Relationship between Serum Renin Concentration, Renal Renin Content, and Juxtaglomerular Apparatus in Hypertensive Patients

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On a variety of 30 hypertensive patients and 3 controls, relationship between serum renin concentration, renal renin content, and juxtaglomerular apparatus (JGA) was studied. A highly significant correlation was found between serum renin concentration and renal renin content. The correlations between serum renin concentration and juxtaglomerular granulation index (JGI), and between renal renin content and JGI were also significant. The correlation coefficients, however, were significantly lower than that between serum renin and renal renin. Several factors including staining techniques may be related to this difference. From these results, it is concluded that renin levels are related to the changes in the JGA on a variety of hypertensive patients, although these relations are still problematic in a few cases.

The evidence that the production and release of renin is intimately linked to the JGA of the kidney has been obtained by various techniques, such as renin assays on extracts of different fragments of microdissected renal tissue1-3 and immunofluorescence4,5. Most of these works were done in animals. However, in man little information is available about the changes in the JGA and renin levels, perhaps because of technical difficulties. Recently we6 have introduced a method which clearly delineates the individual granule in JG cells in man. In the present studies, utilizing this method, we studied the relationship between the changes in the JGA and renin levels in hypertensive patients.

Materials and Methods

Thirty cases of a variety of hypertensive patients, ranging in age between 16 and 75 years, and three cases of normotensive patients selected as control, were used for this study. The kidneys of three cases were nephrectomy specimens and one was biopsy specimen, taken at operation. The remaining kidneys of twenty nine cases were taken at autopsy which came to autopsy less than 10 hours post mortem.

The hypertensive patients include: (a) 2 patients with renovascular hypertension; (b) a patient with primary aldosteronism; (c) a patient with pheochromocytoma; (d) 2 patients with malignant hypertension; (e) 2 patients with Kimmelstiel-Wilson syndrome; (f) 9 patients with chronic renal failure due to glomerulonephritis or gout; (g) 13 patients with essential hypertension who died of myocardial infarction or cerebral vascular accidents.

For measurements of serum renin concentration, blood specimens were drawn from the brachial or subclavian vein.

For measurement of renal renin content, and for observation of the JGA, approximately 2 g of renal cortex was used. One gram was used for measurement of renin content and remaining was used for observation of the JGA.

Serum renin concentration was measured by the method of Brown et al.9 with minor modification10. Renal renin content was measured by the method of Haas et al.11. These results were expressed in Goldblatt unit.

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Observation of JGA was done by the method which was previously developed in our laboratory. That is, renal tissues were fixed in Bouin solution and embedded in epoxy resin by the method of Luft et al. From each epon-embedded block forty to fifty sections 0.5–1.0 μm thick were cut in identifying the vascular pole of the glomerulus. After the epoxy resin was removed by the method of Mayor et al., the sections were stained by Bowie’s technique. The changes in the JGA were evaluated both by a method of evaluation based on their granule content which was reported by Hartroft and by counting JG cells per glomerulus.

Serum sodium and potassium were measured by flame photometry.

**RESULTS**

The data examined on all patients are summarized in Table I A), B), and the microscopic appearances of the JGA in several cases were shown in Fig.6–10. The averages of serum renin concentration and of renal renin content in controls were $5.2 \times 10^{-2}$ Goldblatt unit/L and $5.0 \times 10^{-3}$ Goldblatt unit/g of renal tissue, respectively. The averages of JGI and of JGCC/G (juxtaglomerular cell count per glomerulus) were 7.8 and 6.0, respectively.

In hypertensive patients, the averages of serum renin concentration and of renal renin content were $5.8 \pm 1.5 \times 10^{-2}$ and $6.5 \pm 1.4 \times 10^{-3}$, respectively. The averages of JGI, and of JGCC/G were $18.1 \pm 10.7$ and $8.6 \pm 2.0$, respectively.

In the patients with renovascular hypertension, serum renin concentration and renal renin content were markedly increased. However, the increase in JGI was slight, although JGCC/G showed the highest counts.

In the patient with primary aldosteronism, JGI and JGCC/G were significantly lower than the averages of JGI, and of JGCC/G, respectively. These low counts were accompanied by low renin levels.

In the patient with pheochromocytoma, JGI was 0 in spite of the normal level of serum renin concentration.

In the patients with malignant hypertension, serum renin concentration and renal renin content were both increased. JGI was high in the case 8 with low level of serum sodium, but in
### Summary of the data measured in all patients.

<table>
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<th>Case No.</th>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>BP</th>
<th>Serum Na</th>
<th>Serum K</th>
<th>Serum Renin (10^2)GU/L</th>
<th>Renal Renin (10^2)GU/g</th>
<th>JGI</th>
<th>JGCC/G</th>
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</table>

The case 9 with normal level of serum sodium, JGI was lower than the average of JGI in hypertensive patients.

In the patients with Kimmelstiel-Wilson syndrome, similarly to the results in malignant hypertension, in spite of increased levels of renin, JGI was not high in the case 10 with normal level of serum sodium.

In the patients with chronic renal failure, 6 of nine cases showed high counts of JGI, although renin levels were almost normal except two cases. Especially the case 14 showed the highest count of JGI in all examined hypertensive patients.

In the patients with essential hypertension, most of cases except the case 33 showed normal levels of serum renin concentration and renal renin content. The renin levels appeared to parallel with the changes in the JGI and JGCC/G. In the case 33 with essential hypertension, in which bilateral adrenalectomy had been done because of carcinoma of mammary gland and followed with chronic administration of corticosterone, increased levels of serum renin concentration and renal renin content were related to the changes in the JGI and JGCC/G.

### Relationship between serum renin concentration and renal renin content

The relationship between serum renin concentration and renal renin content in hypertensive patients were shown in Fig. 1. A highly significant correlation was found. \(r = 0.90, p < 0.001\)

### Relationship between serum renin concentration, JGI and JGCC/G

A significant correlation was found between serum renin concentration and JGI. \(r = 0.61, p < 0.01\) (Fig. 2) This correlation was higher than that between serum renin concentration and JGCC/G which was shown in Fig. 3. \(r = 0.48, 0.01 < p < 0.05\)

### Relationship between renal renin content, JGI and JGCC/G

The correlation coefficients between renal renin content and JGI, and between renal renin content and JGCC/G were 0.40 and 0.48, respectively. (Fig. 4, 5) These correlations were slightly significant, but were lower than those between serum renin concentration and JGI, and between serum renin concentration and JGCC/G.
Fig. 1. Correlation of serum renin concentration with renal renin content in hypertensive patients.

Fig. 2. Correlation of serum renin concentration with JGI.

Fig. 3. Correlation of serum renin concentration with JGCC/G.

Fig. 4. Correlation of renal renin content with JGI.

**DISCUSSION**

The technique used in the present study for observation on the JGA, demonstrated to be a easy and reliable method for obtaining a series of sections in which JG cells are sharply and clearly observed. As these sections are cut in identifying fields containing the vascular pole of the glomerulus by staining with methylene blue prior to

Fig. 5. Concentration of renal renin content with JGCC/G.

Fig. 6. Vascular pole of the glomerulus in the case 31 with essential hypertension. The glomerulus is shown at the upper part of the field. X1200

Fig. 7. Hypergranulated juxtaglomerular cells in the case 16 with chronic renal failure. The glomerulus is located at the upper part of the field. X1200

Fig. 8. Vascular pole of the glomerulus in the case 18 with chronic renal failure. Although the glomerulus and the vascular pole are destroyed and marked interstitial fibrosis is evidenced, juxtaglomerular granules are dispersed near the vascular pole. X1200

staining reactions of JG granules were similar to those in paraffine sections.

The changes in the JGA in a variety of hypertension observed by this technique, are, in general, in agreement with those described in the literature. For example, the significant cellular hyperplasia was observed in cases of renovascular hypertension and the moderate cellular hyperplasia was observed in cases of malignant hypertension and chronic renal failure. In addition, the counts of JGI were quite variable from 0 to 72.5 in agreement with the previous report done by KIHARA and the highest count was found in a case of chronic renal failure.

In all examined hypertensive patients, a sig-
significant correlation was found between JGI and serum renin concentration, and a slightly significant correlation was found between JGI and renal renin content. These correlation coefficients, however, were significantly lower than that between serum renin concentration and renal renin content. One of the reasons of this difference may be attributable to the staining procedure. Bowie's stain used in this study has been supposed to be a most useful stain for demonstrating specific granules in JG cells, but recently it was demonstrated that it does not discriminate between specific and nonspecific granules. This lack of selectivity may have some bearing on the problem of this difference. For instance, this fact is most evident in the case 26, in which the highest level of JGI was found, in spite of the slight increase in serum renin concentration.

On the other hand, in view of the opposite results which were found in a few cases with renovascular hypertension, malignant hypertension and Kimmelstiel-Wilson syndrome, there is the possibility that other factors also may be related to this difference.

In the past, Parker, who noted JG cell hyperplasia in human renal artery stenosis, not granules as in animals, supposed that renin, at the moment when it is being secreted from the JGA, does not stain. As a matter of fact, in view of our present results in a variety of hypertension, it may be supposed that JG granules undergo the changes of staining reaction under certain conditions.

From these studies, it can be concluded that some correlation is found between renin levels and the changes in the JGA in hypertensive patients, although the correlation is still problematic in a few cases.

In future to make clear the more precise role of the JGA in a variety of human hypertension, it is necessary to discuss the relationship between the more definite morphologic appearance of JGA observed by electron microscopy and renin levels.

**Summary**

Relationship between serum renin concentration, renal renin content, and juxtaglomerular apparatus (JGA) was studied in a variety of 30 hypertensive patients and controls.

Measurement for serum renin was done by the method of Brown et al., and measurement for renal renin was done by the method of Haas et al., JGA was observed by light microscopy in thin sections (0.5–1.0 μ) stained with Bowie's tech-
nique.

In hypertensive patients, significant correlations were found between serum renin and juxtaglomerular granulation index (JGI), and between renal renin and JGI. These correlation renin coefficients were, however, significantly lower than that between serum renin and renal renin. As the selectivity of Bowie’s stain is more limited than formerly believed, this factor may be related to the difference. However, in view of the results that JGI was not high in a few patients with increased renin levels, there is the possibility that the other factors may be related to this difference.

From these observations, it is concluded that renin levels are related to the changes in the JGA in a variety of hypertensive patients, although these relationships are still problematic in a few patients.

Acknowledgment

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REFERENCES