Studies on the Renal Humoral Mechanism of Chronic Experimental Hypertension

By ALBERTO C. TAQUINI, M.D., PEDRO BLAQUIER, M.D., AND ALBERTO C. TAQUINI, JR.

The renin content of the kidneys from chronic renal hypertensive dogs rises when the kidneys are transplanted to the neck of a normotensive nephrectomized animal. This elevation precedes and accompanies the elevation of the blood pressure of the recipient. This type of experiment does not allow one to draw conclusions concerning the humoral mechanism of chronic renal hypertension.

In previous investigations we have shown that the renin content of the blood and of the kidneys of patients with hypertension and of dogs with chronic hypertension due to renal ischemia is similar to that found in controls of both species. Clamping of the renal artery brings about a rapid increase within the first 20 minutes in the amount of renin in the kidney. This usually reaches a peak within 60 minutes after the initiation of the ischemia. If the renal ischemia is prolonged, the quantity of renin diminishes, even though the blood pressure remains elevated, and in a variable number of days decreases to normal. These experiments, which are in keeping with observations made in man and in experimental animals, suggest that renin may play some role during the acute phase of the hypertension in those cases in which there is an impairment of the renal circulation, but serious doubts arise as to its possible participation in chronic hypertension.

The grafting of a normal kidney to the neck of another normal dog does not result in the elevation of the blood pressure of the recipient. The grafting of a kidney taken from a dog with chronic hypertension due to renal ischemia into the neck of a normotensive dog brings about a rise in the arterial pressure of the recipient. These facts became the crucial experimental basis of the humoral theory of renal hypertension. A rapid rise in the renin content of the grafted kidney, which might be the consequence of interference with its circulation after transplantation, could explain the changes in pressure observed. If this were so, these experiments would not reflect the true state of affairs in chronic hypertension of renal origin.

To study this aspect of the problem further we repeated Houssay and Fasciolo’s experiments, measuring the amount of renin present in the kidney at the moment at which the ischemic kidney was removed from the hypertensive animal and after grafting it into the neck of the recipient.

Methods

Arterial hypertension was produced in 10 dogs according to the technic of Goldblatt, with bilateral renal ischemia in 5, and unilateral ischemia and nephrectomy of the remaining kidney in the other 5. After 4 to 65 days a biopsy of the ischemic kidney was obtained under anesthesia. The kidney was later removed and grafted into the neck of a normotensive dog following a technic similar to that used by Houssay and Fasciolo. As soon as the circulation to the grafted kidney was re-established, the blood pressure variations of the recipient were recorded. Arterial blood samples and biopsies of the grafted kidney were obtained in 20 minutes at a time when the blood pressure had usually reached a maximum. The renin content of the samples was determined according to Leloir’s technic as perfected in this laboratory. After destruction of hypertensionase, extracts from plasma or kidney biopsy samples were incubated with an excess of hyper-
RENUAL HUMORAL MECHANISM OF HYPERTENSION

TABLE 1.—Results of Renin Assays in Blood and Kidneys

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Duration of ischemia (days)</th>
<th>B.P. of hypertensive dog (mm. Hg)</th>
<th>Increase in B.P. of the receptor dog (mm. Hg)</th>
<th>Determination of renin: reduction in drops in the Läwen-Trendelenburg preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Before ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Std.*</td>
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<tr>
<td>34</td>
<td>4</td>
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<td>10</td>
<td>5</td>
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<tr>
<td>47</td>
<td>7</td>
<td>180</td>
<td>0</td>
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<td>22</td>
<td>185</td>
<td>0</td>
<td>5</td>
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<td>170</td>
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<tr>
<td>40</td>
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<td>20</td>
<td>10</td>
</tr>
<tr>
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<td>37</td>
<td>165</td>
<td>20</td>
<td>5</td>
</tr>
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<tr>
<td>LK</td>
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<td>170</td>
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<td>6</td>
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<tr>
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<td>10</td>
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<tr>
<td>38</td>
<td>63</td>
<td>165</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

*Std. is a measurement of the reduction in drops resulting from 0.0025 units of hypertensin.

Duration of the ischemia represents number of days after Goldblatt type of renal arterial constriction was instituted.

In situ kidney values were obtained from the donor dog’s kidney before nephrectomy and grafted kidney values are 20 minutes after transplantation. Blood samples were taken from the carotid artery of the receptor dog before and after graft of the ischemic kidney.

**tensinogen.** The hypertensin formed by the reaction was measured by its vasoconstrictor effect using the Läwen-Trendelenburg method of perfusing the hind leg preparation of a toad (*Bufo arenarum hensel*) with Hülse’s solution. The vasoconstrictor effect of an unknown solution was measured in terms of the maximum reduction in the number of drops perfused per minute as compared with the reduction following injection of a standard solution containing hypertensin. The preparation is sensitive to 0.001 units of hypertensin. The standard was 0.0025 units of hypertensin (1 unit of hypertensin is that amount which produces blood pressure elevation of 20 to 30 mm. Hg in the average 10 Kg. dog anesthetized with chloralose). The method permits the determination of very small amounts of renin, since a measurable amount of hypertensin (0.001 units) is formed by incubation of as little as 0.002 units of renin or approximately $2 \times 10^{-4}$ Goldblatt units.

**Results**

The results appear in table 1. The quantity of renin found in the blood and in the tissues obtained by renal cortical biopsy of the hypertensive dogs varied with respect to that found before the ischemia was produced according to the time elapsing between clamping the artery and taking the samples. In 1 animal (no. 34) with ischemia of 4 days duration, a marked increase of kidney renin was observed. In 2 (nos. 47, 53) in which the determinations were made after 7 and 10 days, respectively, the increase was only slight. In 8 of 9 dog kidneys undergoing ischemia of more than 22 days duration, the renin content was almost the same as the control values; in only 1 of these (no. 38) was the renin...
level found to be significantly higher after the ischemia than before.

The renin found in the kidney increased in all cases during the time the grafted organ was in the neck of the receptor. This increase in renin content of 25 to 100 per cent, although moderate, was significant by our method of testing, and appeared regularly in all the kidneys grafted, with the exception of the ischemic kidney of 4 days duration in which the amount of renin in the kidney before removal was very high and remained so during the period in which it was grafted.

The blood pressure of the recipient animal increased in 10 of 12 experiments from 10 to 60 mm. Hg. In 2 animals (nos. 47, 49) no change in blood pressure was observed although the renin content increased 25 per cent in the grafted kidney.

DISCUSSION

The results of these investigations show that the renin content of the kidney returned to normal in all those animals in which the ischemia was sufficiently prolonged. The increase found in 1 dog after 63 days of ischemia is difficult to explain. It may be that the rather prolonged surgical maneuvers necessary to obtain the biopsy gave rise to an ischemia sufficient to cause a transient increase in the renin content.

The remaining results are in keeping with our previous investigations. During the time in which the ischemic kidney from the hypertensive dog was grafted into the normotensive recipient, its renin content was increased. This increase can be explained by a reduction in renal blood flow due to 2 mechanisms: (a) the fact that the kidney must, perforce, be irrigated at the lower blood pressure of the normotensive recipient, and (b) that a reduction of the vascular lumen is brought about at the site of anastomosis of the renal artery to the carotid artery of the receptor.

As we have shown in earlier investigations, an acute, incomplete ischemia gives rise to a rapid increase in kidney renin content. Therefore, these grafting experiments, per se, do not allow a conclusion that the kidney of the animal with chronic hypertension liberates a substance, renin or other, that acts as a mediator for humoral hypertension.

These experiments, as well as our previous studies showing that the amount of renin in human and also in experimental animal kidneys increases during the initial stages of renal ischemia and later returns to normal, lead one to think that renin intervenes in the elevation of blood pressure under circumstances in which the renal blood flow is acutely reduced. When the factor determining the reduced flow is maintained, as happens in the animal with a clamp on the artery, other mechanisms are brought into play so as to maintain the blood pressure at sufficiently high levels to assure an efficient renal blood flow. Under these circumstances the renin content of both kidney and plasma returns to normal levels.

The results obtained in one of our experiments (fig. 1) may be significant in this re-
spect. The grafted kidney obtained from a dog with a mean blood pressure of 170 mm. Hg increased its renin content after being placed in the neck of a dog whose blood pressure was 140 mm. Hg. During the course of the experiment the blood pressure of this latter dog increased 60 mm., reaching 200 mm. Hg. Simultaneously the renin decreased in the grafted kidney to the level found previously when in situ in the donor.

Our results lend further support to the theory that renin is one of the regulating mechanisms in chronic arterial hypertension, but that it can by no means be considered the main agent directly responsible for the maintenance of the elevated blood pressure.

REFERENCES


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