Effects of fludrocortisone withdrawal on plasma angiotensin II, ACTH, vasopressin, and potassium in patients with Addison’s disease

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Abstract. We attempted to answer the question whether excessive rises in endogenous plasma angiotensin II (AII) stimulate ACTH secretion by measuring PRA, AII, AVP, ACTH, and cortisol in 8 patients with Addison’s disease before and after withdrawal of fludrocortisone substitution. Blood was drawn at 14.30 h, exactly 6½ h after the morning dose of hydrocortisone had been taken. PRA and AII were initially higher than normal in 4 patients. After withdrawal of fludrocortisone for 1 or 2 weeks, PRA and AII rose markedly in 4 patients (up to 260 ng/l) without concomitant changes in plasma ACTH levels (r = −0.081, AII vs ACTH). Changes in plasma cortisol could not have obscured a stimulatory effect of AII on ACTH by variable feedback inhibition of ACTH release. The increase in plasma AII levels in the 4 patients was larger than that observed in a previous study in normal subjects after rigorous dietary sodium restriction. In all patients, hyperkalaemia developed after fludrocortisone withdrawal, independent of changes in PRA and AII. Rises in PRA, AII, and plasma potassium were partially reversed by increased sodium intake and further suppressed by resumption of fludrocortisone therapy. Plasma AVP remained in the normal range after fludrocortisone withdrawal, but was slightly elevated after increasing salt intake without fludrocortisone administration. Conclusions: 1) Rises of endogenous plasma AII to levels tenfold higher than normal do not stimulate ACTH release. AII is probably not a physiological modulator of ACTH secretion. 2) Mineralocorticoid substitution in Addison’s disease should be monitored by plasma potassium measurement. Hyperkalaemia may coexist with normal PRA.

Angiotensin II (AII) infusions stimulate plasma ACTH in the dog (Ramsay et al. 1978; Reid et al. 1982) and in man (Rayyis & Horton 1971; Haller et al. 1986). However, the physiological or pathophysiological role of circulating AII in the regulation of ACTH release remains obscure. In untreated patients with the salt-losing form of 21-hydroxylase deficiency, plasma AII or PRA levels are very high (Rösler et al. 1977; Horner et al. 1979) and seem to contribute to the hypersecretion of 17-OH-progesterone and adrenal androgens. Some authors believe that this effect is mediated by ACTH (Rösler et al. 1977), whereas others regard a direct effect of AII on the zona fasciculata the more likely mechanism (Horner et al. 1979). With the study presented here, we tested the hypothesis of a stimulatory effect of endogenous AII on ACTH in patients with Addison’s disease in whom PRA and plasma AII can be raised by the withdrawal of mineralocorticoid substitution (Brown et al. 1968; Oelkers & L’age 1976; Smith et al. 1984).

Patients and Methods

a) Patients

Eight Addisonian patients (6 women, 2 men; 33–59 years of age) gave written consent to participate in the study, the protocol of which had been approved by the Ethical Committee of the Klinikum Steglitz. Primary adrenocortical insufficiency had been detected in the patients between 1950 and 1982. In all patients, the definitive diagnosis was based on a low or undetectable
plasma cortisol level unresponsive to iv or im injection of 0.25 mg of ACTH 1–24 (Synacthen®, Ciba). In 5 patients urinary aldosterone-18-glucuronide was undetectable, whereas in the others, the excretion rates were 1.5, 1.8 and 2.5 nmol/24 h (normal: 8–40 nmol/24 h). In the two men, adrenal tuberculosis was the cause of the disease, whereas the six women had the idiopathic form of Addison's disease, three with and three without adrenocortical antibodies detectable. All patients had been regularly substituted with between 15 and 30 mg of hydrocortisone per day (5 took divided doses) and with between 0.05 and 0.15 mg of 9 alpha-fluorohydrocortisone (Astonin H®, Merck) in the morning.

b) Protocol

For the study protocol, the patients were asked to take their morning dose of hydrocortisone (15 or 20 mg) invariably at 08.00 h, and a possible second dose at 16.00 h. The patients were given a protocol for the registration of their morning weight and of any feelings of ill health.

Blood for measuring hormones, electrolytes, and haematocrit was drawn in the clinic at 14.30 h by venipuncture (Butterfly 19, Venisystems™, no muscle pump) after 30 min of rest in an armchair. Blood pressure was measured twice by sphygmomanometer and heart rate was counted after 20 min in the sitting position.

Blood was sampled on five occasions, the numbers of which correspond to those on the abscissa of the figures: 1. On routine substitution (see above). 2, 1 week after withdrawal of fludrocortisone (Flu). 3. 2 weeks after withdrawal of Flu. 4. 3 weeks after withdrawal of Flu with 7 g per day of extra salt added to the food. Patients received salt capsules, the content of which was spread over the food. 5. 1 week after taking 0.2 mg Flu/day at 16.00 h.

In one patient, step 3 was omitted since she felt weaker than normal, although her blood pressure and heart rate were unchanged. She had lost 1 kg of weight. In one patient step 3 and 4 were omitted since she had orthostatic tachycardia and had lost 2 kg of weight. She received immediately a large single dose of hydrocortisone and proceeded to step 5. The other patients had no complaints, and the objective clinical signs allowed to follow the protocol as planned.

c) Laboratory methods

Sodium, potassium, creatinine in serum and haematocrit were measured by routine laboratory methods. PRA was measured by a modification of the method of Haber et al. (1969). The sensitivities and coefficients of variation of the plasma ACTH and cortisol methods has recently been described (Haller et al. 1985, 1986). Plasma AI1 was measured radioimmunologically by the method of Morton & Webb (1985) after extraction of the plasma on Sep-pak C18 cartridges (Waters Associates, MA). The intra-assay variability of AI1 measurements in our laboratory is 9.0%, the inter-assay variability 10.3%. The normal range in healthy ambulatory subjects is 5.7 to 19.0 ng/l (11.8 ± sd 3.6 ng/l). Plasma AVP was measured according to Morton et al. (1985) with an extraction similar to that used for the plasma AI1 determination. The intra-assay variability in our laboratory is 4.9%, the inter-assay variability 8.8%. The normal range of AVP levels in ambulatory normal subjects on normal fluid intake is 0.45 to 0.92 ng/l (0.71 ± sd 0.13 ng/l; N = 41). The antibodies for AI1 and AVP measurement were kindly provided by Dr J. J. Morton, MRC Blood Pressure Unit, Glasgow, UK. For statistical calculations, Student's paired t-test and coefficients of correlation (Pearson) according to a Stats-2™ programme (release 2.0) of Stat Soft (Tulsa, OK) were used.

Results

After fludrocortisone withdrawal, mean body weight fell from 64.4 ± 4.7 (SEM) to 63.4 ± 4.8 kg (P < 0.01) and rose to 65.4 ± 4.9 kg (P < 0.01) after readministration of Flu. Blood pressure did not change significantly during the study, but heart rate rose from 75 ± 4 to 85 ± 4 beats/min (P < 0.05) at step 2. Mean PRA at the beginning of the study (10.7 ± sem 2.6 μg·l⁻¹·h⁻¹) was significantly higher (P < 0.01) than in normal ambulatory subjects (3.8 ± 2.4 μg·l⁻¹·h⁻¹; N = 50). It was outside the normal range for ambulatory subjects (0.8–6.0 μg·l⁻¹·h⁻¹) in 4 of the 8 Addisonian patients. PRA correlated very closely with plasma AI1 throughout the study (r = 0.943; N = 36; P < 0.001) as one would expect. Fig. 1A shows plasma AI1 rising markedly in 4 of the 8 patients after Flu withdrawal and falling again after salt administration and/or after the high dose of fludrocortisone. Serum potassium rose markedly in all patients, as shown in Fig. 1B, at least to 5.1 mmol/l, but, in 3 patients, serum K⁺ rose to between 6.5 and 7 mmol/l. The changes in plasma AI1 and serum K⁺ after Flu withdrawal were not significantly correlated (Fig. 1D).

Fig. 2 shows mean values of the plasma hormones and of the haematocrit and serum electrolytes during the study. Because of the large variability, the rise in PRA and AI1 at step 2 and 3 was only of borderline significance (P: 0.1–0.05). Administration of extra salt (step 4) led to a marked fall in mean PRA and AI1, but the reduction
Fig. 1.
Changes in plasma angiotensin II (A), ACTH (C), and serum potassium (B) during steps 1 through 5 (see text and legend to Fig. 2) of the study. Each symbol represents 1 patient. D: Relationship between changes in plasma angiotensin II and changes in serum potassium between step 1 and 2 and between step 1 and 3.

became significant only at step 5. Hyperkalaemia at step 3 was significantly reduced by salt administration and more so by Flu. Although PRA and AII rose markedly in 4 patients at step 2 and 3 (maximum AII levels: 88, 171, 248, 260 ng/l), plasma ACTH showed no similar changes (Figs. 1C and 2). Mean ACTH levels fell insignificantly at step 2 and 3. The coefficient of correlation between all pairs of plasma AII and ACTH (N = 36) was −0.081 (ns). For unknown reasons, plasma cortisol levels at 14.30 h (hydrocortisone substitution) were significantly higher at step 2 than step 1, but subsequently the plasma cortisol levels, which exert a feedback on ACTH, were rather constant (Fig. 2) and could not have masked a stimulatory effect of AII on ACTH. Mean plasma AVP was in the low-normal range when it was measured first (step 2). It rose significantly at step 3 and more so after salt administration, although serum sodium had not significantly risen at that time. Plasma AVP slightly exceeded the normal range at step 4 in 3 out of 7 patients studied. Changes in AVP were not significantly correlated with those of plasma AII.
In the present study, mean plasma AII levels rose from 34 to 90 ng/l after fludrocortisone withdrawal (upper normal limit, upright: 19 ng/l) and fell to 21 ng/l after resumption of fludrocortisone therapy. In spite of this large increase in AII levels with individual surges up to 260 ng/l, no parallel changes occurred in plasma ACTH. Apart from step 2, when the plasma cortisol levels measured about 6 h after the morning dose of hydrocortisone were higher than at the other days of blood sampling, changes in plasma cortisol could not have masked a stimulatory effect of AII on ACTH by feedback inhibition. We recently had the opportunity to measure plasma cortisol and ACTH in 6 seated normal subjects at 15.00 h. Plasma ACTH was 9 ± 2 ng/l (lower than in the Addisonian patients) and cortisol was 241 ± 25 nmol/l (slightly higher than in the patients, Fig. 2). In accordance with observations of Scott et al. (1978), the feedback between plasma cortisol and ACTH seems, therefore, to be normal in Addisonian patients substituted with hydrocortisone. This normal relationship does not seem to be modified by markedly increased plasma AII levels. The increase in venous plasma AII after fludrocortisone withdrawal in our patients was greater than that occurring in normal men who were sodium-depleted by giving them furosemide and a very low sodium diet for 5 days (60 ± 10 ng/l; Seifert & Oelkers 1981). The negative finding with regard to an effect of AII on ACTH secretion speaks against the physiological significance of AII infusion experiments in dogs (Ramsay et al. 1978; Reid et al. 1982) and in man (Rayyis & Horton 1971; Haller et al. 1986), in which a slight stimulation of ACTH secretion was

Fig. 2.
Changes in plasma ACTH, cortisol, renin activity (PRA), angiotensin II (AII), serum electrolytes, haematocrit (Hkt) and vasopressin in Addisonian patients from step 1 through 5 (abscissa) of the study. Mean ± SEM are shown. Flu: fludrocortisone. NaCl: amount of salt per day added to the diet. (*) or + : P < 0.05; ** or ++: P < 0.01 (paired t-test) compared with step 1 (*) or with highest mean value (+) after step 3 or 4.
observed. The results are in accordance with angiotensin II infusion studies in Addisonian patients, in whom effects of AII on ACTH were not significant (Haller et al. 1985). In a recently published study by Keller-Wood et al. (1986) in the dog, a stimulatory effect of AII (20 μg · kg⁻¹ · min⁻¹) on ACTH could not be reproduced. Our studies cannot exclude, however, that AII stimulates ACTH secretion in patients more severely sodium-deprived than our patients, e.g. completely untreated patients with Addison’s disease or salt-losing adrenogenital syndrome.

In 4 out of 8 Addisonian patients, PRA was above the normal range at the beginning of the study. Two of these patients had taken 50 μg, the others 100 and 150 μg of Flu per day, respectively. Increased PRA levels in Addisonian patients are believed to indicate inadequate mineralocorticoid substitution (Oelkers & L’age 1976; Smith et al. 1984). However, it is likewise possible that greatly increased ACTH levels during the night (Scott et al. 1978) in patients who take one or two doses of hydrocortisone in the first half of the day, stimulate renin secretion in Addisonian patients. We have recently shown that low-dose ACTH infusions into normal men stimulate renin secretion with a lag period of 6–8 h (Belkien et al. 1983). This stimulatory effect is overridden by sodium retention in normal men when ACTH is being infused for more than 30 h. In Addisonian patients, however, ACTH hypersecretion could not lead to sodium retention. Therefore, ACTH might be an additional determinant of PRA in Addisonian patients who may not be sodium-deficient and ‘appropriately substituted’ despite a slightly increased PRA.

An interesting result of the present study is the dissociation of changes in PRA and plasma AII on the one hand and of plasma potassium concentration on the other hand after withdrawing fludrocortisone substitution (Fig. 1). The increase in PRA and AII probably reflects sodium loss, which is obviously not closely correlated with the increase in extracellular potassium concentration, although both are functions of the mineralocorticoid. This observation is best explained by an effect of fludrocortisone (like aldosterone) on extrarenal potassium homeostasis (Bia et al. 1982) in addition to mineralocorticoid effects on the kidney. In accordance with experience from the pre-steroid era, hyperkalaemia in Addisonian patients can be ameliorated by adding salt to the diet (Fig. 1 and 2). This effect is probably due to facilitated tubular potassium secretion in the presence of an increased tubular sodium load (Brenner & Berliner 1973). The salt-loading step (step 4) was included into the protocol in order to suppress renin and AII (and possibly ACTH) by two different mechanisms: 1. sodium alone, and 2. sodium retained through the effect of fludrocortisone. Since the latter has some glucocorticoid activity (Kley et al. 1973), it was given 22 h before blood sampling at step 5, but it would still have been difficult to attribute a possibly occurring suppression of ACTH to a fall in AII alone. However, ACTH suppression occurred neither at step 4 nor 5, indicating that changes in endogenous plasma AII in this order of magnitude do not significantly affect ACTH secretion.

Another point of interest in our patients, who were normally substituted with cortisol, is the dissociation between changes in PRA/AII and plasma AVP in the phase of sodium deficiency. Plasma AVP only exceeded the normal range in 3 out of 7 subjects after the week of salt substitution, when PRA/AII had already fallen. These observations support the view that cortisol deficiency is an important causative factor for ‘inappropriate antidiuretic hormone secretion’ in Addisonian patients (Salomez-Granier et al. 1983) and that circulating AII, in contrast to earlier reports (Ramsay et al. 1978) has no major effect on AVP secretion (Henrich et al. 1986).

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References


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