Mineralocorticoid Secretion in Essential Hypertension with Normal and Low Plasma Renin Activity

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SUMMARY In 19 control subjects, 33 patients with essential hypertension and normal plasma renin activity (PRA) and 11 patients with low PRA, secretory rates of 18-hydroxy-11-deoxy-cortico-sterone (18-OH DOC), 11-deoxycorticosterone (DOC) and corticosterone were measured. Patients with low PRA were significantly older and had higher arterial pressure and slightly lower plasma potassium levels than patients with normal PRA. Mean 18-OH DOC secretion rate was higher in patients with normal PRA (603 ± 112 SEM μg/24 hr) than in control subjects (219 ± 19) and considerably higher (P < 0.001) in patients with low PRA (1800 ± 472). DOC and corticosterone secretion rates were within normal limits in most hypertensive patients. Plasma aldosterone was significantly higher in the hypertensive population than in control subjects whereas no significant difference was observed between the low- and normal-renin groups. A significant (P < 0.01) mutual positive correlation was found between the secretion rates of 18-OH DOC, DOC and corticosterone in patients with low plasma renin activity. In contrast, there was no correlation between the secretion rates of the three mineralocorticoids in control subjects and patients with normal plasma renin activity. These data suggest a biosynthetic variation of the mineralocorticoid pathways in essential hypertension.

LOW PLASMA RENIN ACTIVITY (PRA) in patients with high blood pressure is an important clue to the diagnosis of primary aldosteronism. However, a significant percentage of patients with essential hypertension (EH) have low and unresponsive PRA and normal aldosterone production. Although this represents a state of inappropriate secretion of aldosterone, an excess of another mineralocorticoid should be considered. Previous investigations based on spot determinations of single mineralocorticoids have favored such an hypothesis at least in some patients. The steroids primarily suggested to be secreted in excess are 11-deoxycorticosterone (DOC) and 18-hydroxy-11-deoxycorticosterone (18-OH DOC).

The problem could only be further clarified by determining the secretion rates of several mineralocorticoids in the same patient. Accordingly, secretory rates of 18-OH DOC, DOC and corticosterone were measured in control subjects and in hypertensive patients with normal and low PRA.

Patients and Methods

A total of 44 white patients with EH and 19 control subjects were studied on the fourth day of a diet containing 135 mEq of sodium and 90 mEq of potassium. All control subjects had blood pressure repeatedly below 140/90 mm Hg and none had a family history of high blood pressure or other cardiovascular disease. Mean age was 34.1 ± 3.23 (SEM) years with a range from 20 to 62 years. A complete physical examination and the usual blood and laboratory tests were within normal limits (table 1). The hypertensive patients underwent a complete clinical examination prior to the investigation to eliminate all known causes of hypertension, such as primary aldosteronism, renal artery stenosis, pheochromocytoma or Cushing's disease. Clinical evaluation included the determination of serum electrolytes, urine analysis and culture, ECG, radiography of the chest, and assessment of renal function as measured by creatinine, creatinine clearance, and rapid sequence intravenous pyelography. The clinical investigation was completed, if the patient so elected, by a renal arteriogram or an isotopic nephrogram. No patient showed advanced hypertensive retinopathy, symptoms or signs of left ventricular failure, atherosclerosis of large vessels or evidence of primary parenchymal kidney disease. All had an arterial pressure of 150/95 mm Hg or more as determined on several different occasions in the outpatient department. However, the average arterial pressure was within normal limits in 18 of 44 patients when it was measured during recumbency 8–12 times per day after a few days of hospitalization (table 1). This effect could be ascribed to the relaxing influence of the hospital environment. Antihypertensive medication (including diuretics) was discontinued at least two weeks before the investigation.

Plasma renin activity was determined by the method of Boucher et al. Every patient had at least two renin determinations, one recumbent with a normal sodium and potassium intake (135 mEq of sodium and 90 mEq of potassium daily) and one or more after stimulation by upright posture and low salt diet for at least three days. The distinction between low and normal PRA was established according to the following limits: 1) on dietary sodium 135 mEq/24 hr, recumbent or upright — undetectable or below 0.1 ng/ml/hr; 2) on dietary sodium 10 mEq/24 hr recumbent or upright — below 0.6 ng/ml/hr. Patients showing at least two PRA values under these limits were considered to have low PRA, while those with responses over this limit were attributed to the group with normal PRA. In addition, a furosemide-test was performed in four patients in the low renin group. All of them showed PRA values below 0.6 ng/ml/hr 4 to 5 hours after 40–60 mg of furosemide. According to these criteria, 11 patients (25%) with EH had low

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PRA and 33 had normal PRA. The main clinical and laboratory data for both groups are presented in table 1.

Blood for aldosterone determination was drawn after overnight recumbency between 8 and 9 a.m. on the fourth day of the normal dietary salt intake. Aldosterone plasma concentration was determined by radioimmunoassay.14 18-OH DOC secretion rate was measured by a double isotopic procedure involving 1) injection of 2 μCi of 14C-labeled 18-OH DOC at 8 a.m. and two consecutive 24-hour urine collections; 2) 18-OH-tetrahydro-DOC (18-OH TH DOC) isolation from urine; 3) periodate oxidation of 18-OH TH DOC to γ-lactone; 4) acetylation with 14C-labeled acetic anhydride and purification in five chromatographic systems to isolate 18-OH TH DOC lactone acetate.

DOC and corticosterone secretion rates were simultaneously measured by a double isotopic derivative assay at random, whenever duration of hospitalization permitted.

In four patients with low PRA, DOC secretion rate was calculated from the determined DOC plasma level and the individual metabolic clearance rate for DOC (mean = 913 ± 23 SEM L/24 hr/m²) using the formula: SR = MCR × P/1000, where SR means secretion rate (μg/hr); MCR is metabolic clearance rate (L/24 hr); and P is plasma concentration (μg/ml). The individual MCRs were measured by a constant infusion technique in patients of the low-renin group and corrected for body surface area. These values varied within a narrow range (between 836 and 965 L/24 hr/m²), which indicates that this parameter is quite stable. Previous investigations have shown that there is good agreement between the calculated and the measured values of the MCR.

An analysis of variance was used for statistical comparisons. In addition, the secretion rates of 18-OH DOC in the three groups were compared by the approximation of Welch.18 Between the values of 18-OH DOC, DOC and corticosterone secretion rates, a linear regression analysis was performed.

Results

Patients with low PRA were older, presented with higher systolic and diastolic arterial pressure and slightly lower plasma potassium levels than patients with normal PRA (table 1). Plasma aldosterone was somewhat higher (P < 0.05) in patients with normal PRA and even higher (P < 0.01) in the low-renin group than in control subjects. No significant difference was found between hypertensives with normal and low PRA.

The mean DOC and corticosterone secretion rates were similar in control subjects and hypertensive patients (table 2). There was also no difference between the normal- and the low-renin groups. In control subjects the 18-OH DOC secretion rates varied within a narrow range (73-267) whereas a wide scatter of values was observed in hypertensive patients. They were, however, significantly higher in the low-renin group when compared to control subjects (P < 0.001) and patients with normal PRA (P < 0.01). In the latter group 18-OH DOC secretion rates were above the normal range (mean ± 2 sD) in 16 of 33 patients and in 9 of 11 patients

**Table 1. Clinical and Laboratory Findings in Control Subjects and in Patients with Essential Hypertension**

<table>
<thead>
<tr>
<th></th>
<th>Controls (N = 19)</th>
<th>Normal PRA (N = 33)</th>
<th>Low PRA (N = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>34.1 ± 3.23</td>
<td>37.8 ± 1.9</td>
<td>50.2 ± 2.5**</td>
</tr>
<tr>
<td>BP (mm Hg) 1</td>
<td>113.1/65.1</td>
<td>170.2/102.6</td>
<td>182.4*/109.5*</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>146.2/90.3</td>
<td>175.4**/103.2**</td>
</tr>
<tr>
<td>Na (mEq/L) (mM)</td>
<td>141 ± 0.82</td>
<td>140 ± 0.47</td>
<td>141 ± 0.71</td>
</tr>
<tr>
<td>K (mEq/L)</td>
<td>4.15 ± 0.08</td>
<td>4.21 ± 0.06</td>
<td>3.95 ± 0.07*</td>
</tr>
<tr>
<td>PRA 135 mEq R</td>
<td>0.32 ± 0.07 (14)</td>
<td>0.60 ± 0.22 (30)</td>
<td>0.02 ± 0.02** (9)</td>
</tr>
<tr>
<td>(ng/ml/hr)</td>
<td>U</td>
<td>0.74 ± 0.09 (29)</td>
<td>0.17 ± 0.08** (6)</td>
</tr>
<tr>
<td>10 mEq U R</td>
<td>3.37 ± 0.55 (14)</td>
<td>2.75 ± 0.40 (26)</td>
<td>0.34 ± 0.09 (6)</td>
</tr>
<tr>
<td></td>
<td>U</td>
<td>4.38 ± 0.05 (22)</td>
<td>0.42 ± 0.04** (8)</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/ml)</td>
<td>5.2 ± 1.2 (13)</td>
<td>9.1 ± 1.1† (21)</td>
<td>12.1 ± 2.4†† (10)</td>
</tr>
</tbody>
</table>

* = P < 0.05, ** = P < 0.01 vs patients with normal PRA.
† = P < 0.05, †† = P < 0.01 vs control subjects.
| Abbreviations: R = recumbent; U = upright; 1) = on day of admission; 2) = mean of 8-12 measurements during recumbency on the fourth day of hospitalization. |

**Table 2. Secretory Rates of DOC, Corticosterone and 18-OH DOC in Control Subjects and Patients with Essential Hypertension (mean ± SEM)**

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>Normal PRA</th>
<th>Low PRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosterone secretion rate (μg/24 hr)</td>
<td>2780 ± 232 (N = 15)</td>
<td>2150 ± 234 (N = 11)</td>
<td>2850 ± 424 (N = 6)</td>
</tr>
<tr>
<td>DOC secretion rate* (μg/24 hr)</td>
<td>175 ± 15 (N = 19)</td>
<td>184 ± 29 (N = 9)</td>
<td>172 ± 41 (N = 7)</td>
</tr>
<tr>
<td>18-OH DOC secretion rate (μg/24 hr)</td>
<td>220 ± 17 (N = 17)</td>
<td>603 ± 112 (N = 33)</td>
<td>1800 ± 472 (N = 11)</td>
</tr>
</tbody>
</table>

*Measured values only.
with low PRA. A weak negative correlation ($r = -0.322$) was seen between the 18-OH DOC secretion rates and the PRA values after stimulation by upright posture when all subjects were considered together.

A significant positive correlation ($P < 0.01$) between DOC and 18-OH DOC secretion rates was present in 11 patients with low-renin EH (fig. 1). Furthermore, the correlation between DOC and corticosterone secretion rates (fig. 2) and between corticosterone and 18-OH DOC secretion rates (fig. 3) were statistically significant ($P < 0.01$) in six patients of the low-renin group, in whom the secretion rates of these mineralocorticoids were measured subsequently. In contrast, no correlation between the secretion rates of the three mineralocorticoids was found in control subjects and in patients with normal PRA.

**Discussion**

One of the main controversies in uncomplicated essential hypertension with low PRA is whether a mineralocorticoid excess could be responsible for the suppression of renin. However, the various reports, low-renin EH may be accompanied by expanded plasma or extracellular fluid volume, or by increased total exchangeable sodium, are not supported by the recent findings of the Glasgow group or by those of Distler et al. As Dunn and Tannen have also pointed out in their careful critical review, there is at present little evidence linking low-renin hypertension to a hypermineralocorticoid state comparable to primary aldo-steronism. This seems to be in contradiction to the present findings as well as to those of Melby and Spark that the secretion or excretion rate of 18-OH DOC is higher in patients with low PRA than in normal renin EH and controls, and to the recent discoveries of an excess of other substances with mineralocorticoid-like activities in the low-renin group.

However, it must be kept in mind that the mineralo-
corticoid potency of 18-OH DOC is several times lower than that of aldosterone. The activity of 18-OH DOC on sodium transport across the membrane of the toad bladder has been estimated at about 1/40 of that of aldosterone whereas the sodium retaining activity in the rat bioassay seems to be nearly equal to that of DOC. Gotshall and Davis have reported that 18-OH DOC had 22% of mineralocorticoid activity of deoxycorticosterone acetate in the dog. Nonetheless, Oliver et al. have shown in the rat and more recently in the dog that the mineralocorticoid effect of 18-OH DOC does not parallel its action on the blood pressure which is more pronounced than the sodium retaining and potassium excretory activity. Fan et al. observed in the sheep that a combined infusion of aldosterone, cortisol, corticosterone, DOC and 11-deoxycortisol caused no significant change in arterial pressure whereas with the addition of 18-OH DOC a small but significant increase occurred. This predominant action on arterial pressure could provide a possible explanation for the relative lack of mineralocorticoid effects in low PRA patients. Our findings of increased 18-OH DOC secretion rates in patients with EH, especially with low PRA, suggest a possible participation of 18-OH DOC in the pathogenesis of high blood pressure and/or the observed slightly lower plasma potassium levels in patients with low PRA. A causal relationship, however, cannot be established before the biological activity of 18-OH DOC in humans has been directly evaluated. The 18-OH DOC excess observed in Cushing's disease, in which renin suppression seems to be rather unusual, argues against a direct renin suppressive effect of this mineralocorticoid, at least under those conditions.

The major finding of our study was the positive mutual correlation between the secretory rates of the three main mineralocorticoids other than aldosterone in low-renin EH, in contrast to the lack of correlation in patients with normal PRA and in control subjects. This correlation exists despite elevations of 18-OH DOC secretion rates up to pathological values while DOC and corticosterone secretion rates remain within physiological limits. The implication is a close interdependence in the secretion of the three mineralocorticoids in EH with low PRA, i.e., a biosynthetic variation of the mineralocorticoid pathways in this instance. This interrelation is obviously absent in hypertensive patients with normal PRA and in control subjects.

Our results of an increased 18-OH DOC secretion rate in one-half of hypertensive patients with normal PRA are at variance with those of Melby et al. who found an increased excretion of 18-OH TH DOC in patients with suppressed PRA only and those of Ulick who found no increase at all in the secretion rate in a small group of low-renin hypertensives. On the other hand, Williams et al. recently observed significantly higher plasma levels of 18-OH DOC in 18 patients with normal renin EH (11.6 ± 1.6 ng/100 ml) than in 18 control subjects (5.4 ± 0.7) on a dietary sodium intake of 200 mEq/24 hr. These discrepancies may in part be due to a different selection of patients and the definition of low PRA hypertension, but also to methodological differences. There is circumstantial evidence that urinary 18-OH TH DOC, as determined by Melby et al., does not reflect the adrenal production of 18-OH DOC and leads therefore to its underestimation. In the present study the radiochemical homogeneity of the doubly labeled urinary metabolite of 18-OH DOC was established in two-thirds of the determinations. The presence of any major impurity such as the "dimer" of 18-OH DOC in the tracer injected was also eliminated by frequent chromatographic verification of radiochemical purity and storage in dry benzene. A methodological error due to some degree of biological instability of tritium atoms in the tracer, which was randomly labeled by the procedure of Wilzbach exchanged with methanol and chromatographically purified cannot, however, be ruled out. Any tritium loss would lower the specific activity of the urinary metabolite in respect to this isotope and the calculated secretion rate would be underestimated to that extent.

The establishment of the limits between normal and low PRA has been based in all previous studies on arbitrary chosen limits using spot determinations of PRA and on the assumption that low-renin hypertension is a stable, well defined state. However, Crane et al. also found that 26% of 85 low-renin patients showed normal renin responsiveness on retesting while Brunner et al. concluded that "some
patients can exhibit normal values for renin and aldosterone secretion at one level of dietary salt intake but abnormal values at another. This variability of PRA response in a group of patients during the course of the disease suggests that low PRA represents rather a stage in the evolution of, or a response to, EH or its treatment. Whether the variations in mineralocorticoid secretion and metabolism are casually related to the low-renin state or merely a coincidental finding in the development of hypertensive disease has yet to be determined.

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