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PLASMA DEOXYCORTICOSTERONE AND ALDOSTERONE IN ESSENTIAL HYPERTENSION

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SUMMARY

Plasma concentrations of deoxycorticosterone (DOC) and aldosterone were measured in a total of 16 control subjects and in 34 patients with essential hypertension (EH) before and 4 and 8 h after an ACTH infusion of 25U. Patients with low plasma renin activity (PRA) were significantly older, presented with higher arterial pressure and significantly lower plasma potassium levels than patients with normal PRA. Furthermore, they showed significantly higher baseline levels and responses in plasma DOC concentrations after 4 and 8 h of ACTH infusion than those with normal PRA. All hypertensive patients showed a more significantly pronounced response of plasma aldosterone to ACTH than control subjects. However, there was no significant difference in the concentrations of plasma aldosterone before and after ACTH stimulation between patients with normal PRA and those with low PRA.

Furthermore, a significant positive correlation between baseline plasma DOC and aldosterone concentrations was seen in 15 patients with low PRA.

The data suggest that an increased sensitivity of the adrenal cortex to ACTH and a specific alteration of the mineralocorticoid pathway might exist in EH with low PRA. Also the cumulative effect of aldosterone and DOC might be responsible for the marked suppression of PRA in low renin hypertension.

INTRODUCTION

With the recent development of various methods for the assay of deoxycorticosterone (DOC) in human plasma it was possible to investigate its role in essential hypertension (EH) [1–3]. The results are, however, contradictory and inconclusive.

Brown *et al.*[2] found that plasma DOC was persistently higher in about one third of patients with low plasma renin activity (PRA), while normal plasma DOC concentrations were obtained in patients with normal PRA. On the other hand, some investigators [3–6] have reported that the plasma concentrations and the secretion rates of DOC in EH with normal PRA, as well as low PRA, were within normal limits. Recently, Grim *et al.*[7] observed that the patients with low renin hypertension showed essentially normal plasma aldosterone levels. They also suggested that abnormal ACTH secretion or increased sensitivity to normal concentration of ACTH may exist in low renin hypertension.

In order to further elucidate these problems, plasma levels of DOC and aldosterone before and after the administration of ACTH, were measured in control subjects and in patients with normal and low PRA.

MATERIALS

Subjects. The control group consisted of 16 normotensive subjects (5 females, 11 males) with ages ranging from 25 to 62 years (mean: 37.8 years) who had no family history of hypertension or other cardiovascular disease and no evidence of any metabolic or endocrine disorders. Thirty-four hypertensive patients (15 females, 19 males) formed the experimental group—19 with normal PRA, while the rest had low PRA by the criteria mentioned below.

Every patient had at least two renin determinations [8]: one recumbent with normal sodium and potassium intake (135 m-equiv. of sodium and 90 m-equiv. of potassium daily), and one or more after stimulation by upright posture and/or low salt diet and/or furosemide. The division between low and normal PRA was established according to the following limits: (i) on dietary sodium 135 m-equiv./24 h, recumbent or upright: undetectable or below 0.1 ng/ml/h; (ii) on dietary sodium 10 m-equiv./24 h recumbent and upright or on dietary sodium 135 m-equiv./24 h + 5 h after furosemide 40–60 mg: below 0.6 ng/ml/h. Patients showing at least two PRA values under these limits were considered as having low PRA, while

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Abbreviations and trivial names used: Aldosterone (ALDO): 11β, 21-dihydroxy-4-pregnene-3, 20-dione-18-al, Deoxycorticosterone (DOC): 21-hydroxy-4-pregnene-3, 20-dione. ACTH: adrenocorticotropic hormone. PRA: plasma renin activity.

those with responses over this limit were attributed to the group with normal PRA.

The mean age for patients with normal PRA was 36.5 years with a range of 17–58 years and for patients with low PRA, 49.4 years with a range of 39–57 years. Antihypertensive therapy, including diuretics, had been discontinued at least two weeks prior to this study. All subjects were studied on the fourth day of a diet containing 135 m-equiv. of sodium and 90 m-equiv. of potassium. The hypertensive patients underwent a complete clinical examination, including renal angiography, prior to the investigation to eliminate all known causes of hypertension. Main clinical and laboratory data on control subjects and hyertensive patients with normal PRA and low PRA are presented in Table 1.

All blood samples for steroid determinations were drawn after overnight recumbency between 8 and 9 a.m. on the fourth day of the normal dietary salt intake. Immediately after the first blood sampling, an 8 h infusion of 25 units of ACTH (Acthar, Armour Pharmaceutical Co.) in 1 liter of 5% dextrose was begun in 7 control subjects, 6 patients with normal PRA and 5 patients with low PRA. Two further samples were collected at 4 and 8 h respectively, after the advent of the infusion.

Plasma DOC was measured by a competitive protein binding method [1]. Plasma aldosterone was determined as previously reported [9].

Statistical comparisons were made by using the Student t test for unpaired data. A linear regression analysis was performed on the values of plasma DOC and aldosterone.

RESULTS

Patients with low PRA were significantly ($P < 0.001$) older than control subjects and patients with normal PRA, whereas the ages of control subjects and patients with normal PRA were comparable (Table 1). The mean ages of the 7 control subjects, 6 patients with normal PRA and 5 patients with low PRA in the ACTH experiment, were 42.0 ± 4.5 (SE), 41.3 ± 4.1, and 51.6 ± 1.2, respectively. The differences between these mean ages were not significant. Patients with low PRA presented significantly ($P < 0.005$) lower plasma potassium levels and slightly higher systolic and diastolic blood pressures than those with normal PRA.

The mean plasma DOC concentrations before and after 4 and 8 h of ACTH infusion were 7.9 ± 1.0 (SE) ng/100 ml, 131.4 ± 25.0 and 159.9 ± 23.1 for control subjects, 6.7 ± 0.7, 101.0 ± 14.5 and 179.8 ± 42.1 for patients with normal PRA and 12.3 ± 2.2, 204.4 ± 19.7, and 310.9 ± 31.5 for patients with low PRA, respectively. The plasma DOC levels before and after 4 and 8 h of ACTH infusion were similar between control subjects and patients with normal PRA. Patients with low PRA showed significantly ($P < 0.005$) higher responses in plasma DOC levels than control subjects after 8 h of ACTH stimulation. Furthermore, when compared with patients with normal PRA, those with low PRA showed significantly higher baseline levels and responses in plasma DOC concentrations after 4 and 8 h of ACTH infusion ($P < 0.02$, $P < 0.005$ and $P < 0.02$, respectively) (Fig. 1).

The concentrations of plasma aldosterone before and after 4 and 8 h of ACTH stimulation were 7.7 ± 1.1 (SE) ng/100 ml, 11.4 ± 1.8, and 10.9 ± 1.1 for control subjects, 8.0 ± 0.8, 19.3 ± 1.9 and 18.6 ± 1.9 for patients with normal PRA, and 8.2 ± 1.0, 19.8 ± 2.4 and 22.5 ± 2.7 for patients with low PRA (Fig. 1). Baseline plasma aldosterone levels were slightly higher in patients with low PRA as compared to those with normal PRA and control subjects. After 4 and 8 h of ACTH stimulation, all hypertensive patients showed significantly higher values than control subjects (Fig. 1). The response to ACTH was slightly more pronounced in the low renin group. However, there was no significant difference in the concentrations of plasma aldosterone before and after ACTH stimulation between patients with normal PRA and those with low PRA.

Furthermore, a significant positive correlation ($P < 0.01$, $r = 0.680$) between baseline plasma DOC and aldosterone concentrations was seen in 15 patients with low PRA, whereas no correlation was

Table 1. Clinical and laboratory findings in controls and in patients with essential hypertension

		Controls (n = 16) Mean ± SE	Patients normal PRA (n = 19) Mean ± SE	Patients low PRA (n = 15) Mean ± SE
Age (years)		37.8 ± 2.7	36.5 ± 2.1	49.4 ± 1.4* #
B.P. (mmHg)	Syst.	114.5 ± 4.6	164.3 ± 5.2	177.7 ± 6.3
	Diast.	76.3 ± 1.8	101.8 ± 2.8	105.3 ± 3.2
Serum Na (mEq/l)		141.0 ± 0.8	141.0 ± 0.8	139.8 ± 0.8
Serum K (mEq/l)		4.2 ± 0.1	4.3 ± 0.1	3.9 ± 0.1 # #**
Plasma DOC (ng/100 ml)		7.9 ± 1.0	6.7 ± 0.7	12.3 ± 2.2 # # #
Plasma ALDO (ng/100 ml)		7.7 ± 1.1	8.0 ± 0.8	8.2 ± 1.0

n = number of determinations.
Significance vs controls: * = $p < 0.001$; ** = $p < 0.005$.
Significance vs patients with normal PRA: # = $p < 0.001$; # # = $p < 0.005$; # # # = $p < 0.02$.

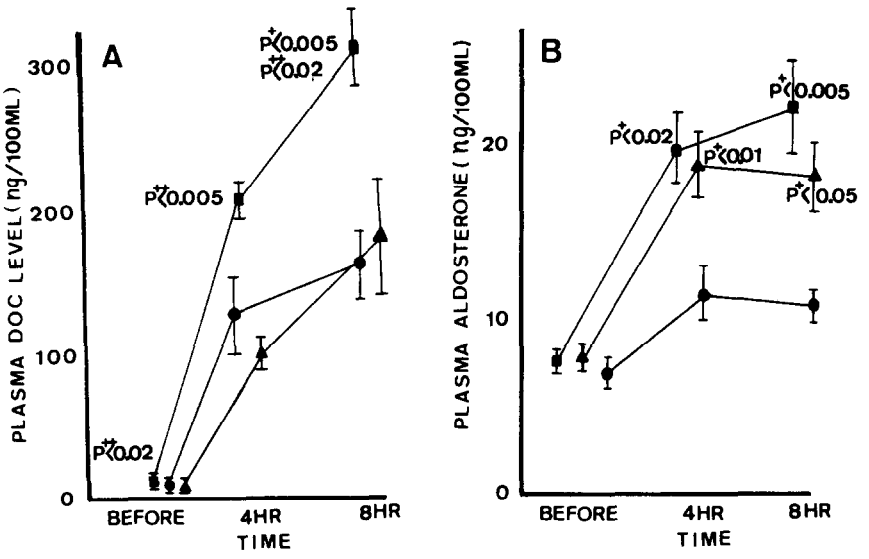

Fig. 1A. Plasma DOC levels before and after 4 and 8 h of ACTH (25U) infusion (mean ± SE).

Fig. 1B. Plasma aldosterone levels before and after 4 and 8 h of ACTH (25U) infusion (mean ± SE). Control Subjects: —●—●—. Patients with normal PRA: —▲—▲—. Patients with low PRA: —■—■—. P^{+}: comparison with control subjects. P^{++}: comparison with patients with normal PRA.

found in patients with normal PRA or in control subjects (Fig. 2).

DISCUSSION

In the present findings, the mean plasma baseline DOC level in the low renin group was slightly higher than in control subjects and significantly higher than in patients with normal PRA. Furthermore, the responses to ACTH infusion in patients with low PRA were more pronounced than in those with normal PRA as well as in control subjects, in spite of the slightly higher mean age in the low PRA group. This seems somewhat surprising, because it has been reported that adrenal response to ACTH stimulation generally decreases with age [10].

In the study of the secretion rate of DOC, Biglieri *et al.*[4] and our laboratory [6] reported that secretory rates of DOC were within the normal range in patients with EH. However, PRA of these patients was not mentioned in either study. In addition, Wood *et al.*[5] found normal secretory rates of DOC in all 8 patients with suppressed PRA. It seems, therefore, that the increase in plasma DOC is due rather to a slight decrease in the metabolic clearance rate (MCR) of DOC than to a real increase in the secretion rate.

In the present study, plasma baseline levels of aldosterone in patients with low PRA were slightly higher than in control subjects and in patients with normal PRA but the difference was not statistically significant. It was previously reported that plasma aldosterone concentrations in baseline conditions were slightly higher in EH with normal PRA and

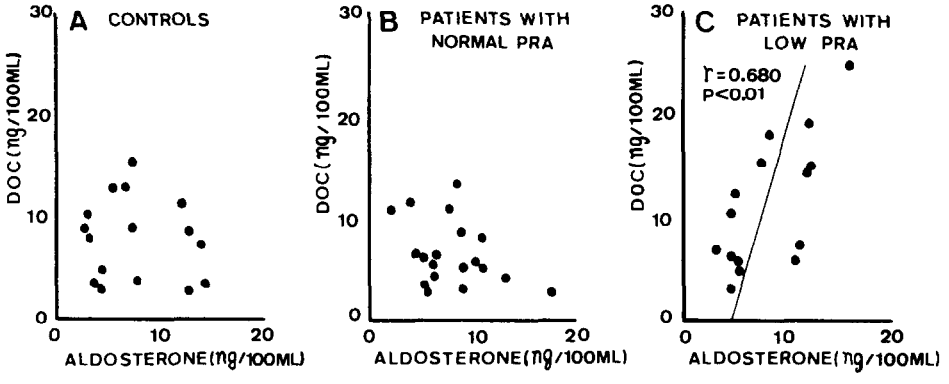

Fig. 2A. Correlation between plasma levels of DOC and aldosterone in control subjects (n = 16).

Fig. 2B. Correlation between palasma levels of DOC and aldosterone in patients with normal PRA (n = 19).

Fig. 2C. Correlation between plasma levels of DOC and aldosterone in patients with low PRA (n = 15).

significantly higher in EH with low PRA when compared to control subjects [11]. The slightly higher plasma levels probably cannot be explained by an increase in secretion rate: Biglieri *et al.*[4] and Wood *et al.*[5] have shown that the secretion rates of aldosterone in EH with normal or low PRA were within or slightly below the normal range which is in good agreement with our previous reports [6, 12]. Similarly, Tuck *et al.*[13] recently reported a significantly decreased aldosterone secretory rate in 22 patients with EH and low PRA.

The slightly higher plasma levels of aldosterone together with a decreased or normal secretion rate could be explained, at least to some extent, by a decrease in the MCR of aldosterone in EH with normal PRA [6, 12]. Recently, it was reported that the secretory rates of aldosterone were significantly higher and the MCR slightly lower in low renin EH than in normal renin EH [14].

In the present study, patients with normal or low PRA showed significantly higher responses in plasma aldosterone to ACTH infusion in spite of more advanced mean age as compared to control subjects. It was reported that the mean age in EH with low PRA is higher than in those with normal PRA [13, 15–17]. Furthermore, it was shown that PRA and urinary aldosterone of normal subjects on unrestricted sodium intake and on day 3 of sodium restriction, decreased with age [18] and that the responsiveness of PRA and urinary aldosterone to stimuli decreased with age in hypertensive patients [13].

Patients with EH showed hyperresponsiveness to ACTH infusion in plasma aldosterone with a simultaneous sharp decrease in the binding to plasma protein fraction, while aldosterone MCR increased significantly [19]. The inverse relationship between the unbound and bound fraction means that ACTH has increased the concentration of the free, physiologically active plasma aldosterone. In the same experiments, the urinary oxoconjugate increased more, and the urinary tetrahydroaldosterone less, in patients than in controls. There also seemed to be a less pronounced decrease in aldosterone binding to plasma fraction in patients with low renin EH than in control subjects. The hepatic blood flow remained unchanged during ACTH infusion.

More recently it was found that ACTH selectively produced a significant increase in the MCR of aldosterone, cortisol and DOC, whereas the MCR of progesterone and corticosterone were less affected [20]. It was concluded that modifications in the circulating protein bound fraction of various steroids could account for this selective effect and that this could be due to a new homeostatic mechanism regulating the plasma concentration. It is conceivable that perturbations in the plasma protein bound fractions can account for some of the observed abnormalities in low renin patients.

The above experiments involving ACTH infusion, concur with recently presented evidence [21] that the MCR of aldosterone determined before and on the third day of chronic ACTH administration to healthy adult male subjects (on high sodium intakes) were substantially increased by ACTH.

It is also possible that in low renin patients the hyperresponsiveness of aldosterone to ACTH is due to increased sensitivity of the adrenal cortex, or parts of it, or that slightly increased secretion of ACTH may exist in these patients. This could be due, at least to some extent, to the significantly lower than normal plasma cortisol concentrations in low renin hypertension [11].

A significant positive correlation between plasma DOC and aldosterone concentrations found in EH with low PRA, while there was no correlation in the other two groups may indicate that plasma concentration of aldosterone in patients with low PRA is controlled to a greater extent by ACTH than in patients with normal PRA.

Many investigators have shown that patients with early EH and normal or low PRA have an increased secretory rate of 18-hydroxy-11-deoxycorticosterone (18-OH-DOC) [22–24], or of another unidentified mineralocorticoid [5, 25]. In other studies, some enzyme abnormalities in steroid biosynthesis, especially a partial deficiency of 17-hydroxylation [6, 23], were suggested. Whatever mechanisms are involved, it may be suggested from the present study and some earlier reports [11, 19, 22–26] that a disproportionately high plasma aldosterone with respect to renin levels and an exaggerated mean aldosterone, DOC and 18-OH-DOC response to ACTH infusion in EH with low PRA, could be partially due to a specific alteration of the mineralocorticoid pathway [11, 19, 27]. Furthermore, it seems possible that the cumulative effect of aldosterone and its two precursors may be responsible for the marked suppression of PRA in low renin hypertension [11, 19]. Only further systematic investigation can prove whether these speculative concepts have merit.

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