Effect of angiotensin II on plasma ACTH in patients with Addison’s disease

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Abstract. Short-term angiotensin II (AII) infusions (3 ng/kg/min) were performed in 5 patients with Addison’s disease in order to assess the effect of AII on ACTH secretion. Baseline ACTH levels were elevated due to a 9-h time lag between hydrocortisone administration and onset of the study. In 2 separate infusion periods of 30-min duration, AII had no unidirectional effect on plasma ACTH. Mean ACTH increased slightly but insignificantly. Mean blood pressure rose by about 10 mmHg. The degree of angiotensinaemia induced is probably similar to the state of moderate to severe sodium deficiency. Short-term changes of AII in this order of magnitude have obviously no major effect on ACTH secretion.

Controversy exists regarding the role of angiotensin II (AII) in the regulation of the hypothalamic-pituitary-adrenocortical system. AII stimulates ACTH release from anterior pituitary cells in culture (Gaillard et al. 1981; Sobel 1983). Intrapituitary infusions of AII into dogs also elicit ACTH release (Maran & Yates 1977). Systemic iv infusions of AII into rats or dogs tend to raise plasma ACTH levels, but large dosages of AII are required (Ramsay et al. 1978; Reid et al. 1982; Rivier & Vale 1983). In man, Rayyis & Horton (1971) demonstrated an acute increase of plasma ACTH together with a fall in plasma cortisol during infusion of 8–12 ng/kg min of AII, while Semple et al. (1979) found a rapid fall in plasma ACTH, measured by a cytochemical assay. In long-term AII infusion experiments (3 days) our own group was unable to find a systematic trend in the fluctuation of ACTH levels during AII infusion (Oelkers et al. 1978). In the present paper we report on effects of AII on plasma ACTH in patients with Addison’s disease with moderately raised ACTH levels. In this state it should be possible to observe a clearcut fall in plasma ACTH if it occurred more reliably than in normal subjects whose ACTH levels are often very low.

Materials and Methods

Five patients with longstanding Addison’s disease (patients’ characteristics in Table I) gave their informed consent to participate in the study. The experimental schedule was approved by the Ethical Committee of the Klinikum Steglitz. The patients were regularly substituted with 20 to 30 mg of hydrocortisone in two divided doses and with 0.05–0.1 mg fludrocortisone per day. One week before the study, the fludrocortisone dose was increased to 0.2 mg/day in order to lower plasma renin activity (PRA) and AII levels (Oelkers & L’age 1976). At midnight preceding the day of AII infusion, the patients took 20 mg of hydrocortisone orally. No hydrocortisone was given in the morning. For this reason, mean plasma ACTH levels ranged between 85 and 400 pg/ml at 9 a.m. At 8 a.m., Abbocat cannulas were placed into both antecubital veins of the recumbent patient. At 9 a.m., blood sampling for the measurement of plasma ACTH was started. The sampling intervals are shown in Fig. 1. From 10 a.m. to 10.30 a.m. and from 11 a.m. to 11.30
a.m., 3 ng/kg/min of AII (Hypertensin-CIBA) was infused iv. The last blood sample was taken at noon, 30 min after stopping the second AII infusion. Blood pressure was measured every 10 min throughout the study by sphygmomanometer.

At 9 a.m., blood samples for measuring haematocrit, plasma renin activity (Oelkers et al. 1974) and plasma concentrations of sodium, potassium, creatinine (routine methods), cortisol (radioimmunoassay kit CEA SORIN) in addition to ACTH were taken. Blood for ACTH measurement was collected into pre-chilled tubes containing K+EDTA. The tubes were then put into crushed ice, centrifuged immediately at 3°C and stored for maximally 4 weeks at −20°C before the radioimmunoassay was carried out. ACTH was measured in 0.1 ml unextracted plasma using a kit distributed by SORIN BIOMEDICA, Saluggia, Italy. The antibody binds ACTH 1–39 (human and porcine) and 1–24 with the same affinity on a molar basis (100%), fragments 1–16, 11–24, 1–10 and 25–39 with 3%, 1.5%, <0.1% and <0.1%, respectively, according to the kit manual. Using the same kit in a previous study on 4 Addisonian patients, we found plasma ACTH suppressed to less than 20 pg/ml in all of them 3–4 h after oral ingestion of 20 mg hydrocortisone in the morning. All ACTH samples of one patient were analyzed within the same assay. At plasma ACTH levels of 25 pg/ml, 450 pg/ml and 880 pg/ml, the intra-assay variability (n = 10 each) was 8.2%, 3.3% and 6.2%, respectively. The inter-assay variability at 50 pg/ml was 12.9% in 8 consecutive assays. The normal range of plasma ACTH at 9 a.m. in our laboratory is <5–50 pg/ml.

Results

Plasma electrolytes, creatinine and haematocrit were in the normal range at the onset of the study (Table 1). Average mean blood pressure ranged between 95 and 115 mmHg in the control period. PRA was in the normal range (0.5–4.5 ng/ml/h) in 2 and slightly elevated in 3 patients. Plasma cortisol (6.8–30 nm/l) was far below normal (200–600 nmol/l) at 9 a.m. and ACTH was elevated. During AII administration, mean blood pressure rose by about 10 mmHg in both infusion periods (Fig. 1). Plasma ACTH levels were not altered by AII infusion in a uniform manner (Fig. 1). The percentage changes of plasma ACTH compared with the individual mean levels of the pre-infusion period are shown in Fig. 2. Patient E.K. exhibited an 80% rise of ACTH in the first infusion period and patient F.S. a 100% rise in the second. Changes in the other patients were small. The mean percentage change in all patients together after 30 min of AII infusion was +20% in the first and +38% in the second period. Because of the small number of subjects and heterogeneous ACTH responses, a statistical evaluation of the results was not attempted.

Fig. 1.
Mean blood pressure (±sd) and individual plasma ACTH levels in 5 patients with Addison’s disease before and during the two periods of AII infusion.
Clinical and laboratory data of the patients investigated. Means ± SD are shown for mean blood pressure and plasma ACTH measurements during the initial control period (n = 5 each).

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<td>s-(Na⁺) mm/l</td>
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<td>2.4</td>
<td>8.9</td>
<td>6.8</td>
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<td>Mean ACTH (pg/ml)</td>
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<td>09.00-10.00 h</td>
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<td>103 ± 12</td>
<td>202 ± 90</td>
<td>86 ± 18</td>
<td>319 ± 100</td>
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<td>30</td>
<td>22</td>
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Discussion

The infusion of 3 ng/kg/min of Asn₁-Val₅-AII has no marked effect on plasma ACTH in Addisonian patients with elevated ACTH levels due to glucocorticoid deficiency. The slight percentage mean increase in plasma ACTH was mainly due to a large rise in one subject during the first and in a different subject during the second infusion period. Since ACTH levels exhibited large fluctuations even in the control period, the changes during AII infusion may be mere chance. An infusion period...

![Graph](https://via.placeholder.com/150)

**Fig. 2.** Percentage changes of plasma ACTH during the first (left) and second (right) period of AII infusion. Upper panel: single individuals with the same symbols as used in Fig. 1. Lower panel: mean changes (± SEM) as compared with the mean ACTH levels of the preceding control period.
of 30 min would be long enough to observe acute stimulation of ACTH secretion by AII, since plasma ACTH is markedly elevated 15 min after an iv injection of corticotrophin-releasing factor (Schulte et al. 1984). According to data compiled by Krieger (1979), the plasma half-life of ACTH in normal subjects is 8—12 min, and 22—28 min in patients with Addison’s disease when N-terminal antibodies are used. After the iv injection of 50 mg hydrocortisone in 2 of our patients, we observed an initial short increase and thereafter a fall of plasma ACTH from 732 to 226 pg/ml and from 261 to 115 pg/ml, respectively, within 30 min. The infusion period is, therefore, also long enough to document an inhibitory effect of AII on ACTH secretion.

The infusion rate of 3 ng/kg/min of AII produced an increase in mean blood pressure by about 10 mmHg. According to previous studies (Oelkers et al. 1972, 1978), arterial plasma AII levels would be increased by 50—100 pg/ml with this dosage. An increase of plasma AII in the same order of magnitude was also observed after 4 days of severe dietary sodium restriction (plus initial furosemide) in normal subjects. These AII levels, therefore, reflect a state of marked activation of the renin-angiotensin system in normal man. Although ACTH regulation may be different from normal in patients with Addison’s disease, it appears that a moderate increase of plasma AII exerts no acute effect on ACTH secretion. This is in accordance with results of more prolonged AII infusion studies in normal subjects (Oelkers et al. 1978) but at variance with findings by Semple et al. (1979) in normal subjects in whom infusions of 2—6 ng/kg min of AII led to a rapid fall in plasma ACTH. In the latter study, ACTH was measured by an extremely sensitive cytochemical assay, while in other studies ACTH was measured by radioimmunoassay. In the animal experiments by Ramsay et al. (1978), Reid et al. (1982) and Rivier & Vale (1983) mentioned earlier, AII infusion rates larger than 10 ng/kg/min or large-dose bolus injections of AII were required to raise plasma ACTH or corticosteroid levels. In a study by Ben et al. (1984) on acute renovascular hypertension in dogs, an increase of plasma AII from about 20 pg/ml to between 60 and 140 pg/ml for several days was not accompanied by a significant change in plasma corticosteroid concentration. Conversely, administration of Captopril to dogs with high plasma AII levels failed to change plasma corticosteroids.

The results of the present study together with most human and animal data published so far speak against an inhibition of ACTH secretion by AII. A mild stimulatory effect of AII on ACTH may exist, which may become more clearcut with larger dosages of AII infused.

References


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