Renal Vein Renin and Juxtaglomerular Activity in Sodium-Depleted Subjects

By Horacio Ajzen, M.D., John L. Simmons, M.D., and James W. Woods, M.D.

In both man and experimental animals, a low sodium intake or sodium depletion increases aldosterone excretion and secretion. Observations on dogs with hyperaldosteronism secondary to chronic sodium depletion revealed that aldosterone secretion decreased markedly following nephrectomy. The large body of evidence showing that the aldosterone-stimulating hormone arises from the kidney and is renin has recently been summarized by Davis. Measurements show an elevated peripheral plasma level of renin in normal human subjects on a low sodium intake or depleted of sodium. Goormaghtigh's hypothesis that juxtaglomerular (JG) cells secrete renin has recently been strengthened by: correlations between renin content and degree of granulation of JG cells under different experimental conditions in rats, microdissection studies, and application of the fluorescent antibody technique. In a postmortem study, the degree of granulation of the juxtaglomerular apparatus was found to be correlated inversely with levels of plasma sodium present during the week prior to death.

Since correlation of renal vein renin and JG granularity in human subjects depleted of sodium has not been reported, the present study was designed to accomplish this.

Methods

Ten patients who required surgery for renal calculi or cysts were admitted to the hospital and were, as volunteers, used for special study. None had hypertension, nephrosis, cirrhosis of the liver or heart failure and all were normally hydrated. Age and sex are shown in table 1. Eight of ten patients required pyelolithotomy, one had a renal cyst excised (tumor could not be excluded), and one, in whom renal tumor was suspected, was found to have a normal kidney at exploration. Base line studies, in addition to history, physical examination, hemogram, and urinalysis, included serum electrolytes, fasting blood sugar, bromsulphalein test, endogenous creatinine clearance, blood urea nitrogen, urinary sodium, urinary potassium, and bio-assay for renin (Helmer aortic strip method) in peripheral venous blood. Five patients ate a regular diet and served as controls. Five patients ate a diet containing 87 mEq of sodium, 75 mEq of potassium with a 40 mEq potassium supplement and received 1 g of chlorothiazide daily for ten days. More drastic sodium restriction was not instituted because of the impending surgery. Urinary sodium and potassium were measured daily and serum electrolytes every third day.

Anesthesia was induced by thiopental sodium and nitrous oxide, and was maintained by means of nitrous oxide and halothane. At operation, samples of peripheral and renal venous blood were obtained for renin bio-assay. An open renal biopsy was taken and an intravenous infusion of physiological saline solution started immediately thereafter. Specimens were always taken shortly after exposure of the kidney and prior to renal surgery. No operative or postoperative complications occurred.

Renal biopsy material was fixed in Helley’s solution and stained with the Bowie stain for determination of the “juxtaglomerular index” (JGI). The JGI was determined without knowledge of the biopsy’s origin by one of the investigators (HA). Blood specimens for bio-assay were collected in heparinized syringes and immediately placed in ice. They were then centrifuged, the plasma removed, the latter acidified to pH 5.5 with 0.1 N hydrochloric acid, and frozen for subsequent bio-assay on the rabbit aortic strip.

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**TABLE 1**

Renal Vein Renin and Juxtaglomerular Index in Sodium-depleted and Control Subjects

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Age</th>
<th>Sex</th>
<th>Renin ng/ml*</th>
<th>Juxtaglomerular index</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>F</td>
<td>30</td>
<td>12.9</td>
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<tr>
<td>2</td>
<td>60</td>
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<td>3</td>
<td>53</td>
<td>F</td>
<td>37</td>
<td>25.4</td>
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<td>4</td>
<td>58</td>
<td>F</td>
<td>0</td>
<td>3.1</td>
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<td>5</td>
<td>51</td>
<td>F</td>
<td>0</td>
<td>4.0</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>F</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>38</td>
<td>M</td>
<td>0</td>
<td>2.2</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
<td>F</td>
<td>0</td>
<td>5.5</td>
</tr>
</tbody>
</table>

*Renin is reported as nanograms of angiotensin II formed per ml plasma.

Results of the renin bio-assays and JG index determinations are shown in table 1. Renal vein renin was significantly elevated in all of the subjects on the sodium-depletion regimen as compared with controls, none of whom had measurable renin (P < 0.01). Calculation of the JG index was not possible in one control subject due to an inadequate biopsy, but the difference between experimental and control subjects was also statistically significant (P < 0.02) with the former showing hypergranularity. An example (subject 2) of a bio-assay record is shown in figure 2. An example of a JG apparatus from a control individual (subject 4) is shown in figure 3 and from a sodium-depleted individual (subject 2) in figure 4. Tests for renin in peripheral...
TABLE 2

Data of Subjects Receiving Sodium-depletion Regimen

<table>
<thead>
<tr>
<th>Day of study</th>
<th>Urinary sodium excretion mEq/24 hrs</th>
<th>Body weight kg</th>
<th>Creatinine clearance ml/min</th>
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<tbody>
<tr>
<td></td>
<td>Subject number 1</td>
<td>Subject number 2</td>
<td>Subject number 3</td>
</tr>
<tr>
<td>Control day</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>1*</td>
<td>145.9</td>
<td>270.0</td>
<td>294.0</td>
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<tr>
<td>2</td>
<td>72.0</td>
<td>202.0</td>
<td>180.5</td>
</tr>
<tr>
<td>3</td>
<td>30.5</td>
<td>120.0</td>
<td>130.0</td>
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<tr>
<td>4</td>
<td>30.1</td>
<td>130.0</td>
<td>65.0</td>
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<tr>
<td>5</td>
<td>26.6</td>
<td>101.1</td>
<td>78.0</td>
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<td>77.8</td>
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<td>45.0</td>
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<tr>
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<td>14.0</td>
<td>60.1</td>
<td>50.6</td>
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<tr>
<td>10</td>
<td>14.2</td>
<td>63.0</td>
<td>47.8</td>
</tr>
</tbody>
</table>

*First day of regimen.

Section of kidney from subject number 4. Lower half of a glomerulus (Glom) occupies the upper left half of the photomicrograph. Glomerular capsule and arterial margin at top center. Arteriole (Art.) is at the upper right. Hypergranularity of IC, arteriole (Art.), and hyperplasia of IC apparatus are present. IC index = 25.3. (Booie stain.)

Section of kidney from subject number 2. The lower half of a glomerulus (Glom) in the upper center of this photomicrograph shows the glomerular margin, arteriole (Art.), and hypergranularity of IC. IC index = 31.4. (Booie stain.)
Discussion

The role of the juxtaglomerular apparatus as a volume receptor is supported by data from many laboratories and results described here parallel those previously reported from animal experiments. It is interesting that hyperplasia and hypergranularity of the JG apparatus and increased renal vein renin were present despite only moderate sodium depletion and also present in two subjects who showed net positive sodium balance at the time the specimens were obtained. Net positive sodium balance in subjects 1 and 9 may be more apparent than real, however, since the sodium in rejected food was not measured, and their intake of sodium may have been less than the 87 mEq allowed. Body weight measurements suggest that positive sodium balance did not occur. In this study, it is not possible to discriminate between reduced plasma volume and decreased total body sodium content as the continuing stimulus for renin secretion. Extrarenal sodium loss was not calculated during this study, but it is assumed that these figures would not have altered significantly the sodium balance data. Creatinine clearance decreased in three of the five patients (numbers 2,3,10). Reduced glomerular filtration with a decrease of filtered sodium is an additional explanation for decreased urinary excretion of sodium. However, net sodium balance was negative in the subjects whose creatinine clearance became less; whereas in the two with no significant change in creatinine clearance, sodium balance was positive.

As pointed out by several workers previously, comparison of results of renin bio-assay from different laboratories is made difficult by the large number of bio-assay methods in use, as well as by the lack of an international standard for angiotensin. The aortic strip method as used in our laboratory yields consistently a 4 to 4.5 cm contraction in response to 0.1 μg of synthetic angiotensin (1-L-asparaginyl-5-L-valyl angiotensin octapeptide-Ciba). In sensitive preparations, as little as 0.005 μg of angiotensin, added to 20 ml of modified Krebs solution in the muscle chamber, can be detected. Helmer has shown that the method is specific for renin.12 We have not been able to demonstrate renin in the peripheral venous plasma of patients with acute glomerulonephritis or coarctation of the aorta. We have found renin rarely in normal subjects and in those with benign essential hypertension, but we have found large amounts in the majority of patients with malignant hypertension. Renin has been found in the peripheral venous blood of only three of sixteen patients with hypertension associated with renal artery stenosis. It was present in the renal venous blood in five of these sixteen individuals. That increased renin activity in peripheral venous blood could be demonstrated in only two of five sodium-depleted subjects is in keeping with the sensitivity of the method as performed in our laboratory. Others5,6,7 using different bio-assay methods have consistently demonstrated renin in the peripheral blood of sodium-depleted subjects.

Summary

Ten patients requiring surgery for renal cysts or calculi and having no evidence of secondary hyperaldosteronism were divided, as volunteers for special study, into experimental and control groups. After base line studies, the experimental group was given a diet containing 87 mEq of sodium and 1.0 g of chlorothiazide daily for ten days. Control subjects ate a normal diet. At operation, samples of peripheral and renal venous blood were obtained for measurement of renin activity and renal biopsy was taken for determination of the juxtaglomerular index.

Increased renin in renal venous plasma and hypergranularity of the juxtaglomerular apparatus were found in sodium-depleted subjects but not in control subjects. These findings confirm results previously found in animals.
Acknowledgment

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References


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