Influence of Repeated Administration of Lithium on Urinary Excretion of Prostaglandins in Rats

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ABSTRACT — The present study was undertaken to examine whether urinary excretions of prostaglandins increase by repeated administration of a non-toxic dose of lithium. Our previous study demonstrated that 2 mEq/kg/day of lithium chloride (LiCl) is not a toxic dose; and therefore, this dose of LiCl in 1 ml vehicle (5% glucose solution) or 1 ml of vehicle alone was injected intraperitoneally for 7 days into Wistar rats. On day 7, 3% body weight of 1% NaCl solution was given orally; and urine for the determination of PGE2 and 6-keto-PGF1α, a metabolite of PGI2, was collected for 6 hr after dosage. Thereafter, blood samples for measuring plasma renin activity (PRA) were obtained. The urinary amounts of PGE2 and 6-keto-PGF1α in the Li-treated rats were significantly greater than those in the control animals. The values of PRA did not significantly differ between the two groups of rats. These findings indicate that the production of prostaglandins, including those of PGE2 and PGI2, are enhanced during repeated administration of a non-toxic dose of lithium. The enhanced production of prostaglandins might not be mediated through the activated renin-angiotensin system.

It is well-known that several endocrine functions are altered during repeated administration of lithium (1). Lithium is a potent pharmacologic agent with a relatively narrow therapeutic dosage range. For this reason, it is important to avoid lithium toxicity since metabolic changes secondary to the weight loss and other sequelae may interfere with the biochemical parameters under observation. Kierkegaard-Hansen reported that plasma renin activity (PRA) does not change in lithium-fed rats who had no signs of intoxication, while PRA increases remarkably in rats with intoxication (2). We also examined the influences of lithium chloride (LiCl) on PRA in rats (3). This study showed that PRA increases significantly by the treatment with 3 mEq/kg/day, but not 2 mEq/kg/day of LiCl for 7 days. These data indicate that 2 mEq/kg/day of LiCl is a nontoxic dose.

Sugawara et al. reported increased urinary prostaglandin E2 (PGE2) excretion during repeated administration of LiCl at 4 mEq/kg/day, intraperitoneally (i.p.) in rats (4). They speculated that the elevated vasopressin enhances renal PGE2 production. However, 4 mEq/kg/day of LiCl, i.p. is considered to be toxic since blood pressure is significantly decreased, and the increment of body weight is significantly blunted in rats treated with this dose of the agent (5). Because angiotensin II stimulates renal PGE2 production (6, 7), it remains possible that the increased urinary PGE2 excretion is mediated through the action...
of the enhanced renin-angiotensin system in their study. Therefore, it is interesting to examine whether the urinary excretion of PGE$_2$ might increase by the repeated administration of lithium without an elevation of PRA.

In the present study, 2 mEq/kg/day of LiCl was injected i.p. for 7 days to rats. Urinary excretion of PGE$_2$ in rats with lithium was compared to that in animals without the agent on day 7. Urinary excretion of 6-keto-PGF$_{1\alpha}$, a metabolite of PGF$_2\alpha$, also was measured to examine whether the influence of lithium on urinary PG, as it exists, is specific to PGE$_2$.

MATERIALS AND METHODS

Male Wistar rats (Charles River Laboratory, Kanagawa, Japan) (10–11 weeks old, 300–350 g) were maintained for more than 2 weeks under conditions of light from 7 a.m. to 7 p.m. and dark from 7 p.m. to 7 a.m. with free access to food and water.

The rats were divided into two groups of twelve each. One milliliter of 5% glucose vehicle or 2 mEq/kg/day of LiCl in 1 ml vehicle was injected i.p., once daily for 7 days (day 1 to day 7). Soon after the administration of LiCl solution or its vehicle alone on day 7, 3% body weight (b.w.) of 1% NaCl solution was given orally to each group of rats, and urine was collected for 6 hr after dosage. Blood samples for PRA and plasma lithium were obtained 24 hr after the final dosage of lithium.

Urinary sodium concentration and plasma lithium concentration were determined by a flame photometer (775-A, Hitachi, Tokyo, Japan). PRA (8) and urinary concentrations of PGE$_2$ (9) and 6-keto-PGF$_{1\alpha}$ (10) were measured by radioimmunoassay.

The results are expressed as means ± S.E. Data are analyzed by analysis of variance and Student’s t-test as appropriate.

RESULTS

Urine volume and urinary excretions of sodium, PGE$_2$ and 6-keto-PGF$_{1\alpha}$ were significantly greater in the Li-treated animals than in the control animals after oral administration of 3% b.w. of 1% NaCl solution (Fig. 1). There
were no significant differences between the two groups in body weight or PRA (Table 1). The value of plasma lithium concentration was 0.58 ± 0.11 mEq/l.

Table 1. Body weight, plasma renin activity (PRA) and plasma lithium (Li) concentration in the control (n = 12) and Li-treated (n = 12) rats

| Parameter  | Group      | day | control     | Li-treated |
|------------|------------|-----|-------------|------------|
| Body weight | 1          | 330 ± 7 | 334 ± 9     |
|            | 7          | 345 ± 8 | 349 ± 9     |
| PRA ng/ml/hr | 8          | 3.5 ± 0.6 | 3.7 ± 0.4   |
| Plasma Li mEq/l | 8          | ND        | 0.58 ± 0.11 |

LiCl solution (Li 2 mEq/kg/day) was injected intraperitoneally to rats once daily for 7 days (day 1 to day 7). Blood samples were obtained 24 hr after the final dosage of LiCl. Mean ± S.E., ND = not determined.

DISCUSSION

A non-toxic dose of lithium must be employed when its effects on endocrine functions are examined. The present as well as previous (3) studies showed that body weight does not decrease by the repeated administration of LiCl at 2 mEq/kg/day for 7 days. This finding is compatible with the observation of Das and Bhargava (5) who used a similar dosage of LiCl in rats. On the contrary, the body weight decreased by treatment with 3 mEq/kg/day of LiCl (3). These findings suggest that 2 mEq/kg/day of LiCl is not a toxic dose. Kierkegaard-Hansen (2) reported that PRA does not change in lithium-fed rats who had no signs of intoxication (mean serum Li = 0.44 mEq/l), while PRA increased remarkably in rats with intoxication (mean serum Li = 1.29 mEq/l). The higher PRA during intoxication might be induced by sodium depletion (11, 12). In the present study, the PRA of rats treated with 2 mEq/kg/day of LiCl did not change significantly, and their trough concentration of plasma lithium was 0.58 ± 0.11 mEq/l. On the other hand, the PRA remarkably increased in rats treated with 3 mEq/kg/day of LiCl and with a trough plasma lithium of 1.36 ± 0.23 mEq/l (3). These data provide additional evidence suggesting that lithium intoxication is not induced by 2 mEq/kg/day of LiCl. In the present study, 3% b.w. of 1% NaCl solution was given orally to each group of rats on day 7. Because even a large amount of water intake is eliminated within 30–40 min in the urine (13), it is unlikely that a volume expansion suppressed PRA levels on day 8. However, the possibility that NaCl given on day 7 influenced the values of this parameter can not be ruled out.

The present study demonstrated that the urinary excretion of PGE2 following oral administration of NaCl solution is enhanced in rats treated with 2 mEq/kg/day of LiCl. Since the PRA values in the Li-treated group were not higher than those in the control group, the increased production of PGE2 might not be mediated through the angiotensin II-related mechanism. The present study also showed that the urinary excretion of 6-keto-PGF1a is greater in the Li-treated animals. Based on these findings, it is assumed that PGs production including PGE2 and PGI2, as reflected in urinary 6-keto-PGF1a, are enhanced during the repeated administration of lithium.

The increased amount of urinary PGs in rats treated with lithium might be accounted for by one or more of the following possible mechanisms: 1) Chronic lithium treatment increases plasma vasopressin concentration (4, 14) which, in turn, not only stimulates PGs production (15, 16), but increases urine volume (17). 2) Formation of c-AMP, which is known to inhibit PGs production (18), is reduced by lithium (19, 20). 3) Urinary PGs excretion increases as the urine flow increases during treatment with lithium (21). 4) Lithium therapy exerts a modulatory effect on α-adrenoceptor sensitivity (22) which in turn stimulates PGs synthesis (23). The present study is unable to rule out any of these possibilities,
and further studies involving pretreatment with vasopressin or α-receptor antagonist are needed to evaluate them.

Diuresis following NaCl solution which is caused by a multifactorial mechanism involving renal and hormonal factors (24–26) was greater in the Li-treated rats than in the control animals. Lithium per se induces a diuresis by several mechanisms (17, 27, 28): 1) inhibition of the hydro-osmotic response of vasopressin in the collecting duct, 2) increased output of tubular fluid from the proximal tubules, 3) lowering of the cortico-medullary osmotic gradient, 4) impaired response of aldosterone to endogenous stimuli and 5) diuretic action of vasopressin. These mechanisms might contribute to the enhanced diuresis observed in the Li-treated rats.

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