Plasma Levels of 18-Hydroxy-11-Deoxycorticosterone in Essential Hypertension

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Synopsis

In order to investigate the role of 18-hydroxy-11-deoxycorticosterone (18-OH-DOC) in essential hypertension (EH), the responses of plasma 18-OH-DOC to 7 stimulation tests (furosemide test, adrenal suppression test, angiotensin II infusion test, adrenal stimulation test, metopirone test, saline infusion test and potassium chloride infusion test) and the circadian rhythm were investigated in 18 patients with essential hypertension (low renin group: 8, and normal renin group: 10).

From the present study, it might be thought that plasma 18-OH-DOC does not play an important role in the suppression of PRA in patients with low PRA.

Up to the present time, many investigators have described abnormalities of steroid metabolism in essential hypertension (EH). We have previously reported abnormalities of 11β- and 17α-hydroxylation in EH (Honda et al., 1977). Recently, novel steroids such as 16β-hydroxydehydroepiandrosterone (Senett et al., 1975), 18-hydroxy-11-deoxycorticosterone (18-OH-DOC) (Melby et al., 1971) and 16,18-dihydroxydeoxycorticosterone (Dale and Melby, 1974) have been implicated in the pathogenesis of EH, especially the type associated with a suppressed plasma renin activity (PRA).

With regard to 18-OH-DOC, several reports (Melby et al., 1971; Nowaczynski et al., 1975) have shown that the secretion rates of 18-OH-DOC and the urinary excretion of 18-hydroxy-tetrahydro-deoxy-deoxycorticosterone (18-OH-TH-DOC) were significantly higher in patients with EH and suppressed PRA. However, plasma levels of 18-OH-DOC in EH have not been investigated systematically.

Therefore, we investigated the role of this steroid in EH, in order to further elucidate the abnormalities in steroid metabolism in EH.

Materials and Methods

All materials (Crystalline 18-OH-DOC, 1, 2-3H-18-OH-DOC, Solvents, Sephadex LH-20, Silica gel and Antiserum) were used as described previously (Den et al., 1977). The measurement of plasma levels of 18-OH-DOC was performed as described in the Den's paper (1977),...
Subjects
Ten male control subjects aged 20 to 45 years (mean ± S.D.; 31.4 ± 3.3) without evidence of any metabolic, endocrine or cardiovascular disorder, and 18 male EH patients aged 20 to 50 years (mean ± S.D.; 35.5 ± 9.1) were studied. These hypertensive patients were divided into low PRA group and normal PRA group. Patients showing PRA of less than 1.0 ng/ml/hr after the intravenous administration of furosemide (0.7 mg/kg) and 2 hr of ambulation were considered to have low PRA, while those with responses over this limit were attributed to the group with normal PRA. According to this criterion, 10 of the hypertensive patients were normal PRA and 8 low PRA. Antihypertensive therapy had been withheld at least three weeks prior to this study. Complete clinical examination (including renal angiography) had excluded known causes of secondary hypertension. Main clinical and laboratory data on hypertensive patients with normal and low PRA are presented in Table 1.

Test procedures
All subjects when studied were on a diet containing 5-8 g NaCl daily. Blood samples for baseline steroid determinations were drawn between 0800 and 0900 hr after overnight recumbency.

All hypertensive patients had been studied according to the following test procedures.
1) Circadian rhythm: Blood samples for circadian rhythm were drawn at 0600, 1600, and 2400 hr on recumbency.
2) Furosemide test: Immediately after the baseline sample was drawn, furosemide (0.7 mg/kg) was administered intravenously and after 2 hr ambulation, another blood sample was collected.
3) Adrenal suppression test: One mg of dexamethasone was administered at 2100 hr orally, and on the next day, the baseline sample was drawn. Immediately afterwards, furosemide (0.7 mg/kg) was administered intravenously, and after 2 hr ambulation, another blood sample was collected.
4) Angiotensin II infusion test: Immediately after the baseline sample was drawn between 1200 and 1300 hr, angiotensin II (8 ng/kg/min., Hypertensin Ciba) was infused intravenously for 30 min and plasma samples were collected 15, 30 and 45 min later.
5) Adrenal stimulation test: Immediately after the baseline sample was drawn, a 4-hr infusion of 12.5 units of ACTH (Acthar, Armour Pharmaceutical Co.) in 500 ml of 5% dextrose was begun, and two other samples were collected 2 and 4 hr later. The subjects remained recumbent throughout the study.
6) Metopirone test: One and half g of metopirone was administered at 2100 hr orally, and on the next morning, another plasma sample was drawn between 0800 and 0900 hr.
7) Saline infusion test: Immediately after the baseline sample was drawn, 1000 ml of saline was infused for one hour and another blood sample was collected.
8) Potassium chloride infusion test: Immediately after the baseline sample was drawn, potassium chloride (0.3 mEq/kg/min.) was infused intravenously for one hour and two other samples were collected 30 and 60 min later. The subjects remained recumbent throughout the study.

Plasma aldosterone and PRA were measured by the use of kit of LE COMMISSARIAT A L’ENERGIE ATOMIQUE, France.

Statistical comparisons were made by the use of Student’s t test.

Results
Table 1 contains the ages, blood pressure and serum electrolyte concentrations for patients with EH. The hypertensive patients with low PRA were on an average older than those with normal PRA. The mean systolic and diastolic blood pressure were slightly but not significantly higher in the low renin group compared to the normal renin group. The patients with low PRA presented significantly (p<0.05) higher plasma sodium levels than those of the other group.

The circadian levels (ng/dl) of 18-OH-DOC (Fig. 1) were 6.8 ± 1.1 (mean ± S.E.) at 0600 hr, 5.1 ± 3.6 at 1600 hr and 1.8 ± 0.4 at 2400 hr in patients with low PRA and
17.8 ± 5.4 at 0600 hr, 7.5 ± 2.9 at 1600 hr, and 4.7 ± 1.5 at 2400 hr in patients with normal PRA. The differences of the circadian levels of 18-OH-DOC between both groups were not statistically significant but the concentrations of plasma 18-OH-DOC in patients with low PRA were relatively lower than in those with normal PRA.

The responses of plasma 18-OH-DOC before and after the administration of furosemide and 2 hr of ambulation were shown in Fig. 2. The mean plasma 18-OH-DOC levels (ng/dl) before and after the stimulation were 3.7 ± 3.3 (mean ± S. D.), and 16.2 ± 15.9 in low PRA group and 4.3 ± 3.1 and 6.5 ± 5.9 in normal PRA group, respectively. The patients with low PRA showed slightly higher responses than those with normal PRA but there was no statistically significant difference between two groups.

The mean concentrations of plasma 18-OH-DOC before and after the administration of dexamethasone (Fig. 3) were 4.0 ± 3.4 (mean ± S.D.) (ng/dl) and 1.8 ± 1.6 in 5 patients with low PRA, and 4.2 ± 3.4 and 1.0 ± 0.2 in 5 patients with normal PRA, respectively. After the administration of furosemide and 2 hr ambulation under dexamethasone, the mean plasma levels of 18-OH-DOC were 2.4 ± 2.3 in 4 patients with low PRA and 1.7 ± 0.6 in 3 patients with normal PRA. There was no significant difference in the levels of this steroid between two groups either before dexamethasone or before and after furosemide under dexamethasone.

The mean plasma concentration of 18-OH-DOC before and after 15, 30, and 45 min of angiotensin II infusion (Fig. 4) was 0.9 ± 0.9 (mean ± S. D.) (ng/dl), 0.5 ± 0.2, 2.5 ± 3.6, and 1.8 ± 1.7 for 4 patients with low PRA, and 2.6 ± 2.8, 10.5 ± 7.5, 7.3 ± 6.7 and 3.5 ± 2.0 for 4 patients with normal PRA, respectively. Three of 4 patients with normal PRA showed the increased response to angiotensin II infusion, while only one subject of low PRA group showed the increased response after 30 min of
angiotensin II infusion. After 15 min of angiotensin II infusion, the mean plasma levels between these two groups were significantly different ($p<0.05$).

The mean levels of plasma 18-OH-DOC before and after 2 and 4 hr of ACTH infusion (Fig. 5) were $2.9\pm0.4$ (mean $\pm$ S.E.) (ng/dl) 76.9 $\pm$ 16.7, and 81.7 $\pm$ 17.5 for 8 patients with low PRA, and 8.5 $\pm$ 3.2, 69.2 $\pm$ 10.7, and 88.2 $\pm$ 24.0 for 10 patients with normal PRA. There was no significant difference between the levels of 18-OH-DOC in both groups.

The mean plasma levels (ng/dl) of 18-OH-DOC before and after the administration of metopirone were $4.1\pm3.4$ (mean $\pm$ S. D.) and $10.3\pm8.2$ in 5 patients with low PRA, and $5.9\pm4.8$ and $12.9\pm9.1$ in 6 patients with normal PRA (Fig. 6). The mean plasma levels of 18-OH-DOC after the administration of metopirone in both groups were slightly higher than the mean baseline levels, and there was no statistically significant difference between two groups.

In the study of saline infusion (Fig. 7), the mean levels of 18-OH-DOC before and after the infusion were $3.5\pm2.7$ (mean $\pm$ S. D.) (ng/dl) and $1.3\pm1.0$ in 6 patients.
with low PRA, and $3.8 \pm 1.7$ and $2.4 \pm 1.2$ in 5 patients with normal PRA. The mean plasma levels of 18-OH-DOC after saline infusion in both groups were slightly decreased from the baseline levels, but there was no significant difference between the levels of 18-OH-DOC in both groups.

In the study of potassium chloride infusion test (Fig. 8), 2 patients with low PRA and 4 patients with normal PRA were used. One of the low PRA group and 2 of the normal PRA group showed the increased responses to potassium chloride infusion. On the other hand, serum potassium levels after potassium chloride infusion were significantly increased from the baseline levels, individually. Plasma aldosterone levels after 30 min of potassium chloride infusion were increased in 2 low PRA patients and 3 normal PRA patients, while levels of PRA after the infusion were not changed in both groups.

Discussion

With regard to the studies of the urinary excretion of 18-OH-TH-DOC and the secretion rates of 18-OH-DOC in EH, several investigators (Melby et al., 1971; Nowaczynski et al., 1975) have reported some interesting results. But there are a few papers (Mason and Fraser, 1975; Chandler et al., 1976; Dale et al., 1976; Nakajima et al., 1977) about plasma levels of 18-OH-DOC and the results are contradictory and inconclusive.

Up to now, Melby et al. (1971) reported the increased levels of the urinary excretion of 18-OH-DOC in only low renin EH. Nowaczynski et al. (1975) presented the increased secretion of 18-OH-DOC in EH with low and normal PRA. However, studies of plasma levels of 18-OH-DOC in EH have not been performed systematically.

In the present studies, the levels of plasma 18-OH-DOC in circadian rhythm were slightly lower in patients with low PRA than in those with normal PRA. The discrepancy among the increased urinary excretion of 18-OH-DOC, the increased secretion of 18-OH-DOC and the low plasma levels of 18-OH-DOC would be due, at least to some extent, to the increased metabolic clearance rate of 18-OH-DOC or modifications in the circulating protein-

![Fig. 8. Responses of plasma 18-OH-DOC, plasma aldosterone, serum K and PRA before and after potassium chloride infusion test (0.3 mEq/kg, 1 hr). A patient can be identified by the number in small letters at the end of the lines in the 4 parts (18-OH-DOC, serum K, aldosterone and PRA). Low PRA group (-- -- --). Normal PRA group (——).](image)
bound fraction of 18-OH-DOC.

In the responses of plasma levels of 18-OH-DOC after the administration of furosemide and 2-hr ambulation, there was no significant difference between these two groups. But some of patients with low or normal PRA showed the markedly increased responses to the test. Probably, these responses would be due to increased ACTH levels induced by 2 hr of ambulation. Furthermore, Dale et al. (1976) reported that the sensitivity of 18-OH-DOC to ACTH stimulation was more pronounced than that of other steroids.

In the study of adrenal suppression test, plasma levels of 18-OH-DOC after the treatment of dexamethasone decreased from baseline levels as shown in control subjects by Dale et al. (1976).

In the furosemide test under dexamethasone, plasma levels of 18-OH-DOC were unchanged. From these results, it is possible that 18-OH-DOC was not increased by endogeneous angiotensin II induced by furosemide and 2 hr of ambulation. However, Nowaczynski et al. (1975) reported that the secretion rates of 18-OH-DOC increased after sodium deprivation in three healthy normotensive control subjects. Probably, this discrepancy between their and our results might depend on the difference in these both stimulation tests.

On the other hand, the infusion of exogenous angiotensin II induced the increased levels of 18-OH-DOC in patients with normal PRA, while the other group did not show the increased levels of 18-OH-DOC.

Recently, Nakajima et al. (1977) reported that angiotensin II infusion increased moderately plasma 18-OH-DOC in control subjects and the renin-angiotensin system played a minor role in the steroid secretion.

On the other hand, the responses of 18-OH-DOC to ACTH infusion in both groups were the same, and ACTH stimulation produced 20-fold increase in plasma concentration. Furthermore, the responses of 18-OH-DOC after metopirone were similar in both groups.

In the study of plasma DOC levels to ACTH stimulation, we previously reported that patients with low PRA showed higher responses in plasma DOC levels after ACTH infusion than those with normal PRA (Honda et al., 1976). Therefore, it is suggested that plasma DOC and 18-OH-DOC in patients with low PRA were sensitive and not sensitive to angiotensin II, respectively, while those in patients with normal PRA were sensitive to ACTH as well as to angiotensin II.

In the experiments of saline infusion, the levels of 18-OH-DOC were decreased similarly in both groups as the circadian rhythm of cortisol. It may be concluded that 18-OH-DOC concentrations in patients with EH was not influenced by saline infusion.

In the study of potassium chloride infusion test, there was not any significant difference between 2 groups and there was no correlation between 18-OH-DOC and PRA, serum K levels or aldosterone levels. Some of patients with EH showed the increased levels of 18-OH-DOC to potassium infusion. Through these results, it is suggested that a part of 18-OH-DOC may be temporarily secreted from adrenal by a stimulation of potassium chloride.

Finally, it might be thought that plasma 18-OH-DOC does not play an important role in the suppression of PRA in patients with low PRA from the present study.
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References