Endocrine Sodium and Volume Regulation in Familial Hyperkalemia With Hypertension

Paul Isenring, Marcel Lebel, and John H. Grose

The hormonal regulation of sodium and volume homeostasis was investigated in three patients (two related) with the syndrome of familial hyperkalemic acidosis and hypertension with normal glomerular filtration rate. Recumbent plasma renin activity was low during normal sodium intake (135 mmol daily), and the response to upright posture or to low sodium diet (10 mmol daily) was blunted. Recumbent plasma aldosterone levels were normal in two patients and high in one, and the standing values were elevated in one; responses to upright posture were brisk on low sodium diet. Angiotensin II infusion induced a marked increase in plasma aldosterone. Plasma atrial natriuretic peptide was at the upper limit of normal during normal sodium intake, decreased during diuretic therapy, and increased during sodium chloride infusion in one patient. Basal urinary prostaglandin E$_2$, prostaglandin F$_3$, and 6-ketoprostaglandin F$_1x$ excretion rates were decreased, and thromboxane B$_2$ was increased. Total blood and plasma volumes were subnormal, whereas extracellular fluid volume and exchangeable sodium values were close to or above (in one patient) the mean normal values. Chronic treatment with hydrochlorothiazide in two patients corrected the hyperkalemic acidosis and hypertension, but on its discontinuation (in one patient) all biochemical abnormalities promptly reappeared. (Hypertension 1992;19:371–377)

KEY WORDS • hyperkalemia • renin • aldosterone • prostaglandins • atrial natriuretic peptides • body fluid compartments

The syndrome of familial hyperkalemia and hypertension (FHH), also named Gordon's syndrome or type II pseudohypoaldosteronism, was first described by Paver and Pauline. Since then, over 30 additional patients have been reported worldwide. Its clinical and biochemical features as well as various pathogenetic hypotheses have been recently reviewed. It is still unclear whether the syndrome is the result of a primary renal tubular defect or of abnormal humoral mechanisms that regulate renal electrolyte transport.

We report three patients (two related) in whom the endocrine factors (renin, aldosterone, atrial natriuretic peptide, and renal eicosanoids) that control body fluid homeostasis and blood pressure were investigated under controlled conditions. The effects of diuretic therapy and its withdrawal were also studied.

Patients 1 and 2 were two of three affected siblings of family A (Figure 1). The presence of Gordon's syndrome was first diagnosed in the oldest sibling of this family (not included in this report) during an investigation performed in another hospital for gastrointestinal problems. He had moderate hypertension with persistent hyperkalemia and hyperchloremic metabolic acidosis with normal renal function. Urinary sediment and excretory urography were normal. Serial urine pH measurements showed pH below 5.5. Serum calcium, phosphate, and uric acid concentration were normal. She had two children, one of which had elevated serum potassium (K$^+$) at 5.2 mmol/l.

Patient 2, aged 42 years, was also asymptomatic at the initial consultation. His blood pressure was 160/110 mm Hg, and fundoscopic examination revealed grade II Keith-Wagener changes. Physical examination was otherwise normal. Preliminary laboratory investigations revealed persistent hyperkalemia and hyperchloremic metabolic acidosis with normal renal function. Urinary sediment and excretory urography were normal. Serial urine pH measurements showed pH below 5.5. Serum calcium and phosphate levels and uric acid concentration were normal. One of his two daughters had a serum K$^+$ level at 5.3 mmol/l and serum chloride (Cl$^-$) at 111 mmol/l (Figure 1).

Patient 3 (Figure 1, family B) was 33 years old. Hyperkalemia and metabolic acidosis were disclosed during routine screening tests for asthenia. She was 78 years old, in good health, and normokalemic; the father, who died suddenly in his forties, probably transmitted the disease.

Patient 1, aged 39 years, had no significant previous medical problem. She was investigated as part of a screening process of the family because of the diagnosis of FHH in their brother. Her blood pressure was 150/100 mm Hg. Physical examination was otherwise normal. Preliminary laboratory investigations revealed persistent hyperkalemia and hyperchloremic metabolic acidosis with normal renal function. Urinary sediment and excretory urography were normal. Serial urine pH measurements showed pH below 5.5. Serum calcium and phosphate levels and uric acid concentration were normal. She had two children, one of which had elevated serum potassium (K$^+$) at 5.2 mmol/l.

Patient 2, aged 42 years, was also asymptomatic at the initial consultation. His blood pressure was 160/110 mm Hg, and fundoscopic examination revealed grade II Keith-Wagener changes. Physical examination was otherwise unremarkable. Preliminary laboratory investigations also showed elevated serum K$^+$ (5.8–6.1 mmol/l) and normal anion gap metabolic acidosis with normal renal function. Urinary sediment was normal. Maximal urine specific gravity after an overnight fast was 1.028. Repetitive pH measurements showed normal urinary acidification ability with pH ranging from 4.5 to 5.3. Serum calcium, phosphate, and uric acid were normal. One of his two daughters had a serum K$^+$ level at 5.3 mmol/l and serum chloride (Cl$^-$) at 111 mmol/l (Figure 1).

Patient 3 (Figure 1, family B) was 33 years old. Hyperkalemia and metabolic acidosis were disclosed during routine screening tests for asthenia. She was
otherwise in good health without any relevant past medical history except for an isolated urolithiasis episode 10 years ago. Blood pressure was borderline hypertensive (120-140/80-100 mm Hg) during outpatient visits but was normal most of the time during her hospitalization. Serum K⁺ was consistently high (Table 1) with hyperchloremic metabolic acidosis. The urinary sediment and excretory urography were normal. Urine specific gravity measurement after an overnight fast was normal, and the urinary pH was below 5.5. After a standard bicarbonate (HCO₃⁻) intravenous load to increase urinary pH to 8, the urinary Pco₂ rose to 74 mm Hg, indicating normal distal hydrogen ion secretory response. No aminoaciduria, glycosuria, or phosphaturia was detected. Urinary calcium excretion was slightly elevated, ranging from 6.7 to 7.2 mmol/day (normal values, less than 6.2 mmol/day). One of the patient's two daughters had hyperkalemia at age 10 years ago. Blood pressure was borderline hypertensive (120-140/80-100 mm Hg) during outpatient visits but was normal most of the time during her hospitalization. Serum K⁺ was consistently high (Table 1) with hyperchloremic metabolic acidosis. The urinary sediment and excretory urography were normal. Urine specific gravity measurement after an overnight fast was normal, and the urinary pH was below 5.5. After a standard bicarbonate (HCO₃⁻) intravenous load to increase urinary pH to 8, the urinary Pco₂ rose to 74 mm Hg, indicating normal distal hydrogen ion secretory response. No aminoaciduria, glycosuria, or phosphaturia was detected. Urinary calcium excretion was slightly elevated, ranging from 6.7 to 7.2 mmol/day (normal values, less than 6.2 mmol/day). One of the patient's two daughters had hyperkalemia at age 10 years ago.
1-hour urine collection was obtained, and a blood sample was drawn at the end of each urine collection to calculate the transtubular K⁺ gradient. On an outpatient basis, patient 2 received 9α-fluorohydrocortisone (0.3 mg daily), and the effect of this treatment on serum electrolytes and HCO₃⁻ was assessed after 3 days. Patient 1 received the same dose but for an additional 4 days (1 week total) to evaluate the effect of a longer administration of 9α-fluorohydrocortisone since the shorter treatment in her brother (patient 2) had produced only a slight modification of hyperkalemia and acidosis.

Patients 1 and 2 received hydrochlorothiazide (50 mg/day) for their hypertension. Blood pressure and electrolytes were assessed 6 weeks later. In addition, the effect of hydrochlorothiazide on blood pressure, body weight, hematocrit, serum electrolytes, plasma renin activity, plasma aldosterone, and plasma ANP was reassessed after 4 months in patient 1. Hydrochlorothiazide was then withdrawn, and 3 weeks later the same measurements were repeated and then on the same day an infusion of 1 l of 0.9% sodium chloride was administered over a 60-minute period to further study the effect of volume expansion on plasma ANP.

Plasma renin activity was determined by radioimmunoassay measuring angiotensin I. Plasma aldosterone was measured by specific radioimmunoassay after purification of plasma extracts on Sephadex LH-20 columns. Plasma ANP was determined by a radioimmunoassay using reagents from Immuno Nuclear B.V., Amsterdam, The Netherlands. Total blood volume was measured by standard dilution principles using sodium radiochromate (¹⁰⁶Cr) autologous tagged red blood cells as previously described. Plasma volume was calculated from hematocrit levels corrected for trapped plasma and adjusted for large vessel hematocrit values. Extracellular fluid volume sodium space and exchangeable sodium were also determined by isotope (⁷⁵Na) techniques after correction for urinary loss. Interstitial fluid volume was obtained by subtracting plasma volume from extracellular fluid volume. All volume results were expressed as milliliters per square meter of body surface. Urinary PGE₂, PGF₂α, 6-keto-PGF₁α, and TXB₂ were measured by specific radioimmunoassays after organic solvent extraction and Sephadex LH 20 column chromatography. Inulin clearance (Cᵢₐ) and p-aminohippurate clearance (Cₐₜₐ) were performed under water load as previously described. Fractional sodium excretion was calculated as the ratio of sodium and inulin clearances and expressed as percent of Cᵢₐ. Fractional distal Cl⁻ reabsorption (FDCR) was calculated as follows:

\[
\text{FDCR} = \frac{C_{\text{HCO}_3}/C_T}{C_{\text{HCO}_3} \times 100}
\]

Free water clearance (Cᵢₐₐ) was calculated as the urine flow rate minus osmolar clearance. Renal vascular resistance was estimated as mean blood pressure divided by effective renal plasma flow (Cᵢₐₐ). The transtubular potassium gradient (TTKG), an index of the activity of the potassium secretory process in the cortical collecting duct, was derived from the relation

\[
\text{TTKG} = \frac{\left[\text{K}^{+}\right] \text{urine}/(U/P) \text{ osm}}{\left[\text{K}^{+}\right] \text{plasma}}
\]

where U is urine, P is plasma, and osm is osmolality.

**Results**

Table 1 shows the physical and biochemical characteristics of our three patients with FHH syndrome. Their height and stature were comparable to their parents and siblings. During normal sodium intake, levels of recumbent plasma renin activity were below the normal range in two patients, and the response to upright position or to low sodium diet was blunted (Table 2). Supine plasma aldosterone level was normal in two patients and was high in the third. Upright plasma aldosterone was normal in two patients and was increased in the third; on a low sodium diet, responses to upright position were brisk in two patients (Table 2). Before the beginning of the angiotensin II infusion, plasma aldosterone levels were 3.0, 9.2, and 2.3 ng/dl in our three patients. After 45 and 90 minutes of angiotensin II infusion, the levels rose to 41.5, 65.4, and 21.1, and 39.5, 28.2, and 26.7 ng/dl, respectively. Normal values ±SEM in six control subjects, aged 25–37 years, under similar conditions were 4.8±0.7, 7.0±1.4, and 11.4±2.4 ng/dl. A concomitant increased blood pressure sensitivity to angiotensin II was observed; the target diastolic blood pressure of 20 mm Hg was reached after 10, 14, and 17 minutes in the three patients at infusion rates of 4, 2.7, and 5.5 ng/kg/min, respectively (normal, 8–12 ng/kg/min). Plasma ANP levels were at the upper limit of normal during normal sodium intake in patients 1 and 3 (Table 2) and returned to normal after diuretic administration in patient 1. The acute intravenous saline load in the latter patient resulted in a 54% increase in plasma ANP level. As seen in Table 3, total blood volume and plasma volume values were subnormal compared with normal subjects studied under the same conditions. Interstitial fluid volume, extracellular fluid volume, and exchangeable sodium values were slightly below normal range in patient 2 and were within or slightly above normal range in patients 1 and 3. Table 4 shows that the excretion rates are decreased in PGE₂, PGF₂α, and 6-keto-PGF₁α, and increased in TXB₂ in our three patients compared with control subjects studied under the same dietary conditions. Results of measurements of renal function and hemodynamics and electrolyte excretion rates that were determined in patients 1 and 3 are presented in Table 5. Effective renal plasma flow (Cᵢₐₐ) was slightly decreased in patient 3, renal vascular resistance was increased, and K⁺ clearance was strikingly low.

The TTKG level in patient 3 was at 5.6 during the control period, and 2 hours after the administration of 0.2 mg 9α-fluorohydrocortisone, it rose to 10.2. The mean TTKG value is 8.7±2.7 (SD) in normal subjects; 2 hours after an acute administration of 0.2 mg 9α-fluorohydrocortisone, it increases to 11.4±2.4. The administration of 9α-fluorohydrocortisone (0.2 mg daily) for 3 days in patient 2 produced only slight modifications of serum K⁺, Cl⁻, and HCO₃⁻ at 5.8, 111, and 20 mmol/l, respectively. This patient's sister (patient 1) received the same dosage for 7 days, which resulted in complete correction of serum K⁺, Cl⁻, and HCO₃⁻ (4.5, 104, and 22 mmol/l).

Treatment with hydrochlorothiazide (50 mg daily) in patients 1 and 2 resulted in complete correction of their hypertension, hyperkalemia, and acidosis as reassessed.
TABLE 2. Plasma Renin Activity, Plasma Aldosterone, and Plasma Atrial Natriuretic Peptide Levels During Normal and Low Sodium Diets

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal sodium diet (135 mmol/day)</th>
<th>Low sodium diet (10 mmol/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine (0.4–3.4)</td>
<td>Upright (1.0–6.0)</td>
</tr>
<tr>
<td></td>
<td>(mean, 1.1)</td>
<td>(mean, 2.3)</td>
</tr>
<tr>
<td>PRA (ng/ml/hr) (n=37)</td>
<td>1 &lt;0.1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>2 0.3</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>3 0.2</td>
<td>ND</td>
</tr>
<tr>
<td>PA (ng/dl) (n=37)</td>
<td>1 7.3</td>
<td>17.9</td>
</tr>
<tr>
<td></td>
<td>2 23.4</td>
<td>21.8</td>
</tr>
<tr>
<td></td>
<td>3 2.9</td>
<td>50.8</td>
</tr>
<tr>
<td>ANP (pg/ml) (n = 16)</td>
<td>1 ND</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>3 47.2</td>
<td>ND</td>
</tr>
</tbody>
</table>

Reference values during normal sodium intake are given in parentheses (normal ranges). Blood samples were taken while patients were in supine (8 AM) and upright (noon) positions. PRA, plasma renin activity; 1, 2, 3, patients 1, 2, and 3; ND, not determined; PA, plasma aldosterone; ANP, atrial natriuretic peptide.

Discussion

The three patients discussed in the present communication exhibit the typical clinical features of FHH or Gordon's syndrome. Two had sustained hypertension and the third had normal blood pressure to borderline hypertension. Hyperkalemia and acidemia persisted despite normal glomerular filtration rate in all three patients.

Plasma renin activity was suppressed during a normal salt diet and remained below normal on a low sodium diet or with hydrochlorothiazide treatment. Plasma aldosterone was normal or slightly elevated during basal conditions but showed a striking increase in response to a low sodium diet (upright position) and during angiotensin II infusion. With the latter stimulus, despite higher blood pressure responsiveness and lower infusion rates, the aldosterone response was still markedly enhanced. This hyperresponsiveness of aldosterone to angiotensin II may be, in part, due to low circulating angiotensin II and decreased occupancy of adrenal angiotensin II receptors as a result of the low plasma renin activity. It may also be related to the associated hyperkalemia since angiotensin II and K+ are two major stimuli for aldosterone synthesis by the adrenal cortex. Since angiotensin II is chronically suppressed in this syndrome, serum K+ level likely becomes the more important determinant of aldosterone synthesis in these patients. Indeed, plasma aldosterone decreased in response to lower K+ concentration during hydrochlorothiazide treatment and increased again with the rise in serum K+ 3 weeks after withdrawal of the therapy despite concomitant renin suppression (Table 6). On the other hand, the chronic low renin state in FHH may limit the full adrenal responsiveness to K+ and may thus account for the inability to attain a maximal aldosterone secretory response necessary to maintain serum K+ within the normal range under normal conditions.

Plasma ANP level was measured in two patients under various conditions. The values were at the upper limit of normal values during normal sodium intake, diminished during volume contraction due to diuretic therapy, and returned to the pretreatment level 3 weeks after hydrochlorothiazide withdrawal (patient 1, Table 6). An acute sodium chloride load in the same patient produced a 54% rise in plasma ANP, which is within the

Table 3. Total Blood Volume, Plasma Volume, Interstitial Fluid Volume, Extracellular Fluid Volume, and Exchangeable Sodium During Normal Sodium Diet

<table>
<thead>
<tr>
<th>Body fluid volumes</th>
<th>Patients</th>
<th>Normal values (±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (F)</td>
<td>2 (M)</td>
</tr>
<tr>
<td>TBV (ml/m² BSA)</td>
<td>1,753</td>
<td>1,955</td>
</tr>
<tr>
<td>PV (ml/m² BSA)</td>
<td>1,130</td>
<td>1,170</td>
</tr>
<tr>
<td>IFV (ml/m² BSA)</td>
<td>8,400</td>
<td>8,709</td>
</tr>
<tr>
<td>ECFV (ml/m² BSA)</td>
<td>9,500</td>
<td>9,879</td>
</tr>
<tr>
<td>NaE (ml/m² BSA)</td>
<td>1,286</td>
<td>1,375</td>
</tr>
</tbody>
</table>

Values are from the three patients from the present study and control subjects from References 6 and 7. TBV, total blood volume; BSA, body surface area; PV, plasma volume; IFV, interstitial fluid volume; ECFV, extracellular fluid volume; NaE, exchangeable sodium.
range observed in normal subjects infused with varying volumes of 0.9% saline.13-15 The present ANP data, although limited in number, suggest an adequate ANP response albeit a tendency to shift toward the upper normal limit during baseline conditions. Until now, little has been known about the implication of ANP and FHH. Plasma values have been reported normal to elevated in six patients, but all were on moderately restricted sodium diets.16 Take et al17 measured plasma ANP in three patients on a diet containing 85 mmol sodium; the values were also at the upper limit of the normal range. Gordon et al10 reported a definite plasma ANP response to saline infusion in one of three patients with FHH. An abnormal natriuretic response to ANP has also been documented in a 14-year-old boy.18 Further controlled studies will be necessary to determine whether ANP release or renal response is abnormal in the FHH syndrome.

Urinary PGE2, PGF2α, and 6-keto-PGF1α were lower and TXB2 was higher in our three patients as compared with control subjects studied in the same conditions. These excretion levels appear comparable to values reported in a subgroup of patients with essential hypertension and low renin profiling.19 Sanjad et al20 also reported low urinary PGE2 in one patient with FHH. They observed a 20-fold increase in PGE2 in the patient during treatment with furosemide with correction of hyperkalemia and hypertension, which led them to propose that renal hypoprostaglandinism might have a pathogenic role in the syndrome. Since salt restriction improved the biochemical abnormalities and the hypertension without elevating urinary PGE2 in this patient, hypoprostaglandinism does not appear to be the primary causal mechanism for this clinical entity. Furthermore, normal levels of prostaglandins have been documented in a 14-year-old boy,18 and urinary 6-keto-PGF1α was not decreased in such patients.17 Thus, the relation of PGs to the FHH syndrome remains unclear.

Our results are consistent with the concept that the hormonal regulation of body electrolytes is relatively normal in FHH and that the primary abnormality is probably related to defective mechanisms in tubular ion handling. Our results on electrolyte clearances and on the TTKG index suggest a defect in renal K+ secretion (channel defect, abnormal tubular avidity, partial resistance to mineralocorticoid activity, or decreased trans-tubular lumen negative potential). Schambelan et al21 reported a case of mineralocorticoid-resistant renal hyperkalemia whose renal potassium excretion increased normally when the distal delivery of sodium was increased with nonchloride anions. They proposed the attractive hypothesis of a distal nephron defect that would enhance the reabsorption rate for chloride relative to that of sodium ("chloride shunt"). This distal nephron abnormality would limit the sodium- and mineralocorticoid-dependent voltage driving force for K+ and hydrogen secretion, resulting in hyperkalemia and acidosis. Along the same line, Take et al27 showed, in patients of the same family, that the excretion of sodium and K+ was increased during an infusion of sodium bicarbonate and sodium sulfate, suggesting that the tubular reabsorption of sodium and chloride was abnormal and might be the basis for the subnormal excretion of K+. However, the fact that the hyperkalemic acidosis can be corrected in some patients by lowering K+ level to normal by polystyrene sodium sulfonate administration22 is difficult to explain only by the chloride shunt hypothesis as is the response to mineralocorticoid re-

| TABLE 4. Urinary Prostaglandin E2, Prostaglandin F2α, 6-Ketoprostaglandin F1α, and Thromboxane B2 Excretion in the Three Patients and in Control Subjects |
|---------------------------------|--------|--------|--------|
| Urinary prostanoids            | Patients | Normal values (±SEM) |
|                                | 1 (F)  | 2 (M)  | 3 (F)  |
| PGE2 (ng/day)                  | 103    | 186    | 105    |
| PGF2α (ng/day)                 | 126    | 308    | 137    |
| 6-keto-PGF1α (ng/day)          | 65     | 155    | 97     |
| TXB2 (ng/day)                  | 144    | 160    | 65     |
| Values for control subjects are from References 9 and 10. PG, prostaglandin; TX, thromboxane. |

| TABLE 5. Renal Function and Electrolyte Excretion Rate During Volume Expansion (Water Load) in Patients 1 and 3 |
|---------------------------------|--------|--------|
| Renal function and urinary electrolytes | Patients | Normal values (±SEM) |
| CN (ml/min/1.73 sq. m)          | 105    | 95     | 108±5  |
| CαM (ml/min/1.73 sq. m)         | 499    | 468    | 536±26 |
| RVR (mm Hg/ml/min)              | 0.23   | 0.20   | 0.16±0.01 |
| CCl (ml/min)                    | 1.1    | 1.0    | 1.3±0.2 |
| Ck (ml/min)                     | 7.5    | 8.0    | 23±3   |
| DFCR (%)                        | 91     | 89     | 88±1.6 |

Cn, inulin clearance; CαM, p-aminohippurate clearance; RVR, renal vascular resistance; CCl, chloride clearance; Ck, potassium clearance; DFCR, distal fractional chloride reabsorption.
ported herein and by others. This raises the possible existence of subgroups or pathophysiological variants within this clinical entity.

Pressure hyperresponsiveness to angiotensin II, chronically suppressed renin levels, and hypertension that is sensitive to salt restriction are all consistent with the phenomenon of sodium/volume overload. Total blood volume, plasma volume, extracellular fluid volume, and exchangeable sodium have been measured in our three patients under strictly controlled dietary conditions. Overall, the results showed that extracellular volumes were subnormal in one patient and were normal to increased in two patients. This interesting finding is in keeping with previous observations that body fluid volumes are not consistently elevated in mineralocorticoid hypertension. During long-standing mineralocorticoid hypertension peripheral vascular resistance is increased. The initiating events that lead to the rise in peripheral vascular resistance are most likely due to the early plasma volume and extracellular fluid volume expansion. The initiating mechanisms of mineralocorticoid hypertension are probably best explained by the studies on the withdrawal of spironolactone treatment from patients with a benign aldosterone-secreting adenoma. Initially, sodium and water retention occurs with a gain in body weight. A similar evolution was observed in patient 1 after discontinuation of hydrochlorothiazide: she gained 1.9 kg, the hematocrit fell from 36.6% to 33.5%, and the plasma renin activity was suppressed while her blood pressure (systolic) began to rise (Table 6). Sustained hypertension probably appears as a late event together with the elevation of peripheral vascular resistance, which may be partly related to increased sensitivity of the vascular tree to circulating vasopressor agents and autoregulation mechanisms. The subsequent rise in peripheral vascular resistance and blood pressure in the presence of normal glomerular filtration rate would result in reduced vascular compliance and increased sodium excretion through the pressure–natriuresis phenomenon. This sequence of events probably accounts for the absence of a net increase in body fluid volumes observed in our patients. During this hemodynamic adaptation process, renal vascular resistance is subsequently increased (Table 5), which dampens the phenomenon of pressure–natriuresis and alters the volume–pressure relation: blood pressure is then relatively too high for the associated circulating volumes. This may explain the low renin status and also the ANP values that are at the upper normal limit in our patients despite body fluid volumes that were not distinctly elevated. However, one should keep in mind that the assessment of body fluid compartments is difficult and is also hampered by methodological limitations.

The effect of mineralocorticoid administration was evaluated in the three patients. A single dose of 9α-fluorohydrocortisone induced an 82% rise in the TTKG in patient 3, indicating tubular responsiveness to mineralocorticoid in this patient. Normokalemia could then possibly be achieved if the distal tubular secretion of K+ was enhanced for a period long enough to induce a decrease in K+ stores. In keeping with this idea, a longer period (1 week) of administration of 9α-fluorohydrocortisone corrected the hyperkalemia in patient 1, whereas a shorter period of treatment was inefficacious in patient 2.

As previously reported, all biochemical abnormalities and the hypertension were completely corrected in two of our patients who received hydrochlorothiazide. There is evidence that this diuretic inhibits the reabsorption of sodium chloride by an electroneutral sodium chloride cotransporter in the distal tubule. It is tempting to speculate that the primary tubular defect in electrolyte handling in FHH is located at this particular segment of the nephron.

In conclusion, the syndrome of FHH appears to be related to an inherited tubular defect in K+ handling with relatively normal endocrine sodium regulatory mechanisms. The body fluid compartment dynamics resemble subgroups of mineralocorticoid excess and low renin essential hypertension.

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