Enhanced Aldosterone Response to Angiotensin II in Human Hypertension

E.S. Kisch, M.D., R.G. Dluhy, M.D., and G.H. Williams, M.D.

SUMMARY Adrenal and vascular responsiveness to graded doses of angiotensin II (A II) were recorded for seven normal subjects and 12 patients with essential hypertension while in balance on an intake of 200 mEq sodium/100 mEq potassium. Patients with essential hypertension had been previously studied and known to have normal responses of plasma renin activity to sodium restriction and upright posture. A II was administered for 30 minutes at rates of 0.1, 0.3, 1, and 3 ng/kg per minute and plasma aldosterone responses were assessed 20 and 30 minutes later; blood pressure was monitored at intervals of 1 minute during infusion of A II at each rate. A significant increment in plasma aldosterone occurred at an infusion rate of 0.3 ng/kg per minute in patients with hypertension. This change was not seen until the infusion rate reached 1.0 ng/kg per minute in the normotensive control subjects. Even at an A II infusion rate of 1 ng/kg per minute, the increment in plasma aldosterone levels in normotensive subjects (4.2 ± 0.6 ng/dl) was significantly less (P < 0.001) than that in patients with essential hypertension (19 ± 3 ng/dl). In both groups, a significant rise in mean arterial blood pressure occurred at an A II dose of 0.3 ng/kg per minute, but the pressor response of the hypertensive group was significantly greater at the highest infusion rate (3 ng/kg per minute) (P < 0.05). Thus, enhanced adrenal and pressor responsiveness to infused A II was observed in the hypertensive subjects, suggesting a change in A II receptor affinity.

ANGIOTENSIN II may play an important role in the control of blood pressure through its vasoconstrictor activity as well as its effects on volume homeostasis exerted through regulation of aldosterone secretion. However, previous studies evaluating adrenal and vascular responsiveness to infused angiotensin II (A II) in hypertensive subjects have yielded conflicting results.1-6 Moreover, recent studies suggest that there may be physiologically important but functionally different receptors for A II on the adrenal cortex and vascular smooth muscle.7,8 An imbalance of the relative responsiveness of these receptors to A II might lead to an imbalance in volume homeostasis or vasoconstrictor activity and thus produce an elevated blood pressure. The present study was designed to compare the relative magnitude of response of blood pressure and aldosterone secretion to graded doses of A II in patients with essential hypertension and normal subjects.

Methods

Twelve patients with essential hypertension and seven normotensive control subjects were studied in the Clinical Research Center of the Peter Bent Brigham Hospital. The normotensive subjects (five male, two female) ranged in age from 23 to 38 years. They denied use of drugs and had no evidence of renal, cardiovascular, or endocrine abnormalities on routine screening. Patients with essential hypertension were all male, four female) ranged in age from 24 to 68 years. The criteria for inclusion of patients with hypertension in the study were as follows: diastolic blood pressure was greater than 90 mm Hg on three different occasions with the outpatient supine and there was documented evidence of hypertension for at least 6 months prior to the study. In addition, the following studies were performed to eliminate secondary causes of hypertension: rapid sequence intravenous pyelography, and measurement of creatinine clearance and excretory rates for urine vanillylmandelic acid (VMA), metanephrines, 17-hydroxysteroids, and 17-keto-steroids. In all subjects stimulated levels of plasma renin activity were normal after 5 days of sodium depletion and upright activity for 3 hours. The normal range under these conditions in our laboratory is between 2.6 and 14.0 ng/ml per hour.10

Normotensive and hypertensive subjects were studied under identical conditions of metabolic balance. Medications were withheld from all hypertensive patients for a minimum of 2 weeks before hospitalization. All subjects received a constant dietary intake of 200 mEq sodium/100 mEq potassium and participated in a defined activity program that was controlled throughout the entire study. In all subjects, a period of 5 days was allowed to achieve metabolic balance on this diet prior to infusion of A II. After an overnight fast and with the patient supine, control blood samples were obtained for blood urea nitrogen (BUN) sodium, potassium, supine renin activity, A II, aldosterone, and cortisol. A II (Hypertensin, CIBA) was then infused with a Harvard Instrument infusion pump at a rate of 0.1, 0.3, 1, and 3 ng/kg per minute. Each dose was infused for 30 minutes. Samples for measurement of levels of A II, aldosterone, and cortisol were obtained at 20 and 30 minutes after initiating each dose. Blood pressure was monitored by an indirect recording sphygmonanometer (Arteriosonde) at intervals of 1 minute throughout the A II infusion, and for 30 minutes prior to the infusion. The protocol was approved by the Human Subjects Committee of the Peter Bent Brigham Hospital, and informed written consent was obtained from each subject.

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LABORATORY PROCEDURES

Daily weights were recorded and 24-hour urine specimens collected from 7 a.m. to 7 a.m. and kept refrigerated for measurement of sodium and potassium. Accuracy of urine collections was checked by daily creatinine determinations. Urine sodium and potassium were measured by flame photometry using lithium as an internal standard. Plasma aldosterone and cortisol levels were measured by radioimmunoassay as previously described. Plasma A II and renin activity were measured by double-antibody radioimmunoassay previously described from this laboratory. Mean blood pressure was calculated as the diastolic pressure plus one-third the pulse pressure.

STATISTICAL EVALUATION

Responses were analyzed statistically by computing the t value for the response at each time and comparing the appropriate control with the pooled variances derived from a two-way analysis of variance. Computations were done on the logarithmic transform of the data. In all cases, the variance was assessed as being homogeneous on the log transform by Bartlett’s test. P values were found in Dunnett’s tables for comparing multiple responses with a single control. Results are expressed as mean ± SEM and significance was P < 0.01 unless otherwise stated. Nonsignificant differences were those with P > 0.05.

TABLE 1 Metabolic Characteristics of Normotensive and Hypertensive Subjects on Day of Study in Balance on a Diet Containing 200 mEq Sodium/100 mEq Potassium

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Hypertensive subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Age (yr)*</td>
<td>23 ± 2</td>
<td>46 ± 5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.0 ± 3.7</td>
<td>81.8 ± 4.1</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>14 ± 1</td>
<td>13 ± 1</td>
</tr>
<tr>
<td>Serum sodium (mEq/liter)</td>
<td>143 ± 2</td>
<td>144 ± 2</td>
</tr>
<tr>
<td>Serum potassium (mEq/liter)</td>
<td>4.2 ± 0.2</td>
<td>4.3 ± 0.1</td>
</tr>
<tr>
<td>Urine sodium (mEq/day)</td>
<td>170 ± 23</td>
<td>160 ± 14</td>
</tr>
<tr>
<td>Urine potassium (mEq/day)</td>
<td>84 ± 9</td>
<td>87 ± 6</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml per hr)</td>
<td>1.8 ± 0.4</td>
<td>2.1 ± 0.3</td>
</tr>
<tr>
<td>Plasma angiotensin II (pg/ml)</td>
<td>22 ± 4</td>
<td>23 ± 3</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td>7 ± 1</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>Plasma cortisol (µg/dl)</td>
<td>12 ± 2</td>
<td>11 ± 2</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>84 ± 1</td>
<td>120 ± 4</td>
</tr>
</tbody>
</table>

Results are given as mean ± SEM.

Age range for normal subjects was 23-38 years; for hypertensive subjects, 24-60 years.

Results

Table 1 shows the metabolic characteristics of the patients with hypertension and the normal controls on the day of study when in balance on the diet providing 200 mEq sodium/100 mEq potassium. Control BUN, serum and urine sodium and potassium, plasma renin activity, A II, and aldosterone levels were not significantly different between the two groups. Mean blood pressure was significantly greater in the patients with hypertension (P < 0.001). The normal controls were significantly younger than the patients with hypertension, but there was a broad overlap between the two groups and seven of the 12 patients with hypertension were in the age range spanned by the normotensive subjects. The hypertensive patients were heavier than the normotensive subjects but this difference was not significant (P > 0.05).

Figure 1 depicts the mean increment in blood pressure, A II, and aldosterone levels in response to the graded infusions of A II in seven normotensive and 12 hypertensive subjects. All subjects were studied while supine and in metabolic balance on a diet containing 200 mEq sodium/100 mEq potassium (mean ± SEM). The scale of the ordinate of the upper panel shows the change in blood pressure.
rise at the dose of 3 ng/kg per minute \( (P < 0.05) \).

There was significant increase \( (P < 0.01) \) in plasma aldosterone at an infusion rate of 0.3 ng/kg per minute in the patients with hypertension but not until the dose reached 1.0 ng/kg per minute in the controls \( (P < 0.05) \). In fact, the increment and absolute level of plasma aldosterone observed in hypertensive patients following the A II infusion at 0.3 ng/kg per minute did not occur until 3.0 ng/kg per minute in the normal subjects. Moreover, the increment in plasma aldosterone following infusion of A II at 0.3 ng/kg per minute was 7 times greater in the hypertensive group. No data for plasma aldosterone are available for the infusion rate of 3 ng/kg per minute for the patients with essential hypertension because the infusion was terminated within 5 minutes in all but two subjects when mean blood pressure increased to a level greater than 135 mm Hg.

**Discussion**

The present study demonstrates an increased responsiveness of the adrenal cortex to A II in sodium-replete patients with normal renin essential hypertension. The aldosterone response was greater at all dose levels with the threshold being one-third that found for the normotensive subjects. Vascular responsiveness of patients with hypertension to A II also was enhanced as manifested by a significantly greater increment in mean arterial pressure at the highest infusion rate, although the threshold dose was the same for the two groups.

More than a decade ago Kaplan and Silah reported that patients with essential hypertension required less A II to raise diastolic blood pressure by 20 mm Hg than did normotensive subjects. In some subsequent studies, the enhanced responsiveness of patients with essential hypertension to A II was confirmed, while in others there were no significant differences between pressor responses of normotensive and hypertensive subjects. Whether or not enhanced pressor responsiveness of subjects with essential hypertension to infused A II was observed in previous studies seems to be dependent on the criteria employed. In the present study, there was a significant difference between normotensive and hypertensive subjects at the end of the dose-response curve where the increase in blood pressure was equivalent to that of studies which used a 20 mm Hg increment. On the other hand, if responses to threshold doses in the current study are compared there are no significant differences between the normotensive and hypertensive subjects. Thus, studies using varied vs. fixed pressor responses as the end point would be expected to yield different conclusions.

There is only a limited number of reports of aldosterone responsiveness to infused A II in hypertensive patients. Mendelsohn et al. evaluated plasma aldosterone responses to a single dose of A II in eight normal subjects and 17 patients with essential hypertension in both the sodium-loaded and sodium-restricted states. They reported no significant difference between normotensive and hypertensive subjects in either the incremental or maximal aldosterone responses to infused A II. However, differences in experimental design between the present study and Mendelsohn's report could account for the differing results. First, the present study used a dose-response curve, thus eliminating a number of the problems related to evaluating responsiveness with a fixed infusion rate. Second, in the present study, the dose of A II infused was standardized according to body weight with the result that the increment in plasma A II concentration was identical for the two groups. In contrast, the mean increment in A II concentration above the basal value in the study of Mendelsohn et al. was different in sodium-loaded hypertensive subjects (30 pg/ml) as compared to normotensive subjects (57 pg/ml). Moreover, Mendelsohn's data could be interpreted as indicative of enhanced adrenal responsiveness in the hypertensive patients because the ratio of the increments in aldosterone to A II in hypertensive patients was more than 2 times greater than that recorded for normotensive subjects.

Two additional studies provide indirect evidence that support the finding of enhanced adrenal responsiveness in sodium-replete hypertensive subjects. Luetcher et al. reported that, when compared with normotensive subjects, patients with essential hypertension on a normal sodium intake showed normal responsiveness to renin but an enhanced plasma aldosterone response to upright posture. Similar findings were reported by Bayard et al., who assessed the relative renin and aldosterone response to furosemide administration in normal controls and patients with essential hypertension on normal and high sodium intakes.

Although a decrease in sodium intake or increase in potassium intake enhances adrenal responsiveness in normal subjects, no significant differences in either basal urine or serum sodium-potassium levels between normotensive and hypertensive subjects were recorded. Other basal parameters measured, i.e., cortisol, aldosterone, A II, renin activity, or BUN also were not significantly different. Second, a greater total dose of A II was given to the hypertensive patients compared to the normotensive controls, since the dose infused was administered as ng/kg per minute and hypertensive patients weighed more. However, there were no significant differences in the measured plasma levels of A II between the two groups. It is unlikely that altered adrenal responsiveness was secondary to age differences between the groups because there was no significant difference between the incremental rise in plasma aldosterone in the present group of normal subjects and that previously reported for a larger group whose mean age was 41.1 years, i.e., similar to that of the patients with hypertension in the present study.

Finally, a decrease of 60% in the metabolic clearance rate of aldosterone previously has been reported for patients with essential hypertension. Accordingly, a decrease in the metabolic clearance of aldosterone could result in a greater A II-stimulated rise in the plasma aldosterone levels. However, if the present data are corrected for this presumed alteration in metabolic clearance, the increment in plasma aldosterone for the infusion rate of 0.3 ng/kg per minute still would be significantly greater for the patients with hypertension (7.2 ng/dl) than for the normal control subjects (1.9 ng/dl).

Thus, it is postulated that in hypertensive subjects there is not only a change in vascular receptor affinity for A II, as
proposed by Brunner et al. but also an enhanced affinity of A II for its glomerulosa cell receptor. However, the current study cannot distinguish a receptor change from a change in one of the intracellular biosynthetic steps necessary for the synthesis of aldosterone. In the presence of enhanced adrenal and vasoactive responsiveness, it might be anticipated that renin or A II levels, or both, should be lower for given levels of aldosterone in patients with essential hypertension in comparison to normal control subjects. In the present study, this was not observed as the preinfusion aldosterone and endogenous A II levels were the same in the two groups. However, since plasma levels of both aldosterone and angiotensin fluctuate rapidly but not simultaneously, in order to document a difference in their resting levels, many more samples would be needed. Thus, the dose-response curves presented in this report would appear to be the more practical way of defining these relationships.

References

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