Role of the Adrenal Glands in the Development of Severe Hypertension

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ABSTRACT

It has been previously shown that angiotensin II is involved in the pathogenesis of severe hypertension resulting from ligation of the aorta between the origins of the renal arteries. To see if part of the effect of the angiotensin II was due to the stimulation of mineralocorticoid secretion, blood pressure and plasma renin activity were studied after ligation of the aorta in adrenalectomized rats receiving maintenance doses of steroids. Rats subjected to adrenalectomy and aortic coarctation developed hypertension as severe as that in rats with intact adrenal glands. Thus, an increase in the secretory rate of adrenal hormones is not a pathogenetic factor in the development of severe hypertension after aortic coarctation.

KEY WORDS malignant hypertension mineralocorticoids in hypertension adrenalectomy in hypertension

Carretero et al. (1) have shown that angiotensin II is involved in the pathogenesis of severe or accelerated hypertension resulting from ligation of the aorta between the origins of the renal arteries. They have found that, after the administration of antibody against angiotensin II, the mean blood pressure begins to decrease immediately; however, the maximum decrease is achieved only after 2 days. If the hypertension were due only to the direct vasoconstrictor effect of the angiotensin II, the maximum decrease in mean blood pressure would follow more quickly after the injection of antibody. Therefore, their results suggest that some other change produced by angiotensin is involved in the pathogenesis of the hypertension.

It is well known that the renin-angiotensin system is involved in the control of aldosterone secretion by the adrenal glomerulosa (2). Furthermore, the aldosterone secretion rate is elevated during the malignant phase of hypertension in man (3, 4). This phenomenon suggests that stimulation of mineralocorticoid secretion by angiotensin after aortic coarctation could be involved in the development of hypertension.

The purpose of the present study was to examine the role of the adrenal glands in the development of severe hypertension after ligation of the aorta. To this end, blood pressure and plasma renin activity were measured after ligation of the aorta in adrenalectomized rats receiving maintenance doses of deoxycorticosterone acetate (DOCA) and hydrocortisone.

Methods

All experiments were performed on albino male Sprague-Dawley rats weighing 200–250 g. They were fed laboratory chow and tap water ad libitum. Ether anesthesia was used for all surgical procedures. To produce hypertension, the aorta was ligated completely between the origins of the two renal arteries (5).

Blood pressure was monitored daily using a polyethylene catheter chronically inserted through the carotid artery into the aorta (6). Blood pressure was recorded by connecting the indwelling cannula to a Statham P23Gb pressure transducer which was, in turn, connected to a Sanborn 350-1100C carrier preamplifier. The rats were conscious and free to move about the cage, restrained only by a small harness. Sodium heparin was injected daily into the catheter to prevent clotting.

Surgical procedures were performed according to the following schedule. The rats were initially adrenalectomized or sham-adrenalectomized. Between 1 and 4 days later, the intra-arterial cannula was inserted and...
ADRENAL GLANDS IN SEVERE HYPERTENSION

aortic constriction or aortic constriction and left nephrectomy performed in a single operation. All adrenalectomized rats received a daily subcutaneous injection of 0.2 mg of DOCA plus 1.0 mg of hydrocortisone in a cottonseed oil suspension from the day of their adrenalectomy to 2 days after the second operation. The daily dose of hydrocortisone was then reduced to 0.5 mg, which was continued to the end of the experiment.

On the seventh day after aortic constriction, to measure plasma renin levels, 0.5 ml of blood was withdrawn through the carotid catheter in a syringe containing 0.02 ml of 3.8% ethylenediaminetetraacetate (EDTA). In one case, heart puncture was used. Plasma renin activity was measured by a modification of the method of Haber et al. (7). The modification consisted of adjusting the pH of the plasma to 7.4 with 4M Tris-HCl buffer, pH 7.3. Next, a nonequilibrium radioimmunoassay was done. The samples and the cold angiotensin I standards were incubated with antibody for 16 hours at 4°C; then 125I-angiotensin I was added, and the solution was incubated for an additional 6 hours. The free and the bound 125I-angiotensin I were then separated by dextran-coated charcoal. Dextran was used in a concentration ten times higher than that used by Haber et al. (7).

The following experimental groups were used: (1) sham-adrenalectomized rats subjected to aortic coarctation alone (13 rats), (2) sham-adrenalectomized rats subjected to aortic coarctation and excision of the ischemic kidney (left nephrectomy) (11 rats), (3) adrenalectomized rats subjected to aortic coarctation alone (11 rats), and (4) adrenalectomized rats subjected to aortic coarctation and left nephrectomy (11 rats).

All the results are expressed as means ± SE. The statistical significance of the difference in the blood pressure for the four groups was analyzed in three different ways. Analysis of variance and Scheffe's multiple comparison procedure (8) were both used. Blood pressure readings on the seventh day for the four experimental groups were compared by these two tests. In addition, readings over the 6 days were averaged for each group, and then the averages were compared by these two tests. Moreover, growth-curve analysis (9) was also used. An analysis of the response patterns of the six follow-up blood pressures among the four groups was done.

To determine the significance of the difference in the plasma renin values for each of the four groups, the natural logarithms of the mean and the SD were used for Scheffe's test to reduce heteroscedasticity (unequal variance).

A P value greater than 0.05 was considered not significant.

Results

Figure 1 shows the comparison of the mean blood pressure measured throughout the investigation for the four experimental groups. The rats subjected to adrenalectomy (receiving maintenance doses of steroids), aortic coarctation, and left nephrectomy (group 4) maintained relatively constant mean blood pressures of approximately 142 mm Hg. The rats subjected to sham-adrenalectomy, aortic coarctation, and left nephrectomy (group 2) also maintained approximately constant mean blood pressures of 132 mm Hg. There was no significant difference between these two groups with any of the three statistical tests.

The rats in group 3 (adrenalectomy, maintenance doses of steroids, aortic coarctation, and intact ischemic kidney) showed an increase in mean blood pressure, rising to 182 mm Hg by the seventh day. The rats in group 1 (sham-adrenalectomy, aortic coarctation, and intact ischemic kidney) exhibited a similar rise in blood pressure, reaching 184 mm Hg by the seventh day. There was no significant difference between these two groups with any of the three statistical tests.

However, using an analysis of variance followed by Scheffe's test, there was a significant difference between the two groups with the intact left kidney (groups 1 and 3) and the two groups with the left nephrectomy (groups 2 and 4) for both the seventh day and the average of the six blood pressures. The former groups had significantly higher mean blood pressures (P < 0.01) (Fig. 1). These results are consistent with the growth-curve analysis.

The results also agree with the renin values in Figure 2. Rats with an intact ischemic kidney showed far higher (more than tenfold) average plasma renin levels than did the rats subjected to left nephrectomy. When the plasma renin activity in the adrenalectomized rats lacking the ischemic kidney (group 4) was compared with that in the adrenalectomized rats with the ischemic kidney intact (group 3), the log difference was significant (P < 0.01). Similarly, when the plasma renin activity in the sham-adrenalectomized rats lacking the ischemic kidney (group 2) was compared with that in the sham-adrenalectomized rats with the ischemic kidney intact (group 1), the difference was significant (P < 0.01). There was no significant difference, however, in plasma renin activity when both groups of nephrectomized rats (groups 2 and 4) were compared or when both groups of nonnephrectomized rats (groups 1 and 3) were compared (P > 0.10).

Discussion

The results of this experiment indicate that an increase in the secretion of adrenocortical hormones is not necessary for the development of severe hypertension after aortic coarctation. As can be...
seen in Figure 1, adrenalectomized rats with aortic coarctation, given hormone substitution therapy with DOCA and hydrocortisone, developed hypertension as severe as that in rats with their adrenal glands intact. This increase was significantly greater than that observed in the adrenalectomized rats subjected to a left nephrectomy. It is obvious that the adrenalectomized rats could not increase the secretion of mineralocorticoids. However, the exogenous administration of the maintenance doses of the steroids was necessary for the survival of the rat. When we tried the same experiment on adrenalectomized rats without giving them steroid support, they all died after the second operation.

Administration of excess glucocorticoids and mineralocorticoids has been shown to produce hypertension in mice (10) and rats (11) in a dose-dependent manner. It might be argued, therefore, that in the adrenalectomized rats maintained with DOCA and hydrocortisone the substitution therapy itself was a contributing factor in the development of the hypertension. Although the mean blood pressures of the rats in group 4 (adrenalectomy, aortic coarctation, left nephrectomy, and substitution therapy) were 10 mm higher than those in group 2 (sham-adrenalectomy, aortic coarctation, and left nephrectomy with no hormone treatment), this difference was not significant. Furthermore, on the third day after aortic coarctation, the dose of hydrocortisone was reduced by one-half, yet the mean blood pressure of group 4 rats showed no tendency to decline as would be expected if the hydrocortisone injections themselves were involved in the pathogenesis of the hypertension. Thus, it seems unlikely that the steroid support therapy played a direct role in the development of the hypertension in group 3 rats (adrenalectomy, aortic coarctation). Moreover, the plasma renin activity was higher in the rats that were adrenalectomized and given steroid support than it was in those subjected to sham-adrenalectomy. Although the difference was not significant, this finding suggests that the doses of mineralocorticoids were not sufficient to bring the renin down to the expected levels, indicating that the adrenalectomized rats could have had a small degree of mineralocorticoid insufficiency.

These results are consistent with those of McAllister et al. (4), who observed that antihypertensive therapy resulted in a return of plasma renin.

FIGURE 1
Mean blood pressure for the four experimental groups. The lower case x above the kidney indicates adrenalectomy, and the capital X in place of the kidney indicates nephrectomy. The vertical bars indicate ± se. Group 1 = solid circles, group 2 = solid triangles, group 3 = open circles, and group 4 = open triangles.

FIGURE 2
Plasma renin activity on the seventh day after aorta coarctation. The lower case x above the kidney indicates adrenalectomy, and the capital X in place of the kidney indicates nephrectomy. The vertical bars indicate ± se.
activity to normal but that aldosterone secretion rate remained elevated for longer periods of time. His patients had malignant hypertensive crises, with elevated plasma renin activity and elevated aldosterone secretion rates. This dissociation of blood pressure and plasma renin activity from aldosterone secretion rate might indicate the secondary nature of the increased aldosterone secretion rate in relation to the accelerated hypertension.

Results similar to ours have been obtained in rats with renal hypertension produced by clipping one renal artery (12). However, this model should not be confused with the model of rats with aortic coarctation, since the latter developed more severe hypertension (malignant phase) and a much higher renin level than the former. We have also shown in a previous report (13) that the same antibody that is effective in reducing blood pressure in rats with accelerated hypertension produced by aortic coarctation is not effective in reducing blood pressure in rats with one kidney clamped and the contralateral kidney untouched (benign phase).

To explain how angiotensin II is involved in the pathogenesis of the severe hypertension produced by aortic coarctation between the renal arteries, one must examine modes of action of angiotensin II other than the stimulation of mineralocorticoid release. These other modes of action of angiotensin II must also provide an explanation for the gradual decrease in mean blood pressure observed after the injection of antiangiotensin II into the severely hypertensive rats of this model. Several possibilities are presented below.

Angiotensin II in pharmacological doses (10–50 μg/ml) can stimulate the in vitro release of catecholamines from the adrenal medulla. Furthermore, the hypertensive effect of a single 0.1-μg injection of angiotensin II can be decreased by one-half by adrenalectomy (14, 15). However, such a release of catecholamines does not appear to be important in the development of hypertension in this study, since our adrenalectomized rats developed hypertension.

Other modes of action of angiotensin II must be examined to account for the hypertension and the gradual decrease in mean blood pressure after antiangiotensin II injection.

Peach et al. (16) found that physiological doses of angiotensin II inhibited the uptake of norepinephrine in the perfused rabbit heart. They suggested that this inhibition could result in the observed potentiation of sympathetic stimuli after angiotensin II administration. Consistent with this, Davila and Khairallah (17) found that synthesis of norepinephrine is increased after angiotensin II administration, possibly due to interruption of a negative feedback loop by inhibition of norepinephrine uptake. The delay in blood pressure decrease might then be due to the gradual establishment of an equilibrium between receptor-bound angiotensin II and antibody-bound angiotensin II.

Angiotensin II can also exert an effect on the sympathetic nervous system via the central nervous system (18). Infusion of angiotensin II into the vertebral arteries of the rabbit and dog in a dose small enough to have no systemic effect results in an increase in blood pressure. Specifically, the effect seems to be mediated in the area postrema of the hindbrain where the blood-brain barrier does not exist. Again, the delay in blood pressure decrease might be due to the slow reversal of angiotensin II binding to brain receptors in a manner similar to that suggested above. However, these two possibilities are unlikely, since a much faster equilibrium between the antibody and the receptors would be expected.

Finally, Friedman and Friedman (19) have proposed that arteriolar resistance is controlled by the partition of sodium within the arteriole. They have suggested that angiotensin II exerts its effect by changing this partition; thus, vasoconstriction can be suppressed by inhibiting sodium transfer in the artery by cooling (20). Furthermore, arteries have been shown to contain more sodium than do other types of muscles (21, 22). Such changes in sodium partition might also result in the “water logging” observed by Tobian et al. (23) in the mesenteric arterioles of renal hypertensive rats. Changes such as these might require several days for reversal after the maintenance stimulus is removed and could thus explain the delay in the decrease in blood pressure after antibody injection.

In conclusion, the general inference from this investigation should be that, although steroids are necessary for the survival of the animals and may have a permissive role in the development of this type of hypertension, an increase in adrenocortical secretion does not play a primary role in the development of this high-renin hypertension.

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References


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