Impaired Renal Tubular Secretion of Potassium, Elevated Sweat Sodium Chloride Concentration and Plasma Inhibition of Erythrocyte Sodium Outflux as Complications of Systemic Lupus Erythematosus

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A 23-year-old male with systemic lupus erythematosus and hypocomplementemic glomerulonephritis (creatinine clearance 84 ml/min) developed severe hyperkalemia when given a normal sodium and potassium intake. Potassium excretion increased subnormally in response to ammonium chloride, sodium bicarbonate and a sodium-retaining steroid. Renal conservation of sodium and excretion of ammonium were impaired. These observations are consistent with defects in secretion of potassium and hydrogen ion by the distal tubule. Sodium transport by sweat ducts and normal erythrocytes incubated in the patient's plasma was impaired. The several abnormalities in ion transport could have been caused by a circulating substance(s), possibly acquired as a result of systemic lupus erythematosus.

The kidney can maintain its capacity to excrete potassium despite considerable loss of nephron mass (1, 2). Rarely, renal excretion of potassium may be impaired when nephron mass has not been appreciably reduced (3, 4). This appears to be the case in the subject of the present report, a 23-year-old male with systemic lupus erythematosus and hypocomplementemic glomerulonephritis. The patient developed severe hyperkalemia on a normal

potassium intake (60 mEq/day), at a time when his dietary intake and urinary excretion of sodium were each approximately 100 mEq/day and endogenous creatinine clearance was 84 ml/min.

Hyperkalemia associated with only mild impairment of creatinine clearance is all the more remarkable if the studies of potassium excretion by a remnant kidney in the dog are applicable to man (5). These studies demonstrated an extraordinary ability of the remnant kidney to increase its excretion of potassium in response to potassium administration, and this response did not depend on the rate of sodium excretion or sodium-retaining steroids.

The present studies determine the response of renal potassium excretion to interventions designed to increase potassium secretion and evaluate other tubular functions such as hydrogen ion secretion and sodium reabsorption. They also evaluate ion transport in sweat glands and erythrocytes.

CASE REPORT

DHL, a 23-year-old Caucasian male, developed fever, rigors and pleuritic chest pain with a sterile exudative pleural effusion in October 1969. His fever remitted spontaneously but recurred in January 1970 with progressive dyspnea and a productive cough. Positive LE cell preparations, leukopenia and microscopic hematuria were noted. Serum potassium was 5.3 mEq/liter and serum creatinine 1.2 mg/100 ml.

In February he developed thrombophlebitis of the right calf and pulmonary emboli. In September 1970 phlebitis and pulmonary emboli recurred, and 2 months later, when dyspnea increased and orthopnea and pedal edema appeared, he was admitted to the Clinical Center. Blood pressure was 140/110 mm Hg (it was normal after the first hospital week). A large right pleural effusion, signs of biventricular cardiac failure and bilateral pedal edema were present.

There was persistent proteinuria (1.1 to 7.2 g/day), microscopic hematuria and pyuria with moderate numbers of granular and hyaline casts and occasional fatty and ery-
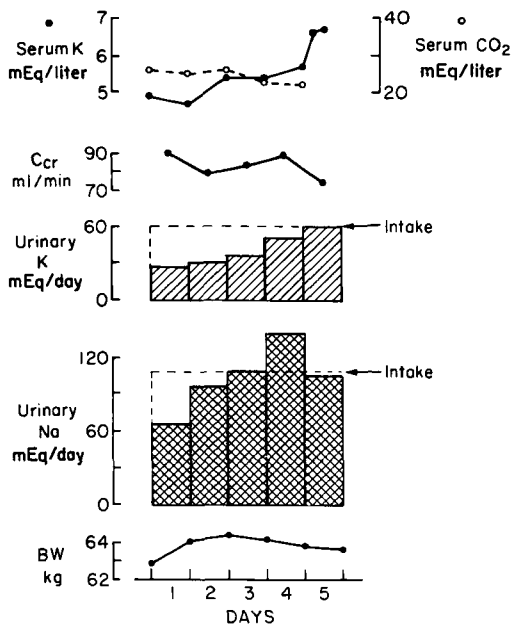
Fig 1. Effect of normal potassium intake on serum potassium (K) and bicarbonate (CO_2), clearance of creatinine (C_{cr}), body weight (BW) and daily urinary excretion of sodium (Na) and potassium. Constant dietary intake of sodium and potassium is indicated by the hatched horizontal lines. (Note that when urinary potassium excretion approximated intake on Day 5, hyperkalemia was manifest.)

throcyte casts. Aminoaciduria was not present. Urine cultures were consistently negative. Hemoglobin was 10 g/100 ml and leukocyte count 2000 cells/cu mm. Type IV hyperlipoproteinemia was present. Blood urea nitrogen (BUN) was 19 mg and creatinine 1.2 mg/100 ml. Sodium was 142, potassium 4.2, chloride 109 and bicarbonate 25 mEq/liter. Calcium was 8.2, magnesium 1.6 and phosphate 3.5 mg/100 ml.

LE cell preparations were positive and cryoglobulins were present. Serum C3 was stable at 43 mg/100 ml (normal: 110 to 175). Serum albumin ranged between 2.5 and 3.1 g/100 ml. Infusion intravenous pyelogram showed enlarged renal shadows bilaterally. Pleural fluid had the characteristics of a sterile exudate.

He was started on a daily regimen of hydrochlorothiazide, 50 mg, spironolactone, 50 mg and digoxin, 0.25 mg. He lost 7 kg in weight and pedal edema disappeared, but serum potassium increased to 4.8 mEq/liter and BUN to 35 mg/100 ml. All of these therapeutic agents were then discontinued and the patient slowly gained 1.5 kg in weight without reappearance of edema. Blood urea nitrogen decreased to 25 mg/100 ml, but serum potassium continued to increase to 6.2 mEq/liter with electrocardiagraphic findings of first degree heart block and *tented* T waves. Treatment with 27 g of Kaexolate [a] (Winthrop Laboratories, NY) in sorbitol, followed by restriction of dietary potassium to 30 mEq/day, maintained serum potassium between 4.6 and 5.9 mEq/liter until balance studies were started 1 month later.

Throughout the study period, the patient took prednisone, 30 mg/day, isoniazid, 300 mg/day, pyridoxine, ferrous sulfate and sodium warfarin (thrombophlebitis and pulmonary embolism complicated his early hospital course). In addition, azathioprine was administered in an average dose of 0.8 mg/kg/day. Only the study in Figure 1 antedated the administration of azathioprine. Investigations of ion transport by erythrocytes and sweat glands were undertaken simultaneously with these balance studies.

The pleural effusion and cardiomegaly gradually regressed. Urinary sediment, 24-hour protein excretion, C3 and hemogram were unchanged. Creatinine clearance on 56 determinations during the study period averaged 82.4 ± 12.6 ml/min (SD). He was discharged in April 1971 on prednisone, isoniazid and restricted dietary potassium.

He was asymptomatic when readmitted 1 month later. His x-ray demonstrated normal heart size and pleural thickening at the base. Urinalysis and sweat electrolytes were unchanged. Creatinine clearance and potassium excretory capacity determined during a metabolic study showed results similar to those in Figure 1. Histologic examination of tissue obtained by percutaneous right renal biopsy revealed focal glomerulitis with crescent formation and mild intestitial fibrosis. Daily stool fat excretion was 1.05 g during a daily intake of 95 g.

There is no family history of renal or collagen-vascular

Fig 2. Effect of the dietary substitution of 100 mEq of bicarbonate ($NaHCO_3$) for 100 mEq of chloride (NaCl) on serum potassium (K) and bicarbonate (CO_2), clearance of creatinine (C_{cr}), urinary excretion of potassium (K) and sodium (Na), and body weight (BW). (Note that this substitution resulted in only a trivial increase in potassium excretion.)
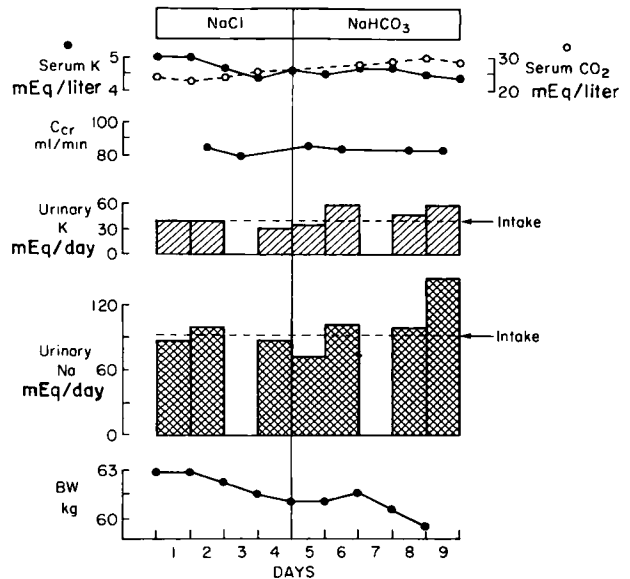
disease or cystic fibrosis of the pancreas. No abnormality in renal excretion of potassium, sweat electrolytes or erythrocyte sodium transport was observed in the patient's mother and son.

MATERIALS AND METHODS

The patient was maintained on an air-conditioned ward and given special diets as indicated. At least a week was allowed to elapse between balance studies. Aliquots of serum were analyzed for sodium, potassium, chloride, bicarbonate and creatinine, and aliquots of urine were analyzed for sodium, potassium and creatinine in the Clinical Laboratories of The National Institutes of Health by methods previously described (6). Urinary pH, ammonium and titratable acidity minus bicarbonate (7) and the secretion of aldosterone (8) were determined by methods previously described.

Sweat rate and composition were determined after pharmacologic and thermal stimulation. Pilocarpine iontophoresis was performed as previously described (9). Thermal stress was produced by timed exposures in an environmental room at 100 and 120° F. Sweat rate was estimated from weight loss associated with evaporation during a timed exposure. Evaporation was essentially complete at the relative humidity employed (12%). The surface residue was quantitatively recovered by repeated baths in distilled water. The bath water was flash evaporated and the electrolyte content determined. This technic was developed by Drs. R. Gordon and R. Thompson, National Institute of Arthritis and Metabolic Diseases. Erythrocyte sodium

concentration, fractional sodium outflux and sodium influx were determined as described previously (10). In the studies of the effect of plasma on normal erythrocytes, fresh heparinized plasma (sodium and potassium concentrations adjusted to 146 and 6 mEq/liter, respectively) was used as the final incubation solution.

RESULTS

Response to Normal Potassium Intake (Figure 1)

The patient was given a constant neutral ash diet estimated to contain 109 mEq/day of sodium and 60 mEq/day of potassium. On this regimen urinary sodium equaled or exceeded intake from Day 2 through Day 5. Urinary potassium was 26 mEq/day on the first day of study and slowly increased to equal intake on Day 5. During the 5-day study period, serum potassium rose from 4.9 to 6.7 mEq/liter. Creatinine clearance varied between 74 and 90 ml/min during the 5 days of study.

Response to Sodium Bicarbonate (Figure 2)

After 4 days on a constant neutral ash diet estimated to contain 109 mEq/day of sodium and 30 mEq/day of potassium, 100 mEq of so-
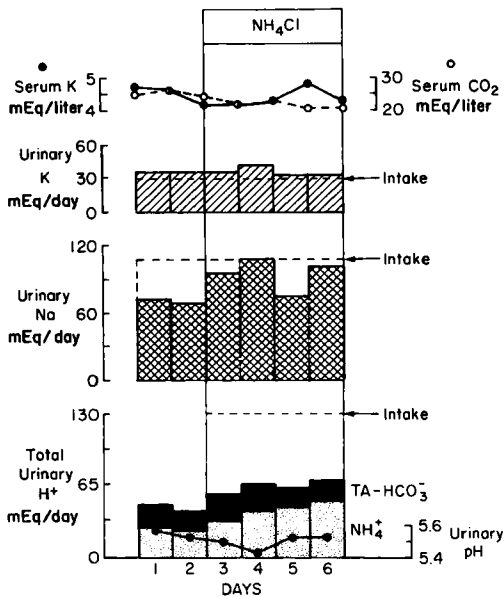
Fig 3. Effect of daily dietary administration of ammonium chloride (NH₄Cl), 130 mEq/day, on serum potassium (K) and bicarbonate (CO₂), and on the urinary excretion of potassium, sodium (Na), total urinary hydrogen ion (H⁺), titratable acidity minus bicarbonate (TA-HCO₃⁻) and ammonium (NH₄⁺). (Note that potassium excretion did not change, and urinary excretion of hydrogen ion was considerably less than intake.)

dium as sodium bicarbonate was substituted for 100 mEq/day of sodium as sodium chloride. During the administration of bicarbonate, serum carbon dioxide content increased to 30 mEq/liter, arterial pH to 7.46 and urinary pH to 7.9. Urinary potassium increased only slightly from 30 to a maximal value of 45 mEq/day; serum potassium did not change. Normal subjects respond to a similar degree of alkalosis with an increase in potassium excretion and a cumulative potassium loss from –79 to –133 mEq for a 3-day period (11).

Response to Ammonium Chloride (Figure 3)

After 9 days on a constant neutral ash diet estimated to contain 109 mEq/day of sodium and 30 mEq/day of potassium, 130 mEq/day of
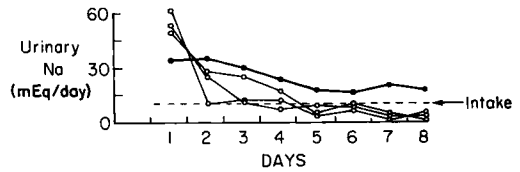
Fig 4. Effect of restricting dietary sodium to 9 mEq/day for 8 days on urinary sodium (Na) excretion in patient DL•—•and in 3 normal subjects o—o.

chloride as ammonium chloride was given for 4 days. Normal subjects responded to an amount of ammonium chloride, similar to that given the patient, by a decrease in urinary pH below 5.3 and an increase in ammonium excretion to values greater than 73 mEq/day (12). The patient's minimal urinary pH was 5.43, and his maximal rate of ammonium excretion was 50 mEq/day. Serum carbon dioxide content decreased from 25 to 21 mEq/liter, and arterial pH decreased from 7.40 to 7.35; urinary potassium did not change. Mean urine flow during the period of ammonium chloride administration was 508 ml greater than the control period. This increase in urine flow is similar in magnitude to that observed in normal subjects given ammonium chloride (12). Therefore, urine flow rate would not explain the difference between normal controls and patient DL (13).

Response to Restriction of Sodium Intake (Figure 4)

After 6 days on a constant neutral ash diet, sodium intake was decreased from 109 to 9 mEq/day for 8 days. During this period of sodium restriction, urinary sodium did not decrease below 17 mEq/day and body weight decreased 1.3 kg. Aldosterone secretion rate on Day 7 was 600 μg/day. Three patients without renal disease during a similar study decreased urinary sodium to intake or below by Day 4 or 5, with a mean cumulative weight loss of only 0.65 kg.

Response to Sodium-Retaining Steroid (Figure 5)

After 5 days on a constant neutral ash diet

Table 1. Composition of Pilocarpine-Induced Sweat in Patients with Lupus Glomerulonephritis

Patient	Age	Sex	Prednisone (mg/day)	Immunosuppressant	Milliequivalents per liter			Induced sweat (mg)
					Cl	Na	K	
DL								
087067			30	Azathioprine	80.2	112	8.6	0.444
				Azathioprine	73.3	96	8.4	0.545
					78.4	106	7.8	0.583
				None	73.0	82	9.4	0.443
					77.6	85	10.4	0.282
NIH								
086948	29	F	5	None	10.2	19	6.6	0.654
					10.6	20	7.4	0.613
060031	36	F	0	Azathioprine	31.7	42	10.0	0.475
086803	28	F	30	None	10.2	23	4.6	0.335
087386	15	F	30	None	22.7	43	9.6	0.362
087376	26	F	30	None	29.6	42	12.6	0.132
087150	55	F	30	None	11.7	20	8.0	0.336
085428	40	M	20	Cytoxan	13.9	20	4.1	0.451
Mean±SD					17.6±9.0	29±11	7.9±2.8	0.336±0.175

2CH₃9αFF
.5 mg/day
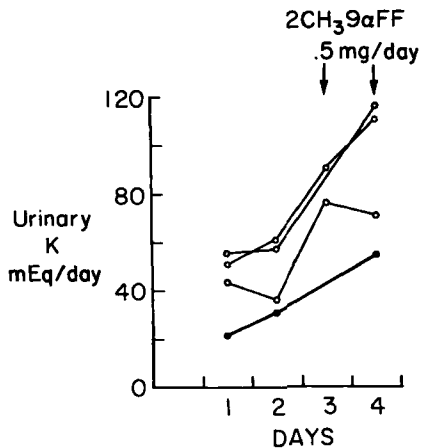
Fig 5. Effect of administering 2-methyl 9-alpha fluorohydrocortisone (2CH₃9αFF), 0.5 mg/day, on urinary potassium (K) excretion in patient DL •—• and 3 normal subjects o—o.

estimated to contain 109 mEq/day of sodium and 30 mEq/day of potassium, 2-methyl 9α-fluorohydrocortisone (0.5 mg/day) was given for 2 days. Urinary potassium increased from 28 to 54 mEq/day. In 3 patients without renal disease the sodium-retaining steroid increased mean urinary potassium from 48 mEq/day to a mean value of 99 mEq/day on Day 2.

Studies of Sweat Gland Function

Table 1 presents the electrolyte composition

of samples of sweat induced by pilocarpine iontophoresis for the patient and 7 other patients with systemic lupus erythematosus. Table 2 presents the electrolyte composition of samples of sweat induced by thermal stress for the patient and normal males of similar age. The patient demonstrates a marked increase in the concentration of sodium and chloride in sweat, independent of sweat rate or mode of induction.

Studies of Erythrocyte Sodium Concentration and Fluxes (Table 3)

Fractional sodium outflux, sodium influx and intracellular sodium concentration in the patient's erythrocytes did not differ significantly $(P > .05)$ from control values (Table 3). When normal erythrocytes were incubated in the patient's plasma (Table 4), fractional sodium outflux was significantly lower $(P > .01)$ than outflux from similar cells incubated in normal plasma. The small decrease in fractional sodium outflux produced in normal cells by the patient's plasma suggests that fractional sodium outflux may have been decreased in the patient's erythrocytes. (A small decrease in fractional sodium outflux may not be statistically significant, because the values for outflux in normal erythrocytes show considerable varia-

Table 2. Sweat Rate and Composition in Response to Thermal Stress

Subject	Environmental temperature (°F)	Sweat rate (ml/sq m/min)	Na (mEq/liter)	K (mEq/liter)
Patient DL	100	1.46	33.0	4.0
	120	5.00	91.3	4.6
Male controls* 4 subjects 12 observations	100	1.11±0.46†	7.42± 4.38	6.96±3.45
Male controls* 22 subjects 58 observations	120	5.39±0.51	26.0 ±17.7	4.82±0.68

*Ages 18 to 25
†Mean±SD

Table 3. Sodium Concentrations and Fluxes in Erythrocytes

	Intracellular Na (mmoles/liter cells)	Fractional Na Outflux H^{-1}	Na influx (mmoles/liter cells H^{-1})
Patient	6.56±.21(4*)	.437±.012(3)	1.74±.12(3)
Controls†	5.47±.66	.500±.060	1.74±.20

*Number of times value was determined in duplicate.
†Values represent mean of duplicate determinations in 16 normal adult subjects±SD.

Table 4. Effect of Plasma on Fractional Sodium Outflux of Normal Erythrocytes in Three Paired Experiments*

Source of plasma	Fractional sodium outflux (H^{-1})		
Normal subjects	0.512	0.490	0.483
Patient	0.436	0.410	0.413

*Cells and plasma obtained from 3 different normal individuals.

tion.) In support of this possibility is the finding that the value for intracellular sodium concentration in the patient's erythrocytes was greater than the mean value for normal subjects.

DISCUSSION

The subject of this report is a young man with systemic lupus erythematosus and active glomerulonephritis which presented clinically as persistent hematuria and proteinuria and was documented by pathologic changes in renal tissue. An unusual feature of his renal disease was an inability to increase urinary excretion of potassium so as to maintain a normal serum potassium during normal intake of potassium (60 mEq/day) and sodium (100 mEq/day) (Figure 1). This impairment in potassium excretion was associated with only modest impairment of creatinine clearance (84 ml/min). Other abnormalities of renal function consisted of impairments in hydrogen ion excretion and sodium conservation.

Impaired hydrogen ion excretion has previously been described in systemic lupus erythematosus (14, 15). [One of the patients in the latter series also had Sjögren's syndrome, a disorder which may be complicated by an unexplained defect in acidification of the urine (16).] Impaired excretion of potassium and hydrogen ion has also been observed in a patient with glomerulonephritis (3) and a patient with an otherwise uncharacterized disorder (4).

A limited ability of the kidney to secrete hydrogen ion could contribute to the observed defect in sodium conservation (7). However, it is unlikely that impaired hydrogen ion secretion and sodium conservation are the cause, per se, for the impairment in excretion of potassium, as these two defects tend to facilitate potassium excretion (7, 17, 18). On the other hand, when potassium secretory capacity is depressed, the ability to produce a steep hydrogen ion gradient is lost and ammonium excretion is depressed (19).

Recent observations in several mammalian species indicate that virtually all of the filtered potassium is reabsorbed by the proximal tubule; potassium secreted by the distal nephron is the source of that excreted in the urine (20–24). Therefore, the failure of potassium excretion to respond normally to a normal potassium intake, and the defect in secretion of hydrogen

ion, suggest that distal tubular function in the patient is disordered. In this regard, interventions which increase the excretion of potassium, such as the administration of ammonium chloride (12, 25, 26) and the induction of alkalosis (11, 27), either did not change potassium excretion (Figure 3) or produced only a trivial increase (Figure 2). Furthermore, the increase in potassium excretion following treatment with a potent, sodium-retaining steroid (28) was less than that observed in normal subjects similarly studied (Figure 5) and consistent with a diminished responsiveness of the potassium secretory mechanism.

Studies of the mechanism of potassium secretion by tubules in Amphiuma suggest that interventions such as potassium administration, which increase net tubular secretion of potassium, do so by stimulation of active transport of potassium from peritubular fluid into the tubule cell with an increase in the cellular transport pool of potassium (29). Presumably the increase in the cellular transport pool of potassium increases the electrochemical potential difference across the luminal membrane so that the net movement of potassium from tubule cell to luminal fluid increases. If these observations in Amphiuma are applicable to man, then the defect in potassium secretion in the patient could be the result of inhibition of active potassium transport across the peritubular membranes of the distal tubule cells. (The presence of an abnormality in transport across the luminal membrane of the cell cannot be excluded.)

To obtain information about the function of the other cellular ion transport processes, the electrolyte concentration of sweat and the sodium concentration and fluxes in erythrocytes were determined. The patient demonstrated striking elevation of sweat sodium and chloride concentration. The process of sweat formation is initiated with the production of isosmotic *presweat* in the coil of the gland (30). During transit through the excretory duct, sodium and chloride are reabsorbed by a cellular process that can be stimulated by sodium-retaining

steroids (31) and is saturated at increased rates of sweating (32). Patients with cystic fibrosis of the pancreas also exhibit a defect in ductular sodium reabsorption, and one hypothesis attributes the cause of the sweat gland abnormality to a humoral factor (33).

The studies of erythrocyte sodium fluxes suggest that there may be a substance(s) in the patient's plasma which can inhibit sodium outflux in the erythrocyte. Such a substance could conceivably inhibit sodium chloride transport by the cells of the sweat duct and potassium secretion by the distal renal tubule, so as to cause the several abnormalities in transport processes observed in this patient with systemic lupus erythematosus.

ACKNOWLEDGMENTS

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