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Lithium treatment reduces the renal kallikrein excretion rate

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Lithium treatment reduces the renal kallikrein excretion rate. Lithium salts are widely used agents for the prophylactic treatment of affective disorders. Lithium salts may be associated with distal nephron dysfunction. Kallikrein is a protease which is generated by the distal nephron. We used an amidolytic assay of chromatographically purified enzyme to determine the urinary excretion rate of active kallikrein in relation to lithium treatment. All plasma lithium concentrations were within the therapeutic range (0.4 to 0.9 mmol/liter). In 15 patients the urinary excretion rate of active kallikrein was 267.4 ± 65.6 mU/24 hrs before lithium treatment, and fell to 117.8 ± 39.6 mU/24 hrs ($P < 0.05$) on day 14 of lithium treatment. This reduction was associated with a decrease of immunoreactive kallikrein in the same urines by 66%. In another 15 patients who had undergone lithium therapy for an average period of 5.6 years, the urinary excretion rate of active kallikrein was 86.1 ± 14.5 mU/24 hrs, while 21 age-matched healthy controls had an excretion rate of 364.1 ± 58.4 mU/24 hrs ($P < 0.05$). Measurements of immunoreactive kallikrein in the same urine samples demonstrated a reduction of kallikrein after long-term lithium treatment by 78%. These observations could not be attributed to changes in creatinine clearance, renal sodium or potassium excretion rates or plasma concentrations of aldosterone and vasopressin. Addition of lithium to the urine in vitro had no demonstrable effect on kallikrein measurement by amidolytic assay. We conclude that lithium in therapeutic plasma concentrations may directly suppress the secretion of kallikrein by renal connecting tubule cells.

The effectiveness of lithium as a prophylactic treatment of affective disorders is well established [1]. The large number of patients afflicted and the necessity to prescribe lithium treatment over prolonged periods—often involving many years [1, 2]—has raised concern about potential side-effects of this medication [3]. In the kidney adverse effects may occur at therapeutic plasma levels of lithium. They include nephrogenic diabetes insipidus [4], defective distal tubular acidification [5] and others [3]. In addition, renal morphological changes have been observed in distal tubular, connecting tubular and collecting duct epithelia [6–12]. Taken together, these observations indicate a preferential involvement of the distal nephron in those adverse effects.

Kallikrein is an enzyme which may generate kinins [13]. In the kidney kallikrein is produced and released by connecting tubular epithelial cells of the distal nephron [13–16]. We were intrigued by the close spatial relationship between the site of kallikrein release and the localization of functional and morphological changes observed after lithium in the kidney. We asked the question whether lithium treatment might also affect renal kallikrein.

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Methods

Patients

To test the effects of short-term and long-term lithium treatment the urinary excretion rate of kallikrein was measured in several groups of patients:

a) In 15 patients suffering from a DSM-III affective disorder (manic depressive disorder) [17], who had never received lithium before. They were consecutive admissions to the Department of Psychiatry of the University of Heidelberg. Measurements were obtained just prior to the beginning of lithium therapy and then again on day 14 of such treatment.

b) In 15 randomly-selected patients who had previously received continuous lithium treatment of an affective disorder for at least one year. All of these patients were cared for by the out-patient clinic of the Department of Psychiatry of the University of Heidelberg.

c) Measurements were simultaneously obtained in 21 age-matched healthy volunteers serving as controls. A plasma lithium concentration of 0.4 to 0.9 mmol/liter is considered therapeutic at our institution; patients included in our study did not exceed this range of concentrations. In all instances lithium therapy had been recommended by the psychiatrists in charge of the patient. All patients had given prior consent to the procedures of the study.

Protocol of evaluation

When a patient was entered into the study, we obtained a history, a complete physical examination and a standardized blood sample at rest. We documented the present symptoms, the indications for lithium treatment, the current medication and any historical evidence of recent dehydration. In the physical examination, we searched for signs of dehydration or plasma volume contraction. All blood samples were drawn at about 3 p.m.; patients were not fasting. After placement of a short indwelling catheter into a forearm vein, the patient rested supine for 40 minutes. A 14 cc blood sample was drawn, immediately partitioned into the appropriate iced tubes, placed on ice and rapidly centrifuged at 3°C, at 4,800 × g for 10 minutes. The following parameters were measured: electrolytes including lithium, magnesium and calcium; creatinine, urea and

urate; total protein and albumin; osmolality; plasma renin activity (PRA); aldosterone and antidiuretic hormone (ADH).

Urine samples. All measurements were based on the consecutive collection of two 24-hour urine specimens. These specimens were pooled and submitted for measurements thereafter. Specific precautions were taken to ensure completeness of collection. While the collection was in progress, urine samples were kept in a refrigerator at 3°C. The following parameters were determined: urinary volume; osmolality; creatinine clearance; electrolytes including magnesium and phosphate; the kallikrein excretion rate was determined by amidolytic assay and by radioimmunoassay (RIA).

Laboratory procedures

Osmolality (normal range: 280 to 300 mOsm/kg H_2O) was measured by freezing point depression on an Osmomat 030 (Gonotec GmbH, Berlin, FRG) as described [18]; sodium, potassium and lithium concentrations (recommended range of lithium: 0.4 to 0.9 mmol/liter) were determined by flame photometry (Beckman Instruments, Munich, FRG); creatinine, urea (normal range: 15 to 45 mg/dl), urate (normal range: 2.0 to 7.0 mg/dl), calcium, albumin and total protein concentrations by autoanalyzer (Technicon, Dublin, Ireland, UK); magnesium concentration by atomic absorption spectrophotometry (Perkin Elmer, model 290, Überlingen, FRG). The plasma aldosterone concentration (normal range: 2.0 to 10.0 ng/dl) was determined by RIA [19]; PRA by the method of Haber et al with minor modifications (range of normal results at rest: 0.3 to 2.0 ng AI/ml × hr) [20]; ADH by RIA as described [21] (the mean plasma ADH concentration in 20 adult volunteers by this assay was 2.9 ± 1.0 pg/ml).

Specific measurements

The amidolytic assay of kallikrein was based on previously described methods [22–27]. In short, aliquots of thawed urine were dialyzed against distilled water for 24 hours. This was followed by dialysis against a phosphate-buffered (10 mM, pH 7.0) KCl solution for an additional 24 hours. Dialyzed urine samples were passed through columns containing DEAE-SEPHADEX A-50 (Pharmacia Fine Chemicals, Freiburg, FRG), 4 cc per column. Kallikrein was eluted with phosphate-buffered KCl solution (700 mM of KCl) after rinsing with 200 mM KCl. No correction was made for losses. Amidolytic activity was determined by incubating 400 μl of eluate with 0.15 mM D-VAL-LEU-ARG-PARANITROANILIDE (S 2266, Kabi Diagnostica GmbH, Munich, FRG) and 500 μl of TRIS-HCl (pH 8.2; 0.2 mol/liter). Incubation was maintained for 30 minutes at 37°C, after which the reaction was stopped by addition of 100 μl of 50% acetic acid. The enzymatic cleavage of S 2266, yielding p-nitroaniline, attributable to the enzymatic activity of kallikrein was measured photometrically (Perkin Elmer 550 A, Oak Brook, Illinois, USA) at 405 nm against a blank. Results of measurements are reported in units (U); one unit is the amount of enzyme capable of cleaving one μmol of S 2266 per minute at 37°C. The range of normal values for urinary kallikrein determined by this assay is reported by our laboratory as 310 to 420 mU/24 hrs.

Table 1. Measurements of plasma and urinary parameters before and after 14 days of lithium therapy in 15 patients with manic depressive disorder (DSM-III affective disorder)

Parameter	Before lithium	After 14 days of lithium	*P*
Measurements in plasma			
Lithium concentration *mM/liter*	—	0.81 ± 0.01	
Urea concentration *mg/dl*	29.0 ± 2.4	30.0 ± 1.8	NS
Urate concentration *mg/dl*	4.6 ± 0.2	4.8 ± 0.3	NS
Osmolality *mOsm/kg*	293.0 ± 1.0	293.0 ± 1.1	NS
Aldosterone *ng/dl*	10.0 ± 1.3	9.1 ± 2	NS
PRA *ng AI/ml × hr*	0.85 ± 0.1	0.96 ± 0.2	NS
ADH *pg/ml*	2.2 ± 0.26	2.6 ± 0.47	NS
Measurements in urine			
Urinary volume *l/24 hr*	1.9 ± 0.2	1.8 ± 0.2	NS
Clearance of creatinine *ml/min/1.73 m²*	99.7 ± 5.0	100 ± 6.9	NS
Sodium excretion rate *mM/24 hrs*	169 ± 22	162 ± 19.9	NS
Potassium excretion rate *mM/24 hrs*	70 ± 4.2	81 ± 11.1	NS

The following parameters were also measured, but remained normal and unaltered: a) plasma concentrations of sodium, potassium, calcium, phosphate, magnesium, albumin and total protein; b) urinary excretion rates of phosphate and osmoles.

Radioimmunoassay of kallikrein

The method used has been described in detail [28]. In the assay an antibody against kallikrein raised in rabbits was used. The lower limit of detection of kallikrein by this assay is 0.5 μg/liter. The range of normal values of kallikrein measured by this assay is reported by our laboratory as 60 to 100 μg/24 hrs.

For measurements of kallikrein by RIA, which will be reported in the subsequent section on results, we routinely employed the same pretreatment of urine samples as described above for amidolytic assay. However, in a subset of 12, randomly-selected urine specimens, we also compared results obtained by amidolytic assay as described above with those by radioimmunoassay without urinary pretreatment. A significant correlation of both measurements was found ($N = 12$; $r = 0.89$; $P < 0.0001$).

Statistics

Results of measurements are reported as mean values ± SEM. The Wilcoxon signed rank test was used for comparison between groups of data.

Results

General observations in short-term lithium treatment

In all 15 patients (women: 9, men: 6; mean age 39 years, range 18 to 67) a diagnosis of DSM-III affective disorder [17] had been established. During the first 14 days of treatment plasma concentrations of lithium were within the therapeutic range (<0.9 mM; Table 1). Lithium therapy was associated with transient diarrhea (2 patients) and increased thirst in one patient. The dosages of additional psychiatric medications remained unaltered throughout the study. Patients did not show

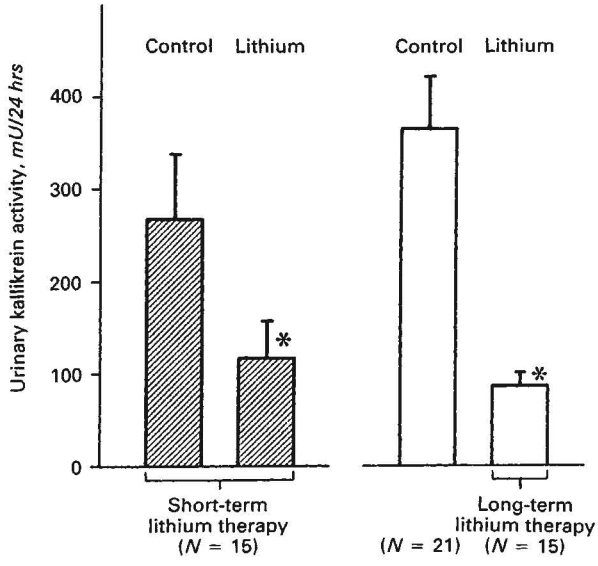

Fig. 1. *Urinary excretion rate of active kallikrein during lithium treatment and control as determined by amidolytic activity of kallikrein.* $^*P < 0.05$

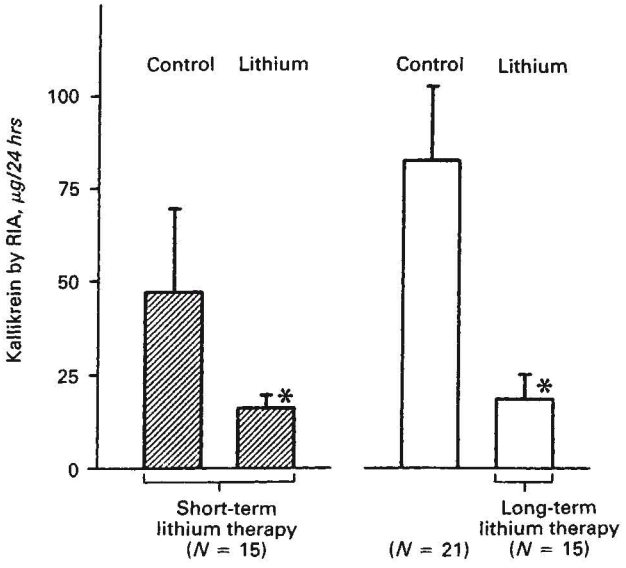

Fig. 2. *Urinary excretion rate of immunoreactive kallikrein in response to lithium treatment and during control as determined by radioimmunoassay.* $^*P < 0.05$

physical signs of dehydration or extracellular fluid volume depletion. The body weight was 69.5 ± 3.3 kg before and 69.9 ± 4.1 kg on day 14 of lithium therapy (P = NS). Oral fluid intake was 2.5 ± 0.3 1/24 hrs before and 2.4 ± 0.3 1/24 hrs on day 14 of lithium therapy (P = NS). Upright mean arterial blood pressure taken after three minutes of standing had a tendency to increase (baseline: 90 ± 4.5 mm Hg, day 14 of lithium therapy: 94.4 ± 3.7 mm Hg), but the change was not significant ($P < 0.09$). Table 1 shows parameters which document hydration, extracellular fluid volume status, creatinine clearance and potential imbalances of renal electrolyte handling at the time of kallikrein measurement. Osmolar clearance was 2.2 ± 0.08 ml/min at baseline and 2.2 ± 0.09 on day 14 of lithium therapy (P = NS); free water clearance at baseline was −0.86 ± 0.07 ml/min, and on day 14 of lithium therapy was −0.97 ± 0.08 (P = NS). All of these data failed to demonstrate any abnormalities or significant changes after the beginning of lithium treatment.

General observations in long-term lithium treatment

The 15 patients (women: 6, men: 9; mean age 39 years, range 14 to 66) underwent an abbreviated evaluation primarily to measure urinary kallikrein excretion. At the time of our study, the average duration of lithium treatment had been 5.6 years. Physical examination demonstrated normal hydration. The 24-hour urinary volume was 2.1 ± 0.3 liter. The serum lithium concentration was 0.8 ± 0.08 mM/liter. Serum electrolytes and concentrations of urea and urate were all within normal limits; the plasma creatinine concentration was 0.99 ± 0.1 mg/dl, which was normal. Urinary protein excretion rate was less than 200 mg/24 hrs in all.

Kallikrein in 24-hour urine samples

Short-term lithium treatment was associated with a significant reduction of the excretion rate of active kallikrein (amidolytic assay) by 56% (Fig. 1). This reduction was apparent as early as 72 hours after the beginning of lithium treatment. Thus, four randomly selected patients who collected urine samples at 72 hours after the beginning of lithium treatment had a reduced excretion of active kallikrein of 117.4 ± 77.8 mU/24 hrs (data not shown in Fig. 1). Figure 1 also demonstrates comparable findings in 15 patients who had undergone long-term lithium treatment over several years. Results of measurements of immunoreactive kallikrein are shown in Figure 2. The measurements were performed on eluates from the same 24-hour urine samples that had also been subjected to amidolytic assay yielding the results reported in Figure 1. The set of observations of active kallikrein (amidolytic assay, Fig. 1) closely resembled the set of observations of immunoreactive kallikrein (Fig. 2). When the results of both methods of measurement were analyzed by regression analysis they were significantly correlated ($N = 66$; $r = 0.62$; $P < 0.00001$).

Influence of lithium on amidolytic assay

Eight control urine samples were selected at random and divided into two aliquots of equal volume. Lithium carbonate was added to each second aliquot yielding a final concentration of 5 mM/liter of lithium. Kallikrein activity was determined subsequently in all 16 samples by a blinded observer. Kallikrein was 412 ± 9.1 mU in the eight samples without lithium addition and 414 ± 10.4 (P = NS) after pretreatment by lithium. Thus, there was no difference between amidolytic measurements in the presence or absence of lithium in urine samples.

Discussion

The urinary kallikrein excretion rate was found to be significantly reduced in association with lithium treatment. This finding was demonstrated by two different methods of assay for urinary kallikrein: the amidolytic assay of active kallikrein and the radioimmunoassay. No attempts were made to measure

inactive kallikrein by amidolytic assay after its activation. We were able to exclude an interference between lithium and the amidolytic assay. Reduced kallikrein excretion was consistently present in different stages of lithium therapy. It could be documented as early as 72 hrs after the beginning of lithium therapy, as well as after 14 days and several years of such therapy. Reduced kallikrein excretion occurred in patients that had plasma lithium concentrations within the therapeutic range. There was no evidence of renal insufficiency [29, 30] in these patients. No changes of ADH [31], aldosterone [32], or potassium and sodium output [33–34] were found that might have contributed to the observed reduction of kallikrein excretion. Therefore, we propose that lithium per se causes reduced renal kallikrein excretion at low plasma concentrations. To our knowledge this has not been reported before. However, as documented in a recent preliminary report from our laboratory, it was possible to reproduce the same finding in experimental animals [35]. The latter observations indicated a reduced urinary excretion rate of kallikrein along with a reduced renal cortical content of kallikrein during lithium treatment in the rat.

Several renal side-effects of lithium have been reported. They are: nephrogenic diabetes insipidus [4, 9, 36], reduced glomerular filtration rate [37–39], hypercalcemia [40] and increased excretion of sodium, potassium, calcium and phosphate by the kidney [41–43]. None of these adverse effects were noted in the patients of our study. Distal tubular acidification, which may also be impaired [5, 44, 45], was not tested. Thus, our findings do not clarify the relationship between the observed reduction of kallikrein and the development of adverse effects of lithium in the kidney. However, we were intrigued by findings in a single patient with lithium intoxication—not mentioned in the above—who had a plasma lithium concentration of 2.8 mM/liter, urinary kallikrein concentration too low to be detectable by our assay, and nonoliguric deterioration of renal function.

In future studies, the establishment of a relationship between the plasma concentration of lithium and any renal side-effects of this medication might be attempted. Conceivably, there could be an order of increasing severity in renal side-effects, in which reduced excretion of kallikrein might be an early event. In addition, in such future studies, it may also be worthwhile to test the effect of lithium—and thereby of reduced kallikrein—on renal perfusion. If a relationship of this kind existed, it might contribute to the understanding of renal lithium toxicity.

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Reprint requests to Dr. Peter Gross, Abteilung Innere Medizin und Nephrologie, Klinikum Steglitz der Freien Universität Berlin, Hindenburgdamm 30, D-1000 Berlin 45, Federal Republic of Germany.

References

1. Baastrup PC, Schou M: Lithium as a prophylactic agent. Its effect against recurrent depressions and manic depressive psychosis. *Arch Gen Psychiat* 16:162–172, 1967
2. Angst J, Dittrich A, Grof P: Course of endogenous affective psychoses and its modification by prophylactic administration of imipramine and lithium. *Int Pharmacopsychiat* 2:1–11, 1969
3. Singer I: Lithium and the kidney. *Kidney Int* 19:374–387, 1981
4. Christensen SC, 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. Battle D, Gaviria M, Grupp M, Arruda JAL, Wynn J, Kurtzman NA: Distal nephron function in patients receiving chronic lithium therapy. *Kidney Int* 21:477–485, 1982
6. Hestbech J, Hansen HE, Amdisen A, Olsen S: Chronic renal lesions following long-term treatment with lithium. *Kidney Int* 12:205–213, 1977
7. McAuliffe WG, Olesen OV: Effects of lithium on the structure of the rat kidney. *Nephron* 34:114–124, 1983
8. Jacobsen NO, Olesen OV, Thomsen K, Ottosen PD, Olsen S: Early changes in renal distal convoluted tubules and collecting ducts of lithium-treated rats. *Lab Invest* 46:298–305, 1982
9. Hansen HE, Hestbech J, Sorensen JL, Norgaard K, Heilskov J, Amdisen A: Chronic interstitial nephropathy in patients on long-term lithium treatment. *Quart J Med* 192:577–591, 1979
10. Kling MA, Fox JG, Johnston SM, Tolkoff-Rubin NE, Rubin RH, Colvin RB: Effects of long-term lithium administration on renal structure and function in rats. *Lab Invest* 50:526–535, 1984
11. Walker RG, Bennett WM, Davies BM, Kincaid-Smith P: Structural and functional effects of long-term lithium therapy. *Kidney Int* (Suppl 11) 21:S13–S19, 1983
12. Aurell M, Svalander C, Wallin L, Alling C: Renal function and biopsy findings in patients on long-term lithium treatment. *Kidney Int* 20:663–670, 1981
13. Scicli AG, Carretero OA: Renal kallikrein-kinin system. *Kidney Int* 29:120–130, 1986
14. Vio CP, Figueroa CD: Subcellular localization of renal kallikrein by ultrastructural immunocytochemistry. *Kidney Int* 28:36–42, 1985
15. Barajas L, Powers K, Carretero O, Scicli AG, Inagami T: Immunocytochemical localization of renin and kallikrein in the rat renal cortex. *Kidney Int* 29:965–970, 1986
16. Proud D, Knepper MA, Pisano JJ: Distribution of immunoreactive kallikrein along the rat nephron. *Am J Physiol* 244:F520–F515, 1983
17. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed). Washington D.C., APA, 1980
18. Gross PA, Pehrisch H, Rascher W, Schömig A, Hackenthal E, Ritz E: Pathogenesis of clinical hyponatremia. *Eur J Clin Invest* 17:123–129, 1987
19. Vecsei P, Gless KH: Aldosterone radioimmunoassay, in *Aldosterone Radioimmunoassay*, edited by Vecsei P, Stuttgart, Enke Verlag, 1975
20. Haber E, Koerner T, Page LB, Kleman B, Purnode A: Application of a RIA for angiotensin I to the physiologic measurement of PRA in normal subjects. *J Clin Endocrinol Metab* 29: 1349–1355, 1969
21. Rascher W, Lang RE, Unger T, Ganten D, Gross F: Vasopressin in brain of spontaneously hypertensive rats. *Am J Physiol* 242: H496–H499, 1982
22. Bönner G, Marin-Grez M: Measurement of kallikrein activity in urine of rats and man using a chromogenic tripeptide substrate. *J Clin Chem Clin Biochem* 19:165–168, 1981
23. Marin-Grez M, Schaechtelin G: The measurement of amidolytic activity in kidney homogenates for the estimation of renal kallikrein. *Kidney Int* 22:697–701, 1982
24. Bönner G, Autenrieth R, Marin-Grez M, Speck G, Gross F: Steroid induced changes of the renal kallikrein kinin system in rats. *Acta Endocrinol* 107:131–140, 1984
25. Nustad K, Pierce JV: Purification of rat urinary kallikreins and their specific antibody. *Biochem* 13:2312–2319, 1974
26. Sustarsic DL, McPartland RP, Rapp JP: Total and kallikrein arginine esterase activities in the urine of salt-hypertensive susceptible and resistant rats. *Hypertension* 2:813–820, 1984
27. Amundsen E, Pütter J, Fiberger P, Knös M, Larsbraten M, Claeson G: Methods for the determination of glandular kallikrein

by means of a chromogenin-tripeptide. *Adv Exp Med Biol* 120A: 83–95, 1979
28. MANN K, GÖRING W, LIPP W, KEIPERT B, KARL HJ, GEIGER R, FINK E: Radioimmunoassay of human urinary kallikrein. *J Clin Chem Clin Biochem* 18:395–401, 1980
29. MITAS JA, LEVY SB, HOLLE R, FRIGON RP, STONE RA: Urinary kallikrein activity in the hypertension of renal parenchymal disease. *N Engl J Med* 299:162–165, 1978
30. O'CONNOR DT, BARG AP, AMEND W, VINCENTI F: Urinary kallikrein excretion after renal transplantation. *Am J Med* 73: 475–481, 1982
31. FEJES-TOTH G, ZAHAJSZKY T, FILEP J: Effect of vasopressin on renal kallikrein excretion. *Am J Physiol* 239:F388–F392, 1980
32. NODA Y, YAMADA K, IGIC R, ERDÖS EG: Regulation of rat urinary and renal kallikrein and prekallikrein by corticosteroids. *Proc Natl Acad Sci USA* 80:3059–3063, 1983
33. HORWITZ D, MARGOLIUS HS, KEISER HR: Effects of dietary potassium and race on urinary excretion of kallikrein and aldosterone in man. *J Clin Endocrinol Metab* 47:296–299, 1978
34. BÖNNER G, AUTENRIETH R, MARIN-GREZ M, RASCHER W, GROSS F: Effects of sodium loading, desoxycorticosterone acetate, and corticosterone on urinary kallikrein excretion. *Hormone Res* 14: 87–94, 1981
35. GROSS P, SCHLENKER A, KOEPPEN-HAGEMANN I, GELARDI R, SAUER H, BERG T, BÖNNER G: Lithium interferes with renal kallikrein. *Proc. 22nd Annual Meeting*, The American Society of Nephrology, Washington, D.C., Dec. 3–6, 1989, pp. 181A
36. SINGER I, ROTENBERG D, PUSCHETT JB: Lithium-induced nephrogenic diabetes insipidus: In vivo and in vitro studies. *J Clin Invest* 51:1081–1091, 1972
37. BENDZ H: Kidney function in a selected lithium population. *Acta Psych Scand* 72:451–463, 1985
38. ALBRECHT J, KAMPF D, MUELLER-OERLINGHAUSEN B: Renal function and biopsy in patients on lithium therapy. *Pharmakopsychiatr* 13:228–234, 1980
39. WALKER RG, ESCOTT M, BIRCHALL I, DOWLING JP, KINCAID-SMITH P: Chronic progressive renal lesions induced by lithium. *Kidney Int* 29:875–881, 1986
40. COLT EWD, KIMBRELL D, FIEVE RR: Renal impairment, hypercalcemia and lithium treatment. *Am J Psychiatr* 138:106–108, 1981
41. MURPHY DL, GOODWIN FK, BUNNEY NE: Aldosterone and sodium response to lithium administration in man. *Lancet* 2:458–460, 1969
42. MARTINEZ-MALDONADO M, STAVROULAKI-TSAPARA A, TSAPARAS H, 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
43. BIRCH NJ, JENNER FA: The distribution of lithium and its effects on the distribution and excretion of other ions in the rat. *Brit J Pharmacol* 47:586–594, 1973
44. MILLER PD, DUBOVSKY SL, MCDONALD KM, KATZ FH, ROBERTSON GL, SCHRIER RW: Central, renal and adrenal effects of lithium in man. *Am J Med* 66:797–803, 1979
45. NORGAARD T, FAARUP P, HANSEN BB, KRISTENSEN AR, CHRISTENSEN S: Correlation between distal nephron enzyme activity, structure and function in rats during lithium and lithium plus neuroleptic treatment. *Renal Physiol* 8:50–61, 1985