 1 m citric acid. 3H-PGE2 (1000 counts/min) was added to the sample to measure recovery rates. The sample was extracted with 10 ml of ethyl acetate, and the remainder of the assay was similar to that reported for plasma (Rector et al., 1972). Recovery of 3H-PGE2 in the experiments reported in this paper was 84 ± 0.9% SEM. Plasma aldosterone was measured by an immunoassay method previously described from this laboratory (Ferris et al., 1973). Iothalamate [125I] (Glofil, Abbott Lab.) in saline was infused at 1 ml/min for measurement of glomerular filtration rate (GFR).

Total renal blood flow and fractional cortical blood flow distribution were determined by the radioactive microsphere method (Rector et al., 1972). Osmolar and free water clearance were calculated in the usual manner. Data is reported as mean ± standard error, and the Wilcoxon rank test was used for statistical analysis of the paired results.

**Results**

Infusion of Li resulted in a mean plasma Li+ concentration of 8.4 ± 0.9 mEq/liter with no significant change in Na+, K+, Cl-, or CO2 concentration. Table 1 demonstrates that during Li infusion urinary volume increased from 0.25 ± 0.03 to 1.8 ± 0.03 ml/min (P < 0.01), osmolar clearance from 1.2 ± 0.1 to 3.5 ± 0.5 ml/min (P < 0.01), and 125I-infusion increased from 1562 ± 148 to 653 ± 35 mOsm/kg per H2O (P < 0.01), but TcH2O increased from 0.88 ± 0.09 to 1.6 ± 1.5 ml/min (P < 0.01). The increase in osmolar clearance was due primarily to an increase in urinary sodium from 39 ± 10 to 139 ± 26 µEq/min (P < 0.01). There was no change in renal blood flow, GFR, or cortical blood flow distribution during Li infusion. Distribution of cortical blood flow before and during Li infusion was: zone I, 45.6 ± 0.5% vs. 43 ± 0.8% (NS); zone II, 33.9 ± 0.8% vs. 34.4 ± 1.3% (NS); zone III, 14.7 ± 0.9% vs. 16.4 ± 0.87% (NS); zone IV, 5.7 ± 1.4% vs. 6.2 ± 1.7% (NS).

To examine whether TcH2O relative to osmolar clearance was decreased during Li infusion, a similar increase in osmolar clearance was induced by saline in six anesthetized hydropenic animals (Fig. 1). At equal osmolar clearance, we could detect no difference in TcH2O relative to GFR in dogs given Li or saline.

Figure 2 shows the effect of Li on MAP, PRA, and UPGE excretion. MAP increased from 143 ± 5 to 154 ± 4 mm Hg (P < 0.05), PRA from 4.5 ± 1.4 to 11 ± 2.7 ng/ml per hour (P < 0.01), and UPGE from 14 ± 0.04 to 7.3 ± 1 ng/min (P < 0.01). To investigate possible mechanisms by which Li increased renin secretion, experiments were conducted after bilateral ureteral obstruction, following administration of α- or β-adrenergic blocking agents and papaverine, and after renal denervation (Fig. 3). After bilateral ureteral obstruction, when variation in sodium delivery to the macula densa was prevented, PRA increased from 10 ± 1 to 44 ± 4.4 ng/ml per hour (P < 0.01). After propranolol, Li infusion increased PRA from 9.1 ± 1.1 to 21 ± 2.3 ng/ml per hour (P < 0.05), papaverine from 6.3 ± 0.09 to 24 ± 5.3 ng/ml per hour (P < 0.05), and phenoxycbenzamine from 5.8 ± 0.05 to 22 ± 4.1 (P < 0.02). In six dogs after renal denervation, Li infusion increased PRA from 2.7 to 13.7 ± 2 ng/ml per hour (P < 0.02).
RENIN AND PGE SYNTHESIS WITH LITHIUM/Nally et al.

The Effect of Lithium on Renal Function

Table 1

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Acute lithium administration

- **Dog 1**, 2, 3, 4, 5, 6: MAP increased from 143 ± 5 to 154 ± 4 mm Hg (P < 0.05) when Li was administered after pretreatment with indomethacin. Indomethacin

- **Uosm** excretion. Urine volume was increased from 0.28 ± 0.04 ml/min to 1.32 ± 0.12 ml/min (P < 0.01), but **U_PGE** excretion was 1.17 ± 0.22 ng/min before and 1.27 ± 0.12 ng/hour (NS) after saline.

To determine the possible role of increased renal prostaglandin synthesis in the renin secretion, indomethacin was administered to dogs prior to Li infusion (Table 1). In this group, although MAP increased from 143 ± 5 to 154 ± 4 mm Hg (P < 0.025), there was no diuresis or natriuresis. Mean PRA did not change, 8 ± 2.7 vs. 5.3 ± 16 ng/ml per hour (NS), and **U_PGE** fell from 4.8 ± 1 to 1.4 ± 0.7 ng/min (P < 0.05) when Li was administered after pretreatment with indomethacin.

![Figure 1](http://circres.ahajournals.org/lookup/doi/10.1161/01.RES.741.11.1039#fig1)  
**Figure 1** TcH2O relative to osmolar clearance in six dogs treated with Li (filled circles) compared to six dogs given intravenous saline in sufficient amount to cause equal change in osmolar clearance (unfilled circle).

![Figure 2](http://circres.ahajournals.org/lookup/doi/10.1161/01.RES.741.11.1039#fig2)  
**Figure 2** The change in MAP, PRA, and **U_PGE** excretion before control (C) and 30 minutes after beginning intravenous LiCl.
caused a decrease in renal blood flow from 467 ± 34 to 343 ± 25 ml/min (P < 0.01) with no significant change in GFR, 56 ± 7 to 61 ± 9 ml/min (NS), filtration fraction increasing from 0.12 ± 0.01 to 0.19 ± 0.03% (P < 0.05).

To determine whether the rise in MAP and increase in UPGE was due to the increase in renin and angiotensin, the A II-converting enzyme inhibitor, SQ20881, was given prior to Li infusion (Fig. 4). In six animals pretreated with the converting enzyme inhibitor, MAP did not increase, 126 ± 6.5 before and 119 ± 5.5 mm Hg after Li, and although UPGE increased slightly from 2.1 ± 0.38 to 3.33 ± 0.5 ng/min, the difference was not statistically significant (P < 0.1). Urine volume increased from 0.19 ± 0.03 to 1.40 ± 0.13 ml/min (P < 0.001) with Li infusion after administration of the converting enzyme inhibitor.

Discussion

Polydipsia and polyuria occur in a significant number of patients taking lithium. Of 96 patients treated in one outpatient clinic, 40% reported polydipsia, and 12% had polyuria greater than 3 liters/day (Forrest et al., 1974). Acute infusions of lithium chloride have been demonstrated to cause polyuria in the dog and rat with an increase in cation excretion (Foulks et al., 1952), but the nephron site where the decreased sodium and water absorption occurs is not clear. In rats with congenital diabetes insipidus, an increase in urinary volume and CH₂O occurred with lithium, suggesting greater delivery of filtrate to the diluting segment, and the increase in urinary phosphate and urate also suggested a decrease in proximal tubular sodium reabsorption (Martínez-Maldonado et al., 1975). However, in normal rats undergoing a water diuresis, CH₂O decreases during lithium administration, suggesting interference with sodium chloride transport in the ascending limb of the loop of Henle (Martínez-Maldonado and Opava-Stitzer, 1977). In man, Li does not interfere with the ability to excrete CH₂O but causes decreased TcH₂O, a finding which also has been found in the monkey (Webb et al., 1975).

Since prostaglandin E₁ and E₂ cause a natriuresis and diuresis when infused systemically or into the renal artery, we carried out these studies to determine if lithium increased UPGE synthesis. The potential mechanism of a diuresis induced by an increase in renal PGE synthesis may involve: (1) decreased reabsorption of sodium in the proximal tubule because of renal vasodilation with change in the postglomerular capillary Starling forces, (2) a possible direct effect of PGE₂ to decrease sodium transport in the collecting tubule (Stokes and Kokko, 1977), (3) antagonism to the hydro-osmotic effect of ADH on the collecting tubule (Grantham and Orloff, 1968), (4) a decrease in medullary tonicity by an increase in medullary blood flow (Solez et al., 1974). We found a striking and consistent increase in UPGE excretion in every dog during lithium infusion which was accompanied by an increase in arterial blood pressure and rise in renin secretion. These findings have not been noted previously. Since indomethacin prevented the natriuresis and diuresis, an attractive hypothesis was that the increase in renal prostaglandin E synthesis was the

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cause of the diuresis and natriuresis. However, indomethacin caused a decrease in renal blood flow with increase in filtration fraction, a hemodynamic change that would increase proximal tubular sodium absorption. When lithium was given after administration of the angiotensin I-converting enzyme inhibitor, SQ20881, a diuresis and natriuresis occurred without significant increase in renal PGE synthesis. Thus, the rise is plasma angiotensin II, induced by renin secretion, was the cause of the increased PGE synthesis rather than Li⁺ per se. Angiotensin is known to increase renal PGE synthesis when infused into the renal artery, and a contralateral increase in renal PGE synthesis occurs after renal artery stenosis (Galvez et al., 1977). The fact that the converting enzyme inhibitor also prevented the rise in arterial blood pressure makes a Li-induced increase in renin secretion with secondary increase in PGE synthesis more likely than Li causing a primary increase in PGE synthesis.

In the rat, an elevation of PRA has been reported after lithium administration, which was thought to be due to the natriuresis since it was prevented by a high sodium intake (Gutman et al., 1973). However, in the isolated rat kidney, a direct effect of lithium on renin secretion has been demonstrated with renin concentration increasing in the renal venous effluent (Gutman et al., 1973). In patients taking lithium, a natriuresis has been documented followed by an increase in aldosterone secretion (Murphy et al., 1969), but after 10 days of lithium administration, the sodium retained was 2-3 times that of the initial natriuresis. In a recent series of seven patients, no change in renin or aldosterone secretion was noted after 6-8 weeks of lithium therapy (Miller et al., 1979). Hypertension has not been reported to occur in patients taking lithium chronically.

The rise in renin secretion seems to be a direct effect of lithium on the juxtaglomerular apparatus since it was not prevented by several maneuvers which are known to effect renin secretion. Thus, renal denervation, ureteral obstruction, α- and β-adrenergic blockade, and papaverine failed to prevent the Li-induced increase in renin secretion. Indomethacin, however, completely prevented the rise in renin secretion with Li. Indomethacin, as well as other structurally dissimilar prostaglandin inhibitors, lowers basal values of PRA and blunts the stimulation of renin secretion after hemorrhage (Romero et al., 1976). Sodium arachidonate infused into the renal artery stimulates renal prostaglandin synthesis, and this probably is independent of change in renal hemodynamics (Larsson et al., 1974), since Weber et al. have demonstrated a direct effect of prostaglandin synthesis on renal secretion (Weber et al., 1976). Using rabbit cortical cells, they found PGE₂ in concentrations from 10⁻¹² to 10⁻⁶ M had no effect on renin release, whereas the prostaglandin endoperoxide PGG₂ and two synthetic endoperoxide analogues increased renin release by as much as 60%. Thus, renin release may be dependent on a prostaglandin other than PGE₂; PGI₆, synthesized in microsomal fractions of blood vessel walls, seems a likely candidate. Whether lithium increases synthesis of prostaglandins other than PGE is not known, but measurement of 6-keto-PGF₁α, the major metabolite of PGI₆, would be of interest.

It is possible that the effect of Li in causing the diuresis was by an increase in medullary blood flow with indomethacin preventing the diuresis through a decrease in medullary blood flow. Prostaglandin inhibition has been shown to decrease and PGE₂ to increase inner cortical blood flow (Solez et al., 1974; Kirschenbaum et al., 1974). Our failure to demonstrate a redistribution of cortical blood flow to inner cortex during lithium administration does not exclude an effect of lithium on papillary blood flow. Few juxtamedullary glomeruli have postglomerular vascular loops which extend into the deep papillae, and inner cortical flow measured by radioactive microspheres is approximately 10% of renal blood flow, a figure higher than medullary flow. A decrease in medullary solute concentration has been reported by Solomon during lithium administration, but the decrease was no greater than a similar diuresis induced by saline or mannitol (Solomon, 1967). In contrast, Forrest et al. found no change in medullary solute concentration in rats given lithium in spite of a daily urine output equal to approximately 50% of body weight (Forrest et al., 1974).

If Li increases medullary blood flow, the failure to demonstrate a decrease in TC₅H₂O in spite of increased PGE synthesis might be explained. PGE₂ is known to antagonize the hydro-osmotic effect of ADH on the collecting tubules which, under most circumstances, would decrease TC₅H₂O. However, if lithium also increases medullary blood flow with reduction in medullary solute concentration, TC₅H₂O could increase or remain the same under circumstances of a high solute load, independent of ADH antagonism. Such an effect has been described in both the rat following experimental papillectomy and in patients with sickle cell nephropathy who have microthrombi in the medullary circulation, where a decrease in maximum urinary concentration is associated with normal TC₅H₂O during solute loading (Lief et al., 1969; Hatch et al., 1967). The antagonistic effect of PGE on the hydro-osmotic effect of ADH in the collecting tubules of the medulla would be impossible to demonstrate if medullary solute concentration did not remain constant, particularly if the effect of PGE on ADH sensitivity is primarily in the medullary collecting tubules.

Li might also cause a natriuresis and diuresis by increasing perfusion in deep cortical nephrons. Deep nephrons are known to have higher filtration and deliver a larger percentage of filtered sodium to the collecting tubules than superficial cortical nephrons (Stein et al., 1976). Since both the renal medulla and cortex synthesize prostaglandins, but
the cortex has greater dehydrogenase activity, increasing renal PGE synthesis may have a greater effect in the renal medulla. The prevention of the natriuresis and diuresis with indomethacin might be due to prevention of a Li-induced increase in perfusion in total renal blood flow. The natriuresis during the acute infusion of lithium was not caused by the hypertension, since it was prevented by indomethacin in spite of an increase in arterial blood pressure and occurred after administration of the converting enzyme inhibitor when MAP did not rise.

These studies bring up the question whether the effect of lithium on prostaglandin synthesis has relevance in its effects on the central nervous system. The increase in thirst seen in patients taking lithium is a central nervous system response, and angiotensin also stimulates thirst (Fitzsimons, 1976). Since the brain is capable of synthesis of both renin and prostaglandins, it is intriguing to speculate whether Li increases central nervous system synthesis of renin and PGE. Obviously, our studies do not bear on this point, but suggest questions about the effect of Li on these biologically important fatty acids in organs other than the kidney.

References


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