Partial Deficiency of Adrenal 11-Hydroxylase
A Possible Cause of Primary Hypertension
GIOVANNI DE SIMONE, ANTONIO P. TOMMASELLI, RICCARDO ROSSI, ROSELLA VALENTINO,
ROSSELLA LAURIA, FRANCESCO SCOPACASA, AND GAETANO LOMBARDI

SUMMARY Results of supraphysiological adrenocorticotropic hormone (ACTH) stimulation of biosynthetic pathways of adrenal zona fasciculata indicate that a deficiency of 11-hydroxylase exists in patients with essential hypertension. The deficiency is suggested by the much greater stimulus of synthesis of deoxycorticosterone (DOC) and deoxycorticosterol in hypertensive subjects than in controls (p < 0.001). No significant difference in the synthesis of cortisol, corticosterone, progesterone, 17-hydroxyprogesterone (17-OHP), and delta-4-androstenedione (D4) was observed between the two groups. The ratios for synthesis of DOC and corticosterone and for deoxycortisol and cortisol found in hypertensive patients were significantly higher than those found in controls (p < 0.001); no significant difference was observed in the synthesis of 17-OHP and progesterone. The synthesis of DOC and deoxycorticosterol was not significantly correlated with either blood pressure or plasma renin activity. Plasma renin activity was significantly lower in hypertensive subjects than in normotensive subjects (p < 0.0001), while no difference was found in aldosterone secretion between the two groups. The 11-hydroxylase deficiency in the adrenal zona fasciculata may be one of the genetic factors causing hypertension together with environmental factors (particularly salt intake and work-related stress). The investigation performed in our study may be useful for the evaluation of adrenal zona fasciculata enzymatic activities during the study of hypertensive patients. (Hypertension 7: 204–210, 1985)

KEY WORDS • adrenal zona fasciculata • deoxycorticosterone • deoxycorticosterol • plasma renin activity • aldosterone

The possibility that adrenal steroids are involved in the pathogenesis of human essential hypertension is still under investigation. Mineralocorticoid activity often has been reported to be increased, especially in low-renin hypertension. Melby and colleagues observed an increased excretion of 18-hydroxydeoxycorticosterone (18-OHDOC) in patients with low-renin hypertension who had marked responses to adrenocorticotropic-hormone (ACTH)-inhibiting doses of dexamethasone. High plasma levels of 18-OHDOC also have been reported in patients with normal-renin hypertension. The capability of deoxycorticosterone (DOC) to induce hyper-
tension has been demonstrated by McCall and co-workers in rats treated with methylprednisolone. Dexamethasone has also been used recently in hypertensive patients with excessive secretion of an unknown mineralocorticoid and in a hypertensive girl with excessive secretion of urinary 17-ketosteroids. Honda and colleagues found abnormalities in the response of adrenal cortex to ACTH infusion in patients with normal-renin and low-renin hypertension that were compatible with a combined functional 17-hydroxylase and 11-hydroxylase failure. Wang and associates have also found 17-hydroxylase deficiency in hypertensive patients. Alterations in excretion and metabolic clearance of several adrenal steroids have been reported by other authors. These observations confirm the possibility that abnormalities in adrenal biosynthetic pathways, similar to those reported in congenital adrenal hyperplasia, may be involved in human essential hypertension.

In this study we evaluated the response of adrenal zona fasciculata to rapid injection of ACTH in patients with mild to moderate essential hypertension and in normotensive controls.
ESSENTIAL HYPERTENSION AND 11-HYDOXYLASE FAILURE

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Materials and Methods

Fifteen patients (6 women and 9 men), aged 19 to 59 (range, 44.7 ± 11.6 years), with mild to moderate essential hypertension (178.7 ± 15.9/108 ± 7.7 mm Hg; WHO grade I or II) and fifteen normotensive volunteers (5 women and 10 men), aged 22 to 59 (range, 42 ± 12 years), with no history of hypertension (131.33 ± 12.17/72.67 ± 5.63 mm Hg) were studied. All the subjects were Caucasian and came from a limited geographical area (the district of Naples). Persons with supposed or verified metabolic or endocrinological alterations, coronary heart disease, heart failure, or abnormal hepatic or renal function test results were excluded, as were all subjects with supine plasma aldosterone levels (measured after the subject awoke in the morning) of more than 150 pg/ml, with 17-ketosteroid or 11-hydroxycorticoid urinary level alterations, and with uncertain responses to urography or renal radiographic angiography. No woman was pregnant. Informed consent was obtained from all subjects.

A fortnight’s washout period was observed before the study. During this period all the subjects received a balanced, normocaloric diet without salt restriction.

The tests were carried out at 0900 to 1200 hours. The women were studied in the precocious follicular phase. No side effects were noted in any subject. Blood samples for baseline determinations of aldosterone and plasma renin activity (PRA) were drawn from the subjects after an overnight recumbency and 2 hours of fast walking. Plasma DOC, corticosterone, deoxycorticosterone, cortisol, progesterone, 17-hydroxyprogesterone (17-OHP), and delta-4-androstenedione (D4) levels were measured at baseline and 30, 60, 90, and 120 minutes after the rapid intravenous injection of 25 IU of a 1-24 polypeptidic fragment of ACTH (Synacthen). All subjects remained recumbent throughout.

Deoxycorticosterone and cortisol levels were measured by radioimmunoassay (antibody, Biodata s.p.a., Milan, Italy) after chromatography on a Sephadex LH20 column,6 which also was used for separation of corticosterone. Corticosterone levels were measured by the method of proteic competition. Deoxycorticosterone levels were measured by proteic competition after chromatography on a Sephadex LH20 column. The 17-OHP levels were measured by radioimmunoassay (antibody, Biomérieux, Charbonnières-les-Bains, France) after extraction in ether. Delta-4-androstenedione and progesterone levels were measured by radioimmunoassay (antibody, Biomérieux) after extraction in petroleum ether and chromatography on a Celite minicolumn (0.5 × 5 cm) adsorbed with methyleneenglycol and ethyleneenglycol, which were eluted with isooctane. The dosed values were corrected for the procedural loss by the pretreatment addition of 3000 d.p.m. to the serum of all the tritiated steroids.

The areas under curves of stimulus were examined to compare the responses of the steroids. Student’s t test for impaired data and the analysis of variance with Neuman-Keuls’ test of multiple comparison were employed to compare the mean values between groups.

Results

The age difference between hypertensive patients and controls was not significant. Mean values with statistical significance are shown in Table 1. The areas of stimulus of DOC and deoxycortisol were significantly greater in hypertensive patients than in controls (p < 0.001). No significant difference was found in the areas of stimulus of cortisol, corticosterone, progesterone, 17-OHP, and D4. Baseline levels of DOC and deoxycortisol were significantly higher in hypertensive patients than in controls (p < 0.02) and were significantly correlated with their respective areas in both hypertensive and normotensive subjects (Figures 1 and 2). The DOC/corticosterone and deoxycortisol/cortisol ratios found in hypertensive patients were significantly higher than those found in controls (p < 0.001). No significant difference between the groups was observed in the 17-OHP/progesterone ratio (Table 1).

The supine and upright PRA as well as its increase (the difference between upright and supine levels) was significantly lower in hypertensive patients than in
controls ($p < 0.001$; Figure 3), while no difference was found in plasma aldosterone levels between the two groups (Table 1). Supine PRA, PRA increase, and mean, systolic, and diastolic blood pressures were not significantly correlated with the areas of DOC and deoxycortisol, the DOC/corticosterone ratio, and the deoxycortisol/cortisol ratio. The relationship between the areas of deoxycortisol and DOC (Figure 4) and between deoxycortisol/cortisol ratio and DOC/corticosterone ratio was significant; the resulting $r$ values were higher in the hypertensive group ($p < 0.0001, r = 0.94; p < 0.0001, r = 0.98$ respectively) than in controls ($p < 0.001, r = 0.77; p < 0.005, r = 0.70$ respectively; Table 2).

The baseline PRA significantly correlated with its increase in both hypertensive ($p < 0.01, r = 0.85$) and normotensive ($p < 0.001, r = 0.83$; Table 2) groups. A significant correlation between age and baseline PRA occurred only in normotensive subjects ($p < 0.05, r = -0.56$; Table 2). The relationship between systolic and diastolic blood pressure and PRA (supine or increase) was not significant in either group.

Five subjects in the hypertensive group overlapped

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**Figure 1.** Correlation between the baseline values of DOC and its areas of stimulus after supraphysiological stimulation with rapid injection of ACTH.

**Figure 2.** Correlation between the baseline values of deoxycortisol ($S$) and its areas of stimulus after supraphysiological stimulation with rapid injection of ACTH.

**Figure 3.** Lying (supine) and standing (upright) PRA and its absolute increase, after 2 hours of fast walking, in hypertensive patients and in normotensive volunteers.
Table 2. Equations of Linear Regression and Relative Statistical Significance for Both Groups

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Hypertensive Equation</th>
<th>Normotensive Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline DOC vs. DOC area</td>
<td>$y = 4488.33 + 210.01x$</td>
<td>$y = 821.30 + 178.00x$</td>
</tr>
<tr>
<td>Baseline S vs. S area</td>
<td>$y = 1410.90 + 205.42x$</td>
<td>$y = 1934.30 + 182.91x$</td>
</tr>
<tr>
<td>DOC/B vs. S/F</td>
<td>$y = 0.38 + 0.28x$</td>
<td>$y = 0.23 + 0.56x$</td>
</tr>
<tr>
<td>S area vs. DOC area</td>
<td>$y = 649.91 + 0.32x$</td>
<td>$y = 1288.60 + 0.23x$</td>
</tr>
<tr>
<td>Baseline PRA vs. PRA increase</td>
<td>$y = 0.23 + 0.56x$</td>
<td>$y = 0.15 + 0.93x$</td>
</tr>
<tr>
<td>Baseline PRA vs. age</td>
<td>$y = 0.23 + 0.56x$</td>
<td>$y = 0.15 + 0.93x$</td>
</tr>
<tr>
<td>DOC/B vs. PRA increase</td>
<td>$y = 0.23 + 0.56x$</td>
<td>$y = 0.15 + 0.93x$</td>
</tr>
<tr>
<td>S area vs. PRA increase</td>
<td>$y = 0.23 + 0.56x$</td>
<td>$y = 0.15 + 0.93x$</td>
</tr>
<tr>
<td>DOC area vs. PRA increase</td>
<td>$y = 0.23 + 0.56x$</td>
<td>$y = 0.15 + 0.93x$</td>
</tr>
</tbody>
</table>

DOC = deoxycorticosterone; S = deoxycortisol; B = corticosterone; F = cortisol; PRA = plasma renin activity; NS = not significant.

Table 3. Areas Under Curves of Stimulus of Deoxycorticosterone and Deoxycortisol for Each Subject

<table>
<thead>
<tr>
<th>Hypertensive subjects</th>
<th>Normotensive subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOC</td>
<td>S</td>
</tr>
<tr>
<td>14415</td>
<td>40545</td>
</tr>
<tr>
<td>4500</td>
<td>12975</td>
</tr>
<tr>
<td>8160</td>
<td>21840</td>
</tr>
<tr>
<td>4155</td>
<td>11490</td>
</tr>
<tr>
<td>3840</td>
<td>10635</td>
</tr>
<tr>
<td>20025</td>
<td>55050</td>
</tr>
<tr>
<td>10305</td>
<td>50340</td>
</tr>
<tr>
<td>15585</td>
<td>41175</td>
</tr>
<tr>
<td>5400</td>
<td>15690</td>
</tr>
<tr>
<td>20370</td>
<td>56775</td>
</tr>
<tr>
<td>12700</td>
<td>34650</td>
</tr>
<tr>
<td>6150</td>
<td>16830</td>
</tr>
<tr>
<td>18075</td>
<td>52950</td>
</tr>
<tr>
<td>15480</td>
<td>42450</td>
</tr>
<tr>
<td>15705</td>
<td>48125</td>
</tr>
</tbody>
</table>

DOC = deoxycorticosterone; S = deoxycortisol.
DOC and deoxycortisol and between the DOC/cortico-
sterone and deoxycortisol/cortisol ratios in the
hypertensive group indicate that a deficiency of 17-hy-
droxylation is unlikely.

As the areas of stimulus of corticosterone and corti-
sol were similar in the two groups, the increase in the
deoxycortisol/cortisol and DOC/corticosterone ratios
in hypertensive patients appears to be caused only by
the increases in deoxycortisol and DOC and shows an
enzymatic deficiency that can be revealed by supra-
physiological stimulation but that is not evident in a
normal state.

The close correlation between the areas of DOC and
deoxycortisol in the hypertensive group suggests that
their response is due to the reduction of the same 11-
hydroxylating system (Figure 4). The functional defi-
ciency of 11-hydroxylase observed in our patients ap-
pears to cause excessive formation of DOC and
deoxycortisol, which may lead to hypertension and
influence PRA because of sodium retention. Increased
levels of known or unknown adrenal steroids seem to
be found more frequently in low-renin hyperten-
sion. The enzymatic deficiencies found in the hyperten-
sive subjects were higher than what the PRA would in-
dicate. Aldosterone has been shown to respond to admin-
istration of ACTH and to take its rhythm. The
ACTH stimulation that is caused by enzymatic impair-
ment may be more important than PRA in aldosterone
formation in these patients and could act to support its
levels. This action may be why aldosterone is reported
within normal ranges in patients with essential hyper-
tension.

The enzymatic activity of 11-hydroxylase of the
gluomerulosa may be normal in the hypertensive
The enzymatic activity is controlled by the genetic
factor that is independent of the levels of aldosterone.

Table 4. Comparison of Areas of Stimulus, Plasma Renin Activity and Aldosterone Among Normal Controls,
Subgroup A, and Subgroup B

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Hypertensive subgroup</th>
<th>p &lt;*</th>
<th>Normal</th>
<th>p &lt;*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOC (ng/dl/120 min)</td>
<td>Subgroup A: 4809 ± 950</td>
<td>0.001</td>
<td>3666 ± 1366</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Subgroup B: 15082 ± 3930</td>
<td></td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>S (ng/dl/120 min)</td>
<td>Subgroup A: 13524 ± 2665</td>
<td>0.001</td>
<td>10517 ± 4648</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Subgroup B: 44390 ± 10656</td>
<td></td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>B (µg/dl/120 min)</td>
<td>Subgroup A: 229 ± 36</td>
<td>NS</td>
<td>291 ± 49</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Subgroup B: 320 ± 50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F (µg/dl/120 min)</td>
<td>Subgroup A: 3025 ± 362</td>
<td>NS</td>
<td>3243 ± 418</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Subgroup B: 3399 ± 391</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P (ng/dl/120 min)</td>
<td>Subgroup A: 4948 ± 859</td>
<td>NS</td>
<td>4031 ± 1409</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Subgroup B: 4501 ± 930</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-OHP (ng/dl/120 min)</td>
<td>Subgroup A: 20744 ± 4891</td>
<td>NS</td>
<td>16018 ± 5283</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Subgroup B: 17172 ± 4247</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOC/B</td>
<td>Subgroup A: 17.75 ± 5.78</td>
<td>0.005</td>
<td>13.13 ± 5.44</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Subgroup B: 47.16 ± 9.48</td>
<td></td>
<td>3.40 ± 1.62</td>
<td>0.001</td>
</tr>
<tr>
<td>S/F</td>
<td>Subgroup A: 4.10 ± 4.60</td>
<td>NS</td>
<td>3.80 ± 1.82</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Subgroup B: 12.97 ± 2.92</td>
<td></td>
<td>0.80 ± 0.42</td>
<td>0.0001</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>Subgroup A: 1.03 ± 0.72</td>
<td>0.05</td>
<td>1.82 ± 0.68</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Subgroup B: 0.67 ± 0.42</td>
<td></td>
<td>0.82 ± 0.42</td>
<td></td>
</tr>
<tr>
<td>Aldosterone (pg/ml)</td>
<td>Subgroup A: 94.24 ± 31.81</td>
<td>NS</td>
<td>92.88 ± 17.85</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Subgroup B: 88.82 ± 27.71</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aSignificance between the two subgroups.
*bSignificance between Subgroups A or B and normal controls.

DOC = deoxycorticosterone; S = deoxycortisol; B = corticosterone; F = cortisol; P = progesterone; 17-OHP = 17-hydroxyprogesterone; D4 = delta-4-androstenedione; PRA = plasma renin activity; NS = not significant.

The influence of salt intake and stress in causing
essential hypertension has been reported in several
studies. The genetically determined enzymatic ac-

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tivities of adrenal zona fasciculata may be the catalyst for salt-intake and stress-related hypertension in many patients. Because of the enzymatic deficiency in hypertensive patients, salt intake cannot exert any control over the secretion of DOC and deoxycortisol in the adrenal zona fasciculata, which depends on cortisol-regulated ACTH secretion; therefore, salt intake regulates the secretion of mineralocorticoids only in the adrenal zona glomerulosa, and not in the adrenal zona fasciculata. Stress-related hypertension may reveal the impaired enzymatic activity by stimulating corticotropin releasing factor formation and ACTH secretion, with consequent excessive production of DOC and deoxycortisol.

In our study the absence of correlation between blood pressure and the areas of both DOC and deoxycortisol might be due to the variable strengths exerted by environmental factors and age on the subjects' genetic tendency. On the contrary, in all the subjects we have injected the same dose of ACTH and have stimulated one of the most important responses to stress. We think that the environmental factors and the enzymatic deficiencies have an inverse relationship: the hypertensive disease is caused either by strong environmental factors acting on a slight enzymatic deficiency or by relatively weak environmental factors acting on a large degree of enzymic deficiency. In congenital adrenal hyperplasia due to either 11-hydroxylase or 17-hydroxylase deficiencies, the enzymatic deficiency is complete and hypertension can develop even without the interference of environmental factors.

The incidence of the enzymatic deficiency in our hypertensive group was substantial (67%). The incidence in five patients in Subgroup A (33%) seemed to indicate that no alterations had occurred in the adrenal biosynthetic pathways. Therefore, the hypertensive disease in the latter group should be attributed to other so far poorly understood mechanisms. On the basis of standard selection of patients with primary hypertension, the five patients in Subgroup A would be considered homogeneous with the patients in Subgroup B. The evaluation of adrenal zona fasciculata enzymatic activities, however, shows that the two hypertensive subgroups are different.

Results of our study indicate that human essential hypertension is associated with abnormalities of adrenal enzymatic activities. This possibility should be considered during clinical investigations of hypertensive patients, when all other causes of disease have been excluded. The confirmation of a causal relationship between development of the disease and adrenal zona fasciculata enzymatic deficiency may provide new therapeutic insight and explain the mechanisms of some therapeutic tools (e.g., low salt diet, aldactone). Furthermore, the discovery of an enzymatic deficiency in hypertensive patients may reduce the epidemiological incidence of so-called primary hypertension.

Acknowledgments

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