Urinary Kallikrein Activity and Renal Vascular Resistance in the Antihypertensive Response to Thiazide Diuretics

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SUMMARY To evaluate the mechanism of chronic thiazide diuretic action in hypertension, we treated 19 essential hypertensive white men for 1-month periods on placebo alone and hydrochlorothiazide alone. During therapy, mean arterial pressure (MAP) fell, but radioisotopically determined intravascular volume remained unchanged, suggesting other mechanisms of thiazide action upon blood pressure. In the renal circulation, thiazides did not change renal plasma flow or glomerular filtration rate, but renovascular resistance was diminished, probably at the afferent arteriole. Concomitant with the decline in blood pressure and renovascular resistance, urinary kallikrein excretion increased, from subnormal (hypertensive) levels back into the normal range. The kallikrein increase did not correlate with changes in plasma aldosterone. In addition, patients with blood pressure responses (reduction ≥ 10%) to thiazides (n = 12) had greater increases in kallikrein excretion than those without such a blood pressure decrement (n = 7), suggesting a role for renal kallikrein in the hypotensive response to thiazide diuretics. (Hypertension 3: 139-147, 1981)

KEY WORDS • kallikrein • thiazide diuretics • renal blood flow • renal vascular resistance • hypertension • plasma volume

BENZOTHIAZIDE diuretics have long been regarded as effective “first line” antihypertensive drugs, but their mode of action in lowering blood pressure remains in doubt, especially during chronic antihypertensive therapy. Proposed mechanisms for thiazide action in hypertension have included: 1) intravascular volume depletion secondary to its natriuretic action and 2) reduction in systemic vascular resistance by mechanisms as yet unspecified, with or without concomitant volume depletion, especially during chronic administration.

With these ideas in mind, we decided to re-examine the mechanism of hydrochlorothiazide antihypertensive action in essential hypertensive humans. Our investigation focused on intravascular volume, the renal vascular bed (as a likely determinant of thiazide hypotensive effect), and the kallikrein-kinin system as a possible mediator of changes in renal and systemic vascular resistance. One proposed index of the renal kallikrein-kinin system is the 24-hour urinary excretion of the enzyme kallikrein (kininogen; E.C. 3.4.21.8), a tissue kallikrein derived from kidney, having the ability to generate vasoactive peptides called kinins. This enzyme system may be important in blood pressure regulation and the determination of renal blood flow, and some evidence suggests it may influence systemic kinin production, although this remains controversial.

Materials and Methods

Patients

We studied 19 white men with essential hypertension. They were patients who had exhibited supine mean arterial pressures (MAP; diastolic pressure plus 1/3 pulse pressure) greater than 105 mm Hg in the outpatient clinic. The mean age was 50.1 ± 2.6 years. Hypertensives were screened for known secondary causes of hypertension with determination of the blood urea nitrogen concentration (BUN) and serum concentrations of sodium, potassium, chloride, and bicarbonate; a hemogram, electrocardiogram, and in-
travenous urogram and roentgenogram of the chest and a 24-hour urinary collection for excretion of catecholamines, metanephrines, vanillylmandelic acid, and 17 hydroxycorticosteroids were also obtained. All subjects were found to be essential hypertensives. Hypertensive patients' medications were discontinued for at least 1 month prior to study. In addition, all patients with evidence of end organ damage from hypertension (e.g., congestive heart failure, myocardial infarction, nephrosclerosis, stroke) were excluded.

To establish a normal range for urinary kallikrein excretion, 13 healthy white male normotensives were also studied. They were paid volunteers on no medication, and matched to the hypertensives for sex (male), race (white), and dietary sodium intake (unrestricted; 149 ± 11 mEq/day for the normotensives versus 162 ± 20 mEq/day for hypertensives on placebo, p > 0.1, ns). The mean age of the normotensives was 36.9 ± 3.2 years, lower than that of the hypertensives (50.1 ± 2.6 years, p < 0.01). However, we have shown previously that the depression of urinary kallikrein excretion seen in essential hypertension is independent of age.13

Every subject gave informed written consent, and the Committee on Human Experimentation of the University of California, San Diego, approved the protocol.

Procedures

In randomized order, the patients were placed either on placebo for 1 month or hydrochlorothiazide orally for 1 month, at a dose individually titrated until blood pressure normalized or a maximum dose of 100 mg/day was reached. The median dose was 50 mg/day with a mean ± SEM of 56.6 ± 4.6 mg/day and a range of 25–100 mg/day. No other medications were utilized, and the diet was unrestricted in fluid and salt. The study was performed in crossover fashion; hence, all patients received both placebo and hydrochlorothiazide, and acted as their own controls. Because of the lengthy placebo period (1 month), no "washout" period was deemed necessary between phases of the study.

At the end of each 1-month study period (both placebo and drug), patients were admitted to the Diagnostic and Treatment Unit of the San Diego Veterans Administration Medical Center for a 2-day protocol. During the admission, each patient was on a diet unrestricted in sodium intake (> 100 mEq/24 hrs), which contained approximately 80 mEq of potassium. Multiple measurements of blood pressure were done in the supine position upon admission, during both placebo and hydrochlorothiazide treatment phases, with a manual sphygmomanometer. These values were averaged and the mean arterial pressure (MAP) was calculated. This MAP value as well as both systolic and diastolic blood pressure values were used for further statistical analysis. The MAP was used as a criterion for degree of response to therapy (see below). Diastolic blood pressure was taken as phase 5 Korotkoff sound (disappearance).

On Day 1 of each admission, a 24-hour urine collection was begun for the measurement of volume, sodium, potassium, chloride, and kallikrein activity. During collection, urine was kept refrigerated at 4°C, and at the end of 24 hours, the volume was measured and an aliquot frozen at −30°C for later analysis.

In the morning of Day 2, blood was obtained for determination of BUN, serum creatinine, serum electrolytes, hemogram, supine and upright plasma renin activity (SPRA, UPRA), and plasma aldosterone concentration. Renal plasma flow was measured using the method of constant infusion of para-aminohippurate (PAH) (13 patients) without urine collection.17 Whole blood volume was then measured in the supine position.

The 13 normotensive white males underwent hospitalization and various measurements exactly as described above, except that they were studied only once and received neither placebo nor hydrochlorothiazide. We report here only these patients' urinary kallikrein activities for purposes of establishing a comparative norm for urinary kallikrein excretion in white normotensive males on unrestricted sodium diet. The other parameters of these 13 patients have been reported by us previously.18

Chemical Assays

Routine chemistries were performed in the clinical laboratory of the San Diego Veterans Administration Hospital. Blood for renin and aldosterone determination was drawn into chilled EDTA tubes which were kept on ice until the samples could be centrifuged and the plasma frozen at −30°C. The PRA was determined by the radioimmunoassay method of Haber et al.,18 with reproducibility in our laboratory as previously described.19 Results are expressed as nanograms of angiotensin I generated per milliliter of plasma per hour (ng A1/ml/hr). Plasma aldosterone concentration was determined by radioimmunoassay utilizing "H-aldosterone as described by Sampson et al.,19 utilizing reagents purchased from Diagnostic Products Corporation, Los Angeles, California. Results are expressed as pg/ml.

Urinary kallikrein activity was measured for p-tosyl arginine methyl ester hydrolysis using the radiochemical method of Beaven et al.20 and Margolius et al.21 under our conditions for the assay, pH 8.5 and 37°C.21 with a purified22 human internal kallikrein standard for recovery. Results are expressed as esrature units (EU) per 24 hours. In separate experiments, hydrochlorothiazide at concentrations up to 100 μg/ml urine did not affect our assay.

Whole blood volume was determined using both 51Cr tagged autologous erythrocytes for red cell mass, and I125 labelled albumin for plasma volume. The isotopes were injected intravenously, and blood was collected at 10 and 20 minutes for counting of whole blood and plasma samples in the Volmetron apparatus.
Statistics
All results are expressed as the mean value ± the standard error of the mean (± SEM). Paired and (where appropriate) unpaired two-tailed Student’s t tests and linear least squares correlation coefficients were performed with standard techniques.24 The null hypothesis was rejected for \( p \) values of 0.05 or less.

Results
Systemic and Renal Hemodynamic Parameters
Changes in these parameters during hydrochlorothiazide therapy are shown in table 1. The MAP fell significantly (\( p > 0.01 \)) in the total treatment group vs the placebo group, from 106.7 ± 2.7 mm Hg down to 92.4 ± 2.0 mm Hg. The blood pressure decline was also significant for both systolic pressure and diastolic pressure (from 140.0 ± 3.4/90.0 ± 2.6 down to 120.7 ± 3.0/78.1 ± 1.9 mm Hg, both with \( p < 0.01 \)). Also of note was a significant decline in systolic (from 167.5 ± 4.3 down to 140.0 ± 3.4 mm Hg, \( p < 0.01 \)), diastolic (from 108.4 ± 2.6 down to 90.0 ± 2.6 mm Hg, \( p < 0.01 \)), and mean (from 128.1 ± 2.8 down to 106.7 ± 2.7 mm Hg, \( p < 0.01 \)) arterial pressures, going from outpatient clinic values before treatment to placebo phase, underscoring the necessity for a placebo period as an appropriate control.

There were, however, no associated changes in whole blood volume or plasma volume (table 1). Body weight declined slightly from 87.2 ± 3.0 kg down to 86.4 ± 3.3 kg (\( p = 0.05 \)).

Evaluation of renal hemodynamic parameters revealed no significant changes in creatinine clearance, PAH clearance, renal blood flow, or renal filtration fraction (table 1). Renal blood flow was calculated from PAH clearance and hematocrit; renal filtration fraction was calculated from the quotient of creatinine clearance/PAH clearance.

Renal vascular resistance (RVR), calculated from simultaneous repeated measurements of MAP and renal blood flow,24 declined significantly (\( p = 0.03 \)) on thiazide therapy, from 7815 ± 728 to 6827 ± 582 dyne·sec·cm⁻².

Biochemical Parameters
Hydrochlorothiazide effects upon the biochemical parameters studied are shown in table 2. The 24-hour urinary kallikrein excretion (table 2, fig. 1) was significantly (\( p < 0.025 \)) depressed in the placebo-treated essential hypertensives, when compared to a group of 13 normotensive controls previously reported from our laboratory12 and matched for sex (male), race (white), and dietary sodium intake (unrestricted, > 100 mEq/24 hrs). Thiazide treatment, however, significantly (\( p = 0.03 \)) elevated kallikrein excretion.

| TABLE 1. Systemic and Renal Hemodynamic Parameters (Before and After Hydrochlorothiazide Treatment) |
|-------------------------------------------------|----------------|----------------|
| Measurement | Placebo | Hydrochlorothiazide | \( p \) |
| Blood pressure (mm Hg) | | | |
| Systolic | 140.0 | 120.7 | < 0.01 |
| | ± 3.4 | ± 3.0 | |
| Diastolic | 90.0 | 78.1 | < 0.01 |
| | ± 2.6 | ± 1.9 | |
| Mean | 106.7 | 92.4 | < 0.01 |
| | ± 2.7 | ± 2.0 | |
| Blood volume (ml) | 5318 | 5578 | > 0.1 (ns) |
| | ± 310 | ± 352 | |
| Blood volume body surface area (ml/m²) | 2564 | 2792 | > 0.1 (ns) |
| | ± 138 | ± 174 | |
| Plasma volume (ml) | 2812 | 3013 | > 0.1 (ns) |
| | ± 162 | ± 212 | |
| Plasma volume body surface area (ml/m²) | 1350 | 1403 | > 0.1 (ns) |
| | ± 72 | ± 83 | |
| Weight (kg) | 87.2 | 86.4 | = 0.05 (ns) |
| | ± 3.0 | ± 3.3 | |
| Creatinine clearance (ml/min) | 105.3 | 107.7 | > 0.1 (ns) |
| | ± 8.4 | ± 8.7 | |
| PAH clearance (ml/min) | 597 | 621 | > 0.1 (ns) |
| | ± 43 | ± 56 | |
| Filtration fraction | 0.20 | 0.19 | > 0.1 (ns) |
| | ± 0.02 | ± 0.02 | |
| Renal blood flow (ml/min) | 1093 | 1119 | > 0.1 (ns) |
| | ± 90 | ± 104 | |
| Renal vascular resistance (dyne · sec · cm⁻²) | 7815 | 6827 | = 0.03 |
| | ± 728 | ± 582 | |
TABLE 2. Biochemical Parameters (Before and After Hydrochlorothiazide Treatment)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Placebo</th>
<th>Hydrochlorothiazide</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary kallikrein activity (EU/24 hrs)</td>
<td>8.9 ± 2.1</td>
<td>17.6 ± 4.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Supine plasma renin activity (ng A/(l)/ml/hr)</td>
<td>0.43 ± 0.08</td>
<td>1.34 ± 0.17</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Upright plasma renin activity (ng A/(l)/ml/hr)</td>
<td>1.59 ± 0.42</td>
<td>3.36 ± 0.63</td>
<td>0.04</td>
</tr>
<tr>
<td>Supine plasma aldosterone (pg/ml)</td>
<td>48.3 ± 8.0</td>
<td>98.4 ± 19.0</td>
<td>0.07 (ns)</td>
</tr>
<tr>
<td>Upright plasma aldosterone (pg/ml)</td>
<td>126.4 ± 23.8</td>
<td>126.6 ± 28.9</td>
<td>&gt;0.1 (ns)</td>
</tr>
</tbody>
</table>

From 8.9 ± 2.1 to 17.6 ± 4.2 EU/24 hrs, back within the normal range. Change in kallikrein excretion did not correlate directly with change in mean arterial pressure (\(r = 0.1, p > 0.1, \text{ns}\)).

Both SPRA and UPRA increased during thiazide therapy (table 2), in the supine position from 0.43 ± 0.08 to 1.34 ng A/\(l\)/ml/hr (\(p < 0.01\)), and in the upright position from 1.59 ± 0.42 to 3.36 ng A/\(l\)/ml/hr (\(p = 0.04\)). These increases in supine and upright PRA occurred in the absence of changes in whole blood volume or plasma volume (table 1).

To examine whether the observed increase in kallikrein excretion could be accounted for by diuretic-induced increase in circulating mineralocorticoid concentrations in these patients, plasma aldosterone concentrations were measured in both the supine and upright positions. Plasma aldosterone did not significantly increase (table 2) when comparing placebo and thiazide in either the supine position (from 48.3 ± 8.0 to 98.4 ± 19.0 pg/ml, \(p = 0.07, \text{ns}\)) or the upright posture (126.4 ± 23.8 vs 126.6 ± 28.9 pg/ml, \(p > 0.1, \text{ns}\)). There was no correlation between change in supine plasma aldosterone concentration and the increase in kallikrein excretion (\(r = 0.33, p > 0.1, \text{ns}\)); nor did change in upright plasma aldosterone concentration correlate with change in kallikrein excretion (\(r = -0.43, p > 0.1, \text{ns}\)). Neither were there significant correlations between change in SPRA and change in supine plasma aldosterone (\(r = 0.54, p > 0.1, \text{ns}\)) or change in UPRA and change in upright plasma aldosterone (\(r = 0.48, p > 0.1, \text{ns}\)).

Clinical Chemistry Values

During thiazide treatment, there were no changes in blood urea nitrogen, serum creatinine, serum sodium, or hematocrit (table 3). There were, however, significant declines in serum chloride (from 103.3 ± 0.4 mEq/liter down to 99.8 ± 0.7 mEq/liter, \(p < 0.01\)) and serum potassium (from 4.1 ± 0.1 mEq/liter down to 3.8 ± 0.1 mEq/liter, \(p = 0.02\)), and a significant rise in serum bicarbonate (from 26.2 ± 0.6 to 28.2 ± 0.8 mEq/liter, \(p = 0.02\)). In addition, there were significant increases in the 24-hour urinary excretion of sodium (\(p = 0.03\)), potassium (\(p < 0.01\)), and chloride (\(p = 0.05\)), while 24-hour urinary volume and
24-hour urinary sodium/potassium ratio were unchanged (p > 0.1, ns). Change in kallikrein excretion did not correlate with changes in either sodium excretion (r = -0.24, p > 0.1, ns), potassium excretion (r = 0.11, p > 0.1, ns), or chloride excretion (r = -0.24, p > 0.1, ns).

**Degree of Response to Hydrochlorothiazide:**

**Involvement of Kallikrein**

Although the blood pressure decrement did not correlate directly with the increase in kallikrein excretion on thiazides (r = 0.1, p > 0.1, ns), we sought further evidence of kallikrein involvement by dividing the subjects into those with a MAP fall on therapy of ≥10% vs those who did not experience such a fall; 24 patients had a MAP fall of ≥10%, while seven did not. The 12 with a greater MAP fall had a significantly greater increase in kallikrein excretion than the seven others (12.9 ± 4.5 vs 1.4 ± 6.3 EU/24 hrs, p = 0.05; fig. 2). During placebo phase, the 12 with a greater MAP response could not be distinguished from the seven others with respect to age, weight, body surface area, blood volume, plasma volume, serum creatinine, creatinine clearance, 24-hour urinary sodium excretion, 24-hour urinary kallikrein excretion, supine or upright PRA, or supine or upright plasma aldosterone concentration (all p > 0.1, ns).

While the 12 with a MAP response ≥10% had outpatient clinic blood pressures (systolic/diastolic/mean pressures of 166.7 ± 6.7/112.2 ± 2.5/129.8 ± 3.7 mm Hg) prior to entry that were similar to those of the other seven subjects (166.6 ± 6.0/105.1 ± 2.3/125.6 ± 3.2 mm Hg) prior to entry, there were differences between responders and nonresponders in placebo phase blood pressures. The 12 responders had systolic/diastolic/mean blood pressures on placebo of 143.9 ± 4.5/94.3 ± 2.6/110.8 ± 3.1 mm Hg vs values for the seven nonresponders of 133.1 ± 4.0/82.7 ± 4.4/99.6 mm Hg on placebo (p < 0.05 for diastolic and mean arterial pressures; p > 0.1, ns, for systolic arterial pressure). That is, many subjects had a substantial fall in blood pressure even on transition from outpatient clinic (on no treatment) to placebo phase. A relative lack of response to thiazides occurred in subjects with lower diastolic and mean blood pressures on placebo alone.

**Discussion**

Our patient group as a whole experienced a significant decline in MAP during thiazide therapy, which was unassociated with any decline in intravascular volume or plasma volume. The modest decline in weight (87.2 ± 3.0 kg down to 86.4 ± 3.3 kg, p = 0.005) with treatment, in the face of unchanged blood volume, has been observed previously.27 It might be argued that significant weight loss (0.8 kg), coupled with an elevation in plasma renin activity (table 2) and an increase in urinary sodium excretion (table 3), suggests intravascular volume contraction on thiazides, of a magnitude insufficient to be detected by our volume techniques. While this possibility must be admitted, other interpretations of the increase in PRA

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Placebo</th>
<th>Hydrochlorothiazide</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>15.9 ± 0.9</td>
<td>15.8 ± 1.1</td>
<td>&gt;0.1 (ns)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.10 ± 0.04</td>
<td>1.14 ± 0.03</td>
<td>&gt;0.1 (ns)</td>
</tr>
<tr>
<td>Serum sodium (mEq/liter)</td>
<td>140.6 ± 0.6</td>
<td>140.9 ± 0.5</td>
<td>&gt;1.0 (ns)</td>
</tr>
<tr>
<td>Serum potassium (mEq/liter)</td>
<td>4.1 ± 0.1</td>
<td>3.8 ± 0.1</td>
<td>=0.02</td>
</tr>
<tr>
<td>Serum chloride (mEq/liter)</td>
<td>103.3 ± 0.4</td>
<td>99.8 ± 0.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hematocrit (volume %)</td>
<td>44.2 ± 0.8</td>
<td>44.9 ± 0.7</td>
<td>&gt;0.1 (ns)</td>
</tr>
<tr>
<td>Urinary sodium excretion</td>
<td>162.4 ± 19.7</td>
<td>225.4 ± 22.9</td>
<td>=0.03</td>
</tr>
<tr>
<td>Urinary potassium excretion</td>
<td>69.1 ± 4.6</td>
<td>94.8 ± 6.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Urinary chloride excretion</td>
<td>126.6 ± 23.5</td>
<td>216.9 ± 30.5</td>
<td>=0.05</td>
</tr>
<tr>
<td>Urinary sodium/potassium ratio</td>
<td>2.34 ± 0.28</td>
<td>2.43 ± 0.26</td>
<td>&gt;0.1 (ns)</td>
</tr>
<tr>
<td>Urinary volume (ml/24 hrs)</td>
<td>1636 ± 180</td>
<td>1993 ± 202</td>
<td>&gt;0.1 (ns)</td>
</tr>
</tbody>
</table>
and urinary sodium excretion exist (discussed below) and an alternative explanation for the weight loss is the diuretic-induced fluid loss from the extravascular extracellular fluid compartments, as has been suggested previously. Although thiazide effects upon blood pressure have been much studied, these effects remain incompletely understood. After acute administration, it seems clear that the hypotensive action of these agents is associated with and may be explained by diminution in extracellular fluid volume, plasma volume, and exchangeable sodium. During chronic antihypertensive therapy, however, many studies show a gradual return of extracellular fluid volume and plasma volume toward (though not quite equalling) pretreatment values. Some studies report complete normalization of plasma volume and extracellular fluid volume and total body sodium during successful antihypertensive therapy with thiazides, although more recent studies have demonstrated persistent slight volume contraction. In our subjects, plasma volume and blood volume did not decline on thiazide vs placebo, regardless of whether placebo or thiazide was given first in the randomized study order. This suggests that there was no bias introduced by an "order effect." Although persistent volume reduction cannot be neglected as a thiazide antihypertensive mechanism, several lines of evidence suggest that other mechanisms besides intravascular volume depletion may play a role in chronic thiazide effects upon blood pressure, namely, diminished systemic vascular resistance after chronic thiazide treatment; or diminished vascular response to infused pressor agents; or antihypertensive superiority of hydrochlorothiazide to furosemide, a more potent natriuretic agent; or the potent antihypertensive effect of the benzothiadiazine derivative diazoxide, even in the face of its characteristic effects of renal sodium retention; or the early finding that the hypotensive effect of intravenous chlorothiazide precedes any natriuresis.

Our approach to thiazide effects on vascular resistance focused upon the renal circulation and on the renal kallikrein-kinin system. We chose the renal circulation because: 1) renal vascular resistance (RVR) is elevated in established essential hypertension, with some evidence indicating the site of increased resistance to be the afferent arteriole; and 2) since the renal circulation represents 25% of total cardiac output, alterations in renal vascular resistance alone may modulate systemic arterial pressure. Our study showed a significant (p = 0.03) decline in RVR on thiazide therapy, suggesting that the antihypertensive effect of the drug may be mediated, at least in part, by diminution in RVR. In addition, constancy of renal plasma flow, glomerular filtration rate, and filtration fraction during treatment point to the afferent arteriole as the site of diminished resistance, suggesting a thiazide-mediated correction of a fundamental renal hemodynamic defect in established essential hypertension.

It is of note that the decline in RVR occurred in spite of significant elevations in both supine (p < 0.01) and upright (p = 0.04) PRA. What mediated the effects of thiazide on the renal (and presumably systemic) circulation? To answer this question, we examined the urinary excretion of the enzyme kallikrein. This enzyme is derived from the distal renal tubule and can act on a substrate, kinogen, to yield peptide products called kinins. The principal kinin produced by renal kallikrein is lysyl-bradykinin, or kallidin. These kinins, in the local renal circulation, have vasodilatory and natriuretic properties. In man, some evidence suggests that the renal kallikrein-kinin system, as reflected by the 24-hour urinary excretion of the enzyme kallikrein, correlates with renal blood flow and may modulate renal vascular resistance. The reported decrease in
Our results pertain to patients treated with thiazide diuretics who are on unlimited dietary salt and water intake. It is conceivable that other antihypertensive mechanisms may come into play in thiazide-treated patients also subjected to dietary sodium restriction, but our data do not bear directly on such patients. For example, Lehto demonstrated mild persistent volume contraction during thiazide antihypertensive therapy in patients on dietary salt restriction of 6 g salt (approximately 100 mEq sodium) per day, while other studies in patients with unrestricted dietary sodium found normalization of plasma volume after long-term thiazides.

Our subjects on unrestricted salt intake excreted 162 ± 20 mEq sodium/day on placebo, suggesting a daily intake of approximately 4 g sodium or 10 g salt/day. This increased on therapy to 225 ± 23 mEq sodium/day (table 3), suggesting a daily intake of approximately 5 g sodium or 13 g salt/day. This phenomenon has been observed previously in thiazide-treated hypertensive animals and man even in the absence of measurable depletion of total body sodium assessed by exchangeable radiosodium. The unrestricted salt intake in our patients with enhanced salt ingestion following thiazides may, in part, explain the lack of plasma volume diminution in our study. In this regard, it should be restated that our study was not a balance study and that dietary sodium was unrestricted although the patients did not report any conscious increase in sodium appetite or intake. It is also conceivable that the increase in kallikrein, with its natriuretic capacity, may have played a role in the increased sodium excretion, although this relationship remains speculative. One must also consider the possibility that the observed kallikrein excretion changes are purely secondary to changes in systemic or renal hemodynamics, since a cause and effect relationship between augmentation of kallikrein excretion and the blood pressure decrement cannot be established on the basis of our data. Likewise, changes in electrolyte excretion may be at least partially consequent on systemic and renal hemodynamics, as well as direct tubular actions of thiazides.

We are unable to offer an immediate explanation for the observed increases in SPRA and UPRA (table 2) in our thiazide-treated patients, in the absence of diminution in intravascular volume. Other factors besides volume, however, modulate renin release. Possible explanations for the renin increases thus include: the fall in blood pressure itself, activating renal or systemic baroreceptors resulting in renin release; changes in sympathetic nervous function, independent of volume, during thiazide therapy, and perhaps the PRA increase may have been related to the fall in serum chloride during thiazide treatment (table 3), since some recent evidence indicates that chloride itself, as well as sodium, may be a modulator of renin release. An elevation of PRA during thiazide treatment, despite normalization of plasma volume, has also been reported by other investigators.

In summary, we have treated chronically a group of essential hypertensive men with hydrochlorothiazide...
and observed the expected fall in blood pressure. Intravascular volume was unchanged on thiazides, suggesting other mechanisms of thiazide action. Concomitant with the fall in blood pressure, we observed a decrease in RVR with an associated increase in urinary excretion of kallikrein, a substance with known vasodilatory and hemodynamic effects. Thus, the kallikrein-kinin system may be involved in the antihypertensive response to thiazide diuretics.

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