Relation of Plasma Renin to Sodium Balance and Arterial Pressure in Experimental Renal Hypertension

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In 1934, Goldblatt and associates constricted the renal arteries in dogs and produced chronic arterial hypertension. Numerous attempts have been made to elucidate the mechanisms responsible for this sustained elevation of arterial pressure and many workers have suggested that there is increased activity of the renin-angiotensin system. In recent years, several studies have indicated that circulating renin and angiotensin II are elevated only in malignant experimental renal hypertension and during the first few days in dogs developing chronic renal hypertension. The possibility remains, however, that there is a small undetectable elevation in plasma renin and angiotensin II which is important in the pathogenesis of chronic renal hypertension.

In a previous study, it was demonstrated that a tenfold elevation in the renin content of the kidney was associated with marked hypersecretion of aldosterone in the dog with experimental malignant renal hypertension. In chronic benign renal hypertension, the renin content of the kidney was only doubled and the rate of aldosterone secretion was normal.

In the first part of the present study (experiment I), plasma renin was measured in dogs with malignant or chronic benign renal hypertension. In the second experiment, the further response of plasma renin to renal artery constriction was studied in dogs with an already high plasma renin and secondary hyperaldosteronism. This high plasma renin and hypersecretion of aldosterone were produced by constricting the thoracic inferior vena cava and by chronic sodium depletion. In a third experiment, the responses in plasma renin and arterial pressure to sodium depletion were observed in chronic renal hypertensive dogs. These experimental conditions provided an opportunity for evaluation of changes in plasma renin in relation to arterial pressure and sodium balance.

Methods

GENERAL METHODS

Only female mongrel dogs weighing 16 to 22 kg were used. They were kept in metabolism cages and fed once daily a synthetic diet which contained 60 mEq of sodium and 18 mEq of potassium, or 3 mEq or less of sodium and 40 mEq of potassium. If the malignant hypertensive animals regurgitated their food, a daily intake of 80 mEq of sodium was maintained by giving intravenous saline. Urinary and fecal electrolytes were determined by flame photometry.

Arterial pressure was measured once daily by...
direct puncture of the femoral artery in unanesthetized dogs that were trained to lie quietly on a table; a Statham transducer and a Sanborn recording system were used. Plasma was acidified, dialyzed and incubated in accordance with the procedure of Helmer; angiotensin II formed during incubation was quantified by rat pressor assay. Evidence for the validity, specificity and reproducibility of this method for plasma renin has been presented elsewhere and the limitations of available renin methods have been discussed by Pickens et al.

EXPERIMENT I
After five to eight days of control studies of plasma renin and arterial pressure in 18 unilaterally nephrectomized dogs, the renal artery was constricted with a Goldblatt clamp under sterile conditions and measurements were continued at one or two day intervals for five to sixteen days. Five of the dogs with chronic hypertension were studied again after fifty to sixty days of hypertension. In five additional animals, a Goldblatt clamp was placed but was not tightened.

EXPERIMENT IIA
Following left nephrectomy, the thoracic inferior vena cava was constricted in 16 dogs. After it was established that sodium retention was almost complete and large amounts of ascites were accumulating, control determinations of plasma renin, arterial pressure and sodium balance were made. Later, 7 to 14 days after caval constriction, the right renal artery was constricted with a Goldblatt clamp in an attempt to produce hypertension and measurements of arterial pressure, plasma renin and sodium balance were continued. In one of these animals, the renal artery clamp was removed after several weeks of study.

EXPERIMENT IIB
In another part of this experiment, the right renal artery was constricted in six sodium-depleted, left nephrectomized dogs. Sodium depletion was produced by means of a low sodium intake (less than 3 mEq/day of sodium) and by administration of 2 cc of meralluride (Mercuhydrin) intramuscularly daily for four days. Subsequently, sodium repletion was accomplished by changing dietary sodium intake from 3 to 60 mEq/day. Sodium depletion was produced again in one dog and the renal artery clamp was removed. Finally, this animal was sodium-repleted and, thus, returned to the original control state. Plasma renin, arterial pressure and sodium balance were measured.

EXPERIMENT III
Five unilaterally nephrectomized dogs with renal artery constriction and chronic benign hypertension were subjected to the sodium de-
pletion regimen outlined previously. Observations were made on plasma renin, arterial pressure and sodium balance.

**Results**

**EXPERIMENT I**

Hypertension developed in 11 of the 18 dogs subjected to renal artery constriction (fig. 1). Five of these 11 animals developed chronic benign hypertension whereas the other 6 dogs were lethargic, appeared acutely ill, had a rapid fulminating course and died within 14 days. In these latter animals arterial pressure increased progressively during the course of the experimental disease. In 5 control dogs a Goldblatt clamp was placed but not tightened; arterial pressure remained at the control level.

The peripheral plasma level of renin was slightly elevated for only the first three days in the chronic hypertensive dogs (fig. 2). After 50 to 60 days of chronic hypertension, the plasma renin level was normal. In the malignant hypertensive dogs, plasma renin was markedly elevated except for days 12 and 13; the highest values were recorded one to two days before death. On the twelfth and thirteenth day, plasma renin was only slightly elevated because measurements were limited to two of the dogs on these days and in these animals plasma renin was not markedly increased until after the fourteenth day. Plasma renin was within normal range throughout the course of the observations in the control series.

**EXPERIMENT IIA**

Four of the 16 dogs with thoracic caval constriction developed hypertension after renal artery constriction and in two of these four animals, malignant renal hypertension occurred. A further striking elevation in the already high plasma renin was observed in both malignant hypertensive dogs (figs. 3 and 4). The marked sodium retention and ascites formation continued unabated through-

![Graph showing plasma renin levels](image-url)
Experimental malignant renal hypertension secondary to constriction of the renal artery in a unilaterally nephrectomized dog with thoracic caval constriction, a high plasma renin, and ascites.

Malignant renal hypertension produced by renal artery constriction in a unilaterally nephrectomized dog with thoracic caval constriction, an elevated plasma renin, and ascites.

out the course of the experimental disease.

The other two dogs with a high plasma renin and aldosteronism secondary to caval constriction developed chronic benign hypertension following renal artery constriction. The results in the animal that was studied most completely are presented in fig. 5. Following constriction of the renal artery, a
PLASMA RENIN, SODIUM AND HYPERTENSION

PLASMA RENIN (FORMED ANGOTENSIN IN ng/cc)

MEAN ARTERIAL PRESSURE (mm Hg)

URINARY Na EXCRETION (mEq/DAY)

FIGURE 5

Production of chronic renal hypertension by constriction of the renal artery in a unilaterally nephrectomized dog with thoracic caval constriction and a high plasma renin. Plasma renin increased further only transiently and then remained at the high control level. Arterial pressure returned to normal following removal of the Goldblatt clamp but the high control level of plasma renin was sustained by thoracic caval constriction.

Further transient elevation in plasma renin occurred in association with the onset of hypertension. After four days, plasma renin returned to the upper limits of the control level while arterial pressure remained high. Removal of the renal artery clamp was followed by a return of blood pressure to normal while plasma renin remained elevated as a consequence of thoracic caval constriction. Sodium retention and ascites formation continued throughout the study. In the second dog, chronic hypertension developed without a further increase above the already high control level in plasma renin, and marked sodium retention was present (table 1).

EXPERIMENT III

Chronic hypertension developed in two of six dogs with a high plasma renin secondary to sodium depletion (fig. 6 and table 1). Plasma renin failed to increase above the high level characteristic of the sodium-depleted state. Extensive observations were made in one of these animals and the data are presented in figure 6. In this chronic hypertensive dog, sodium repletion was begun on the 24th day. Plasma renin returned to normal while arterial pressure remained high. Subsequent sodium depletion increased plasma renin but arterial pressure was unchanged. Removal of the renal artery clamp was followed by a reduction in arterial pressure while plasma renin remained high. Finally, plasma renin returned to the normal control level after sodium repletion.

EXPERIMENT II

Five chronic renal hypertensive dogs were subjected to the sodium depletion regimen and the results of a typical experiment are presented in figure 7. During control observations plasma renin was normal. A marked increase in plasma renin occurred during sodium depletion, but arterial pressure was unchanged. During sodium repletion, plasma renin returned to the normal control level while arterial pressure remained high.

Discussion

The peripheral plasma levels of renin, angiotensin II, or, simply, pressor material have been studied by many workers. Pritchard et al.2 assayed plasma for pressor activity during different phases of experimental renal hypertension in the dog. They found increased pressor material only during the first two weeks after renal artery constriction. Essentially the same result was obtained.
TABLE 1
Effects of Renal Artery Constriction in a Dog with Thoracic Caval Constriction and in a Dog with Sodium Depletion

<table>
<thead>
<tr>
<th>Dates</th>
<th>Arterial pressure</th>
<th>Plasma renin†</th>
<th>Renal sodium excretion*</th>
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</thead>
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<tr>
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<td>140</td>
<td>30</td>
<td>3.0</td>
</tr>
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<td>140</td>
<td>24</td>
<td>2.8</td>
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<tr>
<td>10/8/64</td>
<td>115</td>
<td>28</td>
<td>2.8</td>
</tr>
<tr>
<td>10/9/64</td>
<td>Renal artery constriction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/11/64</td>
<td>160</td>
<td>28</td>
<td>3.3</td>
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<tr>
<td>10/12/64</td>
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<td>16.4</td>
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<td>10/15/64</td>
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<td>150</td>
<td>22</td>
<td>1.7</td>
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</table>

<table>
<thead>
<tr>
<th>Dates</th>
<th>Arterial pressure</th>
<th>Plasma renin†</th>
<th>Renal sodium excretion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/19/64</td>
<td>125</td>
<td>11</td>
<td>48</td>
</tr>
<tr>
<td>11/25/64</td>
<td>135</td>
<td>10</td>
<td>57</td>
</tr>
<tr>
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<td>130</td>
<td>9</td>
<td>63</td>
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<td>11/28/64</td>
<td>Low sodium intake</td>
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<tr>
<td>11/29/64</td>
<td>plus 2 cc of</td>
<td></td>
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<tr>
<td>11/30/64</td>
<td>Mercuhydrin daily</td>
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<td></td>
</tr>
<tr>
<td>12/1/64</td>
<td>125</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>12/2/64</td>
<td>30</td>
<td>.4</td>
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<td>Renal artery constriction</td>
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<tr>
<td>12/5/64</td>
<td>160</td>
<td>25</td>
<td>2.9</td>
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<tr>
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<tr>
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<td>160</td>
<td>16</td>
<td>2.5</td>
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<tr>
<td>12/17/64</td>
<td>155</td>
<td>16</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>Died during removal of Goldblatt clamp</td>
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</tr>
</tbody>
</table>

*Sodium intake was 80 mEq/day except during sodium depletion when sodium intake was continued as 3 mEq/day or less.
†Nanograms angiotensin II formed per ml plasma.

FIGURE 6
Development of chronic renal hypertension following renal artery constriction in a sodium-depleted, left nephrectomized dog. Sodium repletion and subsequent sodium depletion decreased and increased plasma renin respectively but arterial pressure failed to change until the Goldblatt clamp was removed.

independently by Blaquier et al.3 and by Gross et al.4 in the rat; both groups used cross-circulation techniques to detect circulating pressor material. Increased amounts of angiotensin II were reported in blood from renal hypertensive animals during the early
Response of a chronic renal hypertensive dog to sodium depletion. Plasma renin increased but arterial pressure was unchanged.

period of benign hypertension by Gollan et al. and during malignant hypertension by Skeggs. More recently, Scornik and Paladini found an elevation in peripheral blood angiotensin II in dogs from 2 to 13 days following severe constriction of the renal artery in unilaterally nephrectomized animals or after severe bilateral renal artery stenosis. In their chronic hypertensive dogs, the angiotensin II blood level was consistently normal. In a recent preliminary communication, Smeby et al. reported a slight elevation in peripheral plasma angiotensin II in chronic hypertensive dogs.

The present observations on unilaterally nephrectomized renal hypertensive dogs revealed changes in activity of the renin-angiotensin system consistent with the observations on blood angiotensin II by Skeggs and associates and by Scornik and Paladini. Plasma renin was elevated during acute malignant renal hypertension or for only three days following renal artery constriction in dogs developing chronic hypertension. The observations of Scornik and Paladini revealed extremely high values for plasma nonprotein nitrogen in some of their dogs with severe renal artery stenosis and hyperangiotensinemia. It seems plausible to suggest that renal damage occurred in the present study and led to release of renin. Under these circumstances, the increase in plasma renin and the hyperaldosteronism observed previously might contribute to the hypertensive process but neither appears to be essential for chronic experimental renal hypertension in the dog. Renal tissue destruction is probably more important in the pathogenesis of increased renin release in experimental malignant disease than in human renal hypertension since patients with renal artery stenosis, severe hypertension and increased activity of the renin-angiotensin system are in a relatively more chronic state than are dogs with acute malignant hypertension.

The present observations on plasma renin in experimental renal hypertension agree with some of the most recent findings on plasma renin and plasma angiotensin II in patients with renal artery stenosis in that there is increased activity of the renin-angiotensin system only in severe renal hypertension.
Brown et al. found that plasma renin was elevated in only 7 of 11 patients with hypertension and retinopathy; 4 of the 7 cases had renal artery stenosis whereas the other 3 were classified as severe malignant hypertension. In a series of 7 patients with renal artery stenosis, Veyrat and associates found a high plasma renin in only 3 of the 7 patients and these three cases had severe hypertensive disease. Mulrow reported an elevation in plasma angiotensin II in only 2 of 20 cases with aortographic evidence of renal artery stenosis and with hypertension; one of these 2 patients had severe malignant hypertensive disease and the other had experienced renal damage secondary to trauma. Retinopathy was absent in all cases with a normal plasma angiotensin II.

In experiments II and III of the present study, marked changes in plasma renin were produced by maneuvers which altered sodium balance in renal hypertensive dogs. This experimental design permitted comparing the relation of plasma renin to sodium balance and to the hypertensive process. In dogs with thoracic caval constriction, a markedly positive sodium balance and an already high plasma renin, constriction of the renal artery increased plasma renin still more and produced acute malignant hypertension. This observation points to a possible pathogenic role of the extremely high plasma renin in the malignant hypertensive process. Also, increased aldosterone secretion occurs in experimental malignant renal hypertension but not in chronic benign hypertension. The results in two dogs that had chronic caval constriction and also developed chronic hypertension show that a further elevation in plasma renin level is not essential to the hypertensive process. It should be emphasized that the marked sodium retention and ascites formation in dogs with caval constriction were not detectably influenced by renal artery constriction and the development of arterial hypertension.

Similarly, in dogs depleted of sodium, renal artery constriction was followed by a chronic elevation of arterial pressure but plasma renin did not increase above the high control level. Subsequent alterations in sodium balance by depletion and repletion produced increases and decreases in plasma renin without altering the high blood pressure. In experiment III, sodium depletion of hypertensive dogs produced the usual increase in plasma renin observed in normotensive animals but arterial pressure was unchanged. Thus, there was an excellent correlation between sodium balance and plasma renin but neither bore any discernible relation to the level of arterial pressure in chronic hypertension. Similar findings have been reported very recently by Fisher et al. in renal hypertensive rats. The renal juxtaglomerular index, renal pressor activity and the width of the zona glomerulosa increased during sodium depletion, and decreased during ingestion of 1% saline, without an appreciable influence on the degree of arterial hypertension.

Summary

Measurements of plasma renin were made in unilaterally nephrectomized dogs with renal artery stenosis and hypertension. Plasma renin was elevated throughout the course of the malignant renal hypertensive disease, and during the first three days only in chronic hypertension. Hypertension was produced by renal artery constriction in unilaterally nephrectomized dogs with prior thoracic caval constriction and in sodium-depleted, left nephrectomized animals. Plasma renin was high in both dogs with caval constriction and sodium depletion before hypertension was added. When the renal artery was constricted, two of the dogs with thoracic caval constriction developed malignant hypertension and a further striking increase in plasma renin occurred. In two other dogs with caval constriction, chronic hypertension developed but plasma renin increased further in only one of the two animals; this occurred during the first four days of hypertension after which plasma renin returned to the high control level. The sodium-depleted dogs developed chronic hypertension following renal artery constriction but no further elevation in plasma renin.
Plasma Renin, Sodium and Hypertension

Renin occurred. Sodium repletion and sodium depletion of chronic hypertensive dogs produced marked changes in plasma renin without alterations in arterial pressure. The present findings revealed a striking correlation between plasma renin and sodium balance but neither bore any relation to the level of arterial pressure.

References
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