RENIN RELEASE AND THE JUXTAGLOMERULAR APPARATUS IN CHRONIC RENAL FAILURE DUE TO GLOMERULONEPHRITIS

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Changes in renin release with decreasing renal function and juxtaglomerular apparatus in chronic renal failure due to glomerulonephritis were studied. Renin production was still remaining in the contracted kidneys and its release could be stimulated by various stimulations, although the macula densa didn’t seem to play an important role in renin release in the contracted kidneys.

It is well known that renin is produced in the juxtaglomerular apparatus in the kidney and its release is controlled by changes in the stretch of the renal afferent arterioles, alterations in the sodium load or concentration in the macula densa or sympathetic nerve activity. In chronic renal failure where the kidneys are severely contracted and there are considerably fewer intact nephrons, it is reasonable to suppose that the production and release of renin may change markedly. However, until now, no characteristic pattern of plasma renin levels has been found in chronic renal failure due to glomerulonephritis and there have been few studies on the site of renin production and how its release is controlled in human contracted kidneys.

In this study the site of renin production in chronic renal failure due to glomerulonephritis was studied functionally and morphologically, and the mechanism by which renin release is changed with decreasing renal function was examined.

**Key Words:**
- Contracted kidney
- Renin stimulation

**Materials and Methods**

**Patients:**
Eighty-two patients who had chronic glomerulonephritis or chronic renal failure due to glomerulonephritis with creatinine clearances between less than 5 and 118 ml/min, and twelve patients who died of uremia due to glomerulonephritis were studied. The diagnosis of glomerulonephritis was made on the past history, clinical signs and a routine laboratory test. Pathological findings are also used for the diagnosis of sixteen patients. Eleven of these patients were undergoing maintenance hemodialysis.

In general, patients were instructed to follow a normal diet with salt more than 8 g before this study, and medications such as diuretics and antihypertensive drugs were suspended for at least a week before the study. Patients on dialysis were on a diet with 50 g of protein and 6 g of salt.

**Study procedures:**
Experiment I. In order to find the relationship between plasma renin activity and renal function, the plasma renin activity and creatinine clearance were determined in eighty-two
patients with chronic glomerulonephritis or chronic renal failure due to glomerulonephritis. The plasma samples for renin assay were obtained from patients in the morning, in the sitting position. The determination of endogenous creatinine clearance was performed on the different day by collecting 1 hr-urine.

Experiment II. To evaluate the changes in renin release with decreasing renal function, the plasma renin activity was measured in the following 3 groups before and after a low sodium diet for 3 days and a furosemide injection: Group 1 contained six patients with creatinine clearances more than 70 ml/min whose blood pressures were less than 150 mmHg systolic and 90 mmHg diastolic. Group 2 consisted of ten patients with creatinine clearances between 15 ml/min and 69 ml/min. The blood pressures were higher than 150 mmHg systolic and 100 mmHg diastolic in five of the patients and below these values in the other five. Group 3 consisted of four patients with creatinine clearances below 14 ml/min, whose blood pressures were higher than 160 mmHg systolic and 100 mmHg diastolic.

After taking peripheral venous samples in the morning, in the sitting position, the patients were given a low sodium diet containing less than 40 mEq of sodium per day for 3 days. In the morning on fourth day of the sodium restriction, 20 mg of furosemide was administered intravenously and peripheral venous samples were drawn 4 hours later.

Experiment III. In this experiment, changes in plasma renin activity were studied before and after peritoneal dialysis and hemodialysis. In the patients who underwent peritoneal dialysis, renin samples were drawn before and after a 24 hour-peritoneal dialysis in which about 18-20 liters of dialyzing fluid were exchanged. In the patients who underwent hemodialysis, renin samples were drawn before and after an 8 hour-hemodialysis in which most patients had weight reductions between 1.5 and 2.0 kg.

Experiment IV. Morphological studies for the juxtaglomerular apparatus and renin determinations were made on twelve autopsy cases and one nephrectomized case.

Renin assay:
The plasma renin activity was measured by the procedure of Skinner. The normal value of plasma renin activity in our test in the morning, in the sitting position was 1.7 ± 0.4 ng/ml/hr.

Renal renin was extracted by the method of Haas et al. The extracted renin was incubated with renin substrate made by the method of Lever et al. in order to form angiotensin for the bioassay. The units of renin content were expressed as the rate of angiotensin formation in µg/g tissue/hr.

Observations on the juxtaglomerular apparatus:
The observations on the juxtaglomerular apparatus were done by the method developed in this laboratory. The renal cortex was fixed in Bouin's solution and embedded in epoxy resin. The sections were cut about 0.5 µ in thickness. After the epoxy resin was removed, the sections were stained by Bowie's technique.

The method of Hartroft with a minor modification was employed for the estimation of the juxtaglomerular cells and granules.

Tests of statistical significance were done by means of a paired "t" test.

RESULTS
The relationship between creatinine clearance and plasma renin activity:

Figure 1 shows the relation of plasma renin activity to creatinine clearance in patients at various stages of chronic glomerulonephritis or chronic renal failure due to glomerulonephritis. The determinations derived from the studies of the eighty-two patients are plotted. It is obvious that there is no evident correlation between renin activity and creatinine clearance.

Changes in renin release with decreasing renal function:

Figure 2 shows the changes in plasma renin activity before and after a low sodium diet for 3 days and a furosemide injection in the three groups of patients. During this stimulation the patients with creatinine clearance above 15 ml/min lost 0.4 kg to 2.0 kg of their weight (the average; 0.9 ± 0.4 kg).

After this stimulation, the plasma renin activity increased in all six patients with creatinine clearances over 70 ml/min and in nine of ten patients with creatinine clearances between 15 and 69 ml/min. The average rises of plasma renin activity were 0.9 ± 0.4 ng/ml/hr and 0.7 ± 0.3 ng/ml/hr, respectively. These rises in plasma renin activity were statistically significant (0.02 > p > 0.01). In patients with creatinine clearances below 14 ml/min in whom
### Table 1: Plasma Renin Activity, Renal Renin Content and Juxtaglomerular Index in Patients with Chronic Renal Failure Due to Glomerulonephritis

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Sex</th>
<th>Age</th>
<th>BP mmHg</th>
<th>NPN mg/100 ml</th>
<th>Cr Na mEq/L</th>
<th>K Edema</th>
<th>Kidney weight R L</th>
<th>Plasma renin ng/ml/hr</th>
<th>Renal renin ng/g tissue/hr</th>
<th>JGI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T.A.</td>
<td>M</td>
<td>32</td>
<td>200</td>
<td>140</td>
<td>265</td>
<td>32.2</td>
<td>139</td>
<td>5.2</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>S.A.</td>
<td>M</td>
<td>23</td>
<td>180</td>
<td>130</td>
<td>260</td>
<td>25.0</td>
<td>130</td>
<td>5.3</td>
<td>65</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>S.A.</td>
<td>M</td>
<td>34</td>
<td>190</td>
<td>100</td>
<td>259</td>
<td>34.4</td>
<td>121</td>
<td>5.4</td>
<td>68</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>H.H.</td>
<td>F</td>
<td>30</td>
<td>174</td>
<td>90</td>
<td>286</td>
<td>30.7</td>
<td>122</td>
<td>5.3</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>S.A.</td>
<td>M</td>
<td>72</td>
<td>170</td>
<td>100</td>
<td>189</td>
<td>7.4</td>
<td>136</td>
<td>3.9</td>
<td>±</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>M.I.</td>
<td>M</td>
<td>48</td>
<td>234</td>
<td>120</td>
<td>238</td>
<td>19.5</td>
<td>135</td>
<td>5.9</td>
<td>++</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>S.I.</td>
<td>F</td>
<td>33</td>
<td>170</td>
<td>106</td>
<td>85</td>
<td>16.2</td>
<td>124</td>
<td>5.4</td>
<td>+</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>N.S.</td>
<td>M</td>
<td>22</td>
<td>170</td>
<td>100</td>
<td>170</td>
<td>25.5</td>
<td>131</td>
<td>5.8</td>
<td>++</td>
<td>85</td>
</tr>
<tr>
<td>9</td>
<td>E.A.</td>
<td>M</td>
<td>32</td>
<td>200</td>
<td>120</td>
<td>264</td>
<td>20.1</td>
<td>145</td>
<td>6.8</td>
<td>±</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>Y.Y.</td>
<td>F</td>
<td>49</td>
<td>184</td>
<td>116</td>
<td>110</td>
<td>8.0</td>
<td>138</td>
<td>3.4</td>
<td>++</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td>M.U.</td>
<td>M</td>
<td>24</td>
<td>176</td>
<td>104</td>
<td>110</td>
<td>13.5</td>
<td>138</td>
<td>5.0</td>
<td>+</td>
<td>11</td>
</tr>
<tr>
<td>12</td>
<td>A.E.</td>
<td>F</td>
<td>49</td>
<td>170</td>
<td>100</td>
<td>85</td>
<td>14.5</td>
<td>134</td>
<td>5.6</td>
<td>+</td>
<td>70</td>
</tr>
<tr>
<td>13</td>
<td>M.K.</td>
<td>F</td>
<td>38</td>
<td>196</td>
<td>112</td>
<td>180</td>
<td>21.4</td>
<td>134</td>
<td>5.6</td>
<td>++</td>
<td>50</td>
</tr>
</tbody>
</table>

Mean ± S.D. 37±8 188±17* 113±14* 192±70* 20.6±8.5* 133±4 5.3±0.6 68±16* 73±14* 1.9±0.3 1.9±0.6 27.6±24.8*

CONTROL (8) 50±17 131±18 84±7 31±5 1.1±0.2 138±6 4.5±0.3 154±12 149±10 1.7±0.3 1.7±0.5 8.1±7.0

* Values differ statistically from the control level with p value less than 0.01

Values differ statistically from the control level with p value less than 0.05.
Fig. 1. Relationship between plasma renin activity and creatinine clearance in patients with various stages of chronic glomerulonephritis.

Fig. 2. Changes in plasma renin activity before and after a low sodium diet for three days and a furosemide injection upon renin release in patients with various stages of chronic glomerulonephritis.

Weight reduction was less than 0.6 kg (the average; 0.4 ± 0.3 kg) after the stimulation, only one of four patients responded slightly to this stimulation and the average plasma renin activity was 1.4 ± 0.5 ng/ml/hr before, and 1.5 ± 0.7 ng/ml/hr after the stimulation.

These results suggested that patients with chronic renal failure due to glomerulonephritis had greater difficulty in responding to this kind of stimulation with decreasing renal function. To examine the effects of stronger stimulations upon renin release in the patients with less than

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Fig.3. Changes in plasma renin activity before and after peritoneal dialysis or hemodialysis in patients with chronic renal failure due to glomerulonephritis.

5 ml/min of creatinine clearance, peritoneal dialysis and hemodialysis were employed.

As shown in Figure 3, plasma renin activity was stimulated in five of six patients after peritoneal dialysis and seven of eleven patients after hemodialysis. The average plasma renin activity increased from $2.2 \pm 0.5$ to $3.2 \pm 0.7$ ng/ml/hr in patients on peritoneal dialysis ($0.01 > p > 0.02$) and from $1.3 \pm 0.6$ to $1.9 \pm 0.7$ ng/ml/hr in patients on hemodialysis ($0.02 > p > 0.05$). The average plasma renin activity before hemodialysis was significantly lower than that of peritoneal dialysis. This difference in plasma renin activity seemed to be related to some extent to the term of the maintenance dialysis, because most patients on hemodialysis had been undergoing maintenance dialysis for 2 to 3 years.

Observations on the juxtaglomerular apparatus:

The juxtaglomerular apparatus was observed in twelve patients who died of chronic renal failure due to glomerulonephritis and one patient who underwent nephrectomy for transplantation. Table 1 summarizes the results of these thirteen patients.

In this table, controls consist of people aged 16 to 76 who died of accidents or various diseases unassociated with abnormalities of fluid and electrolyte balance or hypertension.

The kidneys of all the patients with chronic renal failure were markedly contracted, but renal renin content per gram tissue was not reduced.

The juxtaglomerular apparatus in those patients was quite different from that seen in the controls. Most glomeruli were hyalinized and pronounced interstitial fibrosis was seen in the contracted kidneys. It was difficult to identify the common elements of the juxtaglomerular apparatus. Especially, it seemed to be difficult to identify the macula densa in most of the juxtaglomerular apparatus. Juxtaglomerular granules, however, could be occasionally observed surrounding the destroyed or hyalinized glomeruli and in the epithelioid cells situated in the small arterioles apart from the glomerulus (Figure 4-6). The juxtaglomerular index which was calculated according to Hartroft and Hartroft's scale varied with each case, but the mean value of the group with chronic renal failure was higher than that of the controls ($0.02 > p > 0.05$). On the other hand, there was no relationship between the juxtaglomerular index and the height of blood pressure.
Fig. 4. The juxtaglomerular apparatus from the patient No. 13 shown in Table I. Note many granules in a part of the destroyed glomerulus (G) and surrounding it. × 1000.

Fig. 5. The juxtaglomerular apparatus from the patient with further advanced chronic renal failure due to glomerulonephritis (No. 11 in Table I). The glomerulus (G) is completely hyalinized but there are a few granules (JGG) surrounding this hyalinized glomerulus. We cannot identify the macula densa. × 1000.
DISCUSSION

It is well known that kidneys gradually contract and their functioning nephrons gradually decrease in numbers as chronic glomerulonephritis or chronic renal failure due to glomerulonephritis proceeds. It is reasonable to suppose that renin, which is formed in the juxtaglomerular apparatus in the kidney, also diminishes with decreasing renal function. However, it is reported that renin levels are not necessarily low in chronic renal failure.7-10

In this study it was found that there was no significant relationship between creatinine clearance and plasma renin activity at various stages of chronic glomerulonephritis. Furthermore, even patients at the terminal stage of chronic renal failure due to glomerulonephritis did not have significantly low levels of plasma renin activity and renal renin content per gram tissue, except for only a few patients on long term maintenance hemodialysis.

These findings were supported by morphological observation. In the contracted kidneys, we observed juxtaglomerular granules surrounding hyalinized glomeruli and in addition, as suggested by Faarup et al., we also found a few granules in the epithelioid cells in the muscular layer of the cortical small arterioles. In No. thirteen case, we observed juxtaglomerular granules in the epithelioid cells in the afferent arterioles in only 11 g of kidney, although the macula densa could not be identified in most nephrons. Therefore, it is certain that renin is still produced even in the contracted kidneys.

There seemed to be a slight discrepancy between JGI and renal renin content. This difference probably stems from the fact that different places were taken for observation of juxtaglomerular apparatus and determination of renal renin content, but we cannot rule out the possibility that non-specific granules were counted as JGI.

The other interesting problem concerning renin in chronic renal failure due to glomerulonephritis is how renin is released from the contracted kidneys. The current belief is that renin release in the normal kidney is controlled by a change of perfusion pressure in the afferent arteriole, the load of sodium on the macula densa or sympathetic nerve.

activity. So several factors which change the plasma volume or sodium excretion are thought to alter renin release. Sodium restriction and a furosemide injection employed in this study are very effective to stimulate renin release in normal subjects. In the patients with chronic glomerulonephritis, this stimulation was also effective to increase renin release. The stimulation, however, gradually became ineffective with decreasing renal function, and no significant changes were observed in plasma renin activity, body weight and urine volume before and after this stimulation in the patients with creatinine clearance below 14 ml/min. Therefore, effects of peritoneal dialysis and hemodialysis which were supposed to be more effective than sodium restriction and a furosemide inject in inducing changes in plasma volume were studied in patients with advanced chronic renal failure.

After an 8 hr-hemodialysis using a kill dialysis most patients lost between 1.5 and 2.0 kg of their body weight and showed significant increases in plasma renin activity as reported by other investigators. It is certain that renin release is stimulated in the patients with markedly contracted kidneys and even in the patients with non-functioning kidney if the plasma volume or water balance is significantly changed. However, different from the normal kidney, it is questionable whether the macula densa plays a role in renin release in the markedly contracted kidney, because a few patients with markedly contracted kidneys on hemodialysis had no urine and it was difficult to identify the macula densa in some of their kidneys.

Although it was demonstrated that renin production and release still occurred in the contracted kidneys, it is difficult to assess the physiological role of renin in the patients with such contracted kidneys. As suggested by recent studies from other laboratories our results may also suggest that renin is probably related to the maintenance of blood pressure and plasma volume in the patients with chronic renal failure due to glomerulonephritis. However, further studies on the relationship between the renin-angiotensin-aldosterone system and the changes of plasma volume, blood pressure and sodium metabolism will be necessary to conclude this problem.

REFERENCES


Renin Production in Chronic Renal Failure
