Plasma aldosterone response to acute stimulation in panhypopituitarism

M. Birkhäuser, A. M. Riondel, R. Gaillard, F. Mantero and M. B. Vallotton

Laboratoire d'Investigation Clinique, Division d'Endocrinologie,
Département de Médecine, Hôpital Cantonal, CH-1211 Genève 4, Switzerland and
Istituto di Semeiotica Medica dell'Università di Padova, Padova, Italy

Abstract. The influence of acute stimulation by ACTH, upright posture and angiotensin II on plasma aldosterone levels was assessed in human panhypopituitarism. While stimulation by ACTH in hypopituitary patients induced a plasma aldosterone increase similar to that observed in healthy controls, stimulation by upright posture or by infusion of angiotensin II resulted in a lower plasma aldosterone response than in controls in most of the patients. These results suggest that the presence of an anterior pituitary hormone, most likely ACTH, directly or indirectly exerts a permissive action on aldosterone secretion in man.

ACTH is a potent stimulus to aldosterone secretion, but the importance of intact pituitary function for normal short- or long-term regulation of aldosterone secretion is still controversial. Although the inner zones of the adrenal cortex undergo atrophic changes after hypophysectomy, the zona glomerulosa remains essentially intact (Swann 1940) and basal aldosterone production is normal or subnormal (Williams et al. 1971) suggesting that it is relatively independent of the pituitary gland.

Müller et al. (1956, 1957) reported that the regulation of aldosterone secretion in panhypopituitarism also depended upon non-hypophyseal factors able to maintain the responsiveness of the zona glomerulosa to ACTH. They observed an immediate and clearcut rise of aldosterone excretion in hypopituitary subjects after ACTH administration. More recently, Williams et al. (1971) reported that hypopituitary patients failed to increase their aldosterone secretion significantly in response to ACTH infusion. This finding is consistent with experiments in hypophysectomized animals (Palmore et al. 1970; Palmore & Mulrow 1967; Ganong et al. 1967). Even so, Dluhy et al. (1974) found significant aldosterone increments after ACTH stimulation in all the hypopituitary patients tested, although these increments were less marked than in healthy subjects.

Salt restriction, another strong stimulus of aldosterone, and mediated by angiotensin II, has also been studied in hypopituitary subjects. In 15 subjects studied during sodium restriction by Williams et al. (1971), 11 had a significant lag in reaching balance, due in part to a delayed rise in aldosterone secretion. On the other hand, Raiti et al. (1968) observed a normal response of aldosterone production to sodium restriction in hypopituitary children receiving long-term treatment with growth hormone extracts. The same finding was reported by Thomas & El-Shaboury (1971) in patients with suppression of ACTH production secondary to prolonged administration of glucocorticoids. Baumann & Müller (1974) demonstrated in the rat that the enzymes involved in the final steps of aldosterone biosynthesis are stimulated by sodium restriction or potassium load independent of the functional state of the pituitary gland.

1 Present address: Universitäts-Frauenklinik, CH-4031 Basel, Switzerland.
Table 1.
Clinical data and endocrine function in 12 hypopituitary patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Aetiology</th>
<th>Duration of insufficiency (years)</th>
<th>Sella turcica (size)</th>
<th>Pituitary-adrenal axis (urinary 17-OH response to metyrapone)</th>
<th>Thyroid function: $^{131}$I scanning 1) conversion in %, or 2) TSH response to iv TRH</th>
<th>GH response to induced hypoglycaemia</th>
<th>Prolactin (basal values µg/ml)</th>
<th>Gonadotrophins (urinary values) (IU/24 h)</th>
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<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>F</td>
<td>Idiopathic</td>
<td>14</td>
<td>normal</td>
<td>none</td>
<td>2%¹</td>
<td>–</td>
<td>1.5</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>F</td>
<td>Idiopathic</td>
<td>25</td>
<td>normal</td>
<td>none</td>
<td>absent²</td>
<td>absent</td>
<td>1.5</td>
<td>undetectable</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>F</td>
<td>Idiopathic</td>
<td>25</td>
<td>normal</td>
<td>none</td>
<td>8%¹</td>
<td>absent</td>
<td>–</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>M</td>
<td>Idiopathic</td>
<td>10</td>
<td>normal</td>
<td>none</td>
<td>5%¹ absent²</td>
<td>absent</td>
<td>1.5</td>
<td>undetectable</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>M</td>
<td>Idiopathic</td>
<td>15</td>
<td>normal</td>
<td>none</td>
<td>5%¹</td>
<td>–</td>
<td>1.5</td>
<td>undetectable</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>M</td>
<td>Idiopathic</td>
<td>20</td>
<td>normal</td>
<td>none</td>
<td>3%¹ absent²</td>
<td>absent</td>
<td>1.5</td>
<td>undetectable</td>
</tr>
<tr>
<td>7</td>
<td>36</td>
<td>F</td>
<td>M. Sheehan</td>
<td>13</td>
<td>normal</td>
<td>none</td>
<td>absent²</td>
<td>absent</td>
<td>1.5</td>
<td>undetectable</td>
</tr>
<tr>
<td>8</td>
<td>51</td>
<td>F</td>
<td>M. Sheehan</td>
<td>15</td>
<td>normal</td>
<td>none</td>
<td>2%¹</td>
<td>–</td>
<td>3.1</td>
<td>blood values: FSH 6.4 mIU/ml LH 3.2 mIU/ml</td>
</tr>
<tr>
<td>9</td>
<td>41</td>
<td>F</td>
<td>Chromophobe adenoma</td>
<td>25</td>
<td>abnormal</td>
<td>none</td>
<td>absent²</td>
<td>absent</td>
<td>18.7</td>
<td>blood values: FSH 0.7 mIU/ml LH 1.7 mIU/ml</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>M</td>
<td>Chromophobe adenoma</td>
<td>2</td>
<td>abnormal</td>
<td>none</td>
<td>3%¹</td>
<td>absent</td>
<td>10.0</td>
<td>blood values: FSH 0.7 mIU/ml LH 5.0 mIU/ml</td>
</tr>
<tr>
<td>11</td>
<td>49</td>
<td>F</td>
<td>Craniopharyngioma</td>
<td>5</td>
<td>abnormal</td>
<td>none</td>
<td>4%¹</td>
<td>absent</td>
<td>–</td>
<td>25</td>
</tr>
<tr>
<td>12</td>
<td>54</td>
<td>M</td>
<td>Metastasis of adenocarcinoma</td>
<td>2</td>
<td>abnormal</td>
<td>none</td>
<td>3%¹</td>
<td>–</td>
<td>1.5</td>
<td>–</td>
</tr>
</tbody>
</table>
This study was designed to define in man the consequence of pituitary failure on the responsiveness of aldosterone to three acute stimuli; ACTH, angiotensin II and upright posture.

Protocols and Methods
The study protocols were approved by the Ethical Committee of the Department of Medicine. They were used in 12 patients aged from 36 to 63 years suffering from longstanding anterior pituitary insufficiency; 1 patient (No. 7) also suffered from a total loss of posterior pituitary function. All gave their informed consent and had a complete medical examination to ascertain that the tests to be done would not involve a potential risk to their health.

Their clinical features and the endocrinological work-up done before the study to confirm loss of anterior pituitary function are shown in Table 1. Thyroid hormone substitution had been interrupted in all cases for 7 days at least and corticosteroid substitution for 24 h before the beginning of the study. Patients were on an unrestricted sodium and potassium diet. The tests were performed between 7 and 9 a.m. on patients who were recumbent and had been fasting for 12 h. At the beginning of the tests, mean plasma potassium and sodium were within the normal range, as expected in patients who had received correct replacement therapy before the study. Basal mean blood pressure, and urinary excretion of Na and K were not significantly different from those in the controls (84 ± 5.7 vs. 85 ± 3.4 mmHg; 132.3 ± 13.9 vs. 165.1 ± 21.7 mEq/day and 58.4 ± 8.3 vs. 7.3 ± 6.9 mEq/day).

Blood samples were drawn for plasma aldosterone, cortisol and renin activity determination from an indwelling catheter while the test substances were injected iv in the other arm.

Acute stimulation tests
1. Upright posture (10 subjects). Blood samples were drawn first in recumbency, then 120 min after assumption of upright posture with quiet ambulation. Control values were obtained in 12 healthy male subjects aged from 24 to 31 years.

2. ACTH administration (12 subjects). β-1-24-ACTH (Synacthen®, Ciba) was infused iv over 120 min at a rate of 0.125 mg/h. Blood samples were drawn at 0, 30, 60 and 120 min. Control values were obtained in 12 healthy male subjects aged from 20 to 35 years.

3. Angiotensin II infusion (9 subjects). (Val5)-Angiotensin-II-amide (Hypertensin®, Ciba) was infused iv at a rate of 7 ng/kg/min. Blood samples were drawn at 0, 30, 60, 90 and 120 min. Control values were obtained in 18 healthy male subjects aged from 20 to 35 years. Blood pressure was measured by auscultation.

Analytical methods
Plasma aldosterone was measured by a double isotope dilution method (Bojesen & Thuneberg 1967) or by the RIA method of Underwood & Williams (1972) evaluated in our laboratory by Gaillard et al. (1976). Plasma renin activity (Vallotton 1971) was determined by radioimmunoassay of angiotensin I. Plasma cortisol was measured by a competition method (Leclerq et al. 1969). Because of the skewed distribution of the observations in the patients, their results are reported as median and range. Statistical evaluation was done by a non-parametric method (Mann-Whitney rank order test).

Results
1. Stimulation by upright posture (Fig. 1, Table 2)
Assumption of upright posture increased plasma aldosterone levels significantly (P < 0.01) in control subjects (Table 2) and in hypopituitary patients (Fig. 1). Median values of plasma aldosterone rose in hypopituitary patients from 2.9 ng/100 ml (range: < 1.0–17.4) to 5.6 ng/100 ml (range: 1.0–49.3). Seven out of 10 patients showed a less marked response than the normal controls. The individual values varied greatly from no response (2 subjects) to an exaggerated one when compared with the more homogeneous pattern in the controls. Median plasma renin activity measured in 8 of the 10 hypopituitary subjects tested increased from a median value of 0.56 ng/ml/h (range: 0.19–2.81) to 1.46 ng/ml/h (range: 1.10–4.47). While the increase of plasma renin activity was significant (P < 0.01) in control subjects (Table 2), the increase was clear but not significant (P > 0.05) in hypopituitary patients (Fig. 1). As expected, plasma cortisol values were extremely low in the patients. Median values were 1.3 μg/100 ml (range: < 1.0–3.0) before and 1.5 μg/100 ml (range: < 1–5.5) after assumption of the upright posture, and were significantly different from the values in healthy controls (P < 0.001; Table 2, Fig. 1).

2. Stimulation by ACTH (Fig. 2, Table 2):
Plasma aldosterone levels increased rapidly and significantly in both groups (P < 0.01) at 30, 60 and 120 min when compared with basal levels. In hypopituitary patients (Fig. 2), peak values were
Table 2.

Response of the control subjects to 3 stimulation tests: assumption of upright posture, ACTH and angiotensin II (mean ± SEM).

<table>
<thead>
<tr>
<th>Posture (n = 12) (min)</th>
<th>ACTH (n = 14) (min)</th>
<th>Angiotensin II (n = 18) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
</tbody>
</table>

Plasma aldosterone ng/100 ml
- 4.52 ± 1.65 ng/100 ml (range: <1-14.3) at 0 min, 17.06 ± 2.6 ng/100 ml (range: 3.1-29.9) at 30 min, 18.14 ± 1.3 ng/100 ml (range: 3.9-34.1) at 60 min and 15.22 ± 1.6 ng/100 ml (range: 3.4-37.6) at 120 min.

Plasma cortisol µg/100 ml
- 11.5 ± 2.6 µg/100 ml (range: <1-4.5) at 0 min, 20.5 ± 1.5 µg/100 ml (range: 3.9-34.1) at 30 min, 22.9 ± 4.9 µg/100 ml (range: 3.1-29.9) at 60 min and 25.4 ± 1.2 µg/100 ml (range: <1-14.9) at 120 min.

Plasma renin activity ng/ml/h
- 1.14 ± 0.15 ng/ml/h (range: <1-23) at 0 min and 1.49 ± 0.46 ng/ml/h (range: <1-23) at 120 min.

Median plasma aldosterone levels were 1.65 ng/100 ml (range: <1-14.3) at 0 min, 13.65 ng/100 ml (range: 3.1-29.9) at 30 min, 16.70 ng/100 ml (range: 3.9-34.1) at 60 min and 12.95 ng/100 ml (range: 3.4-37.6) at 120 min. Median plasma cortisol values were significantly lower (P < 0.001) in hypopituitary patients than in controls at each point measured, yet plasma cortisol levels increased steadily during stimulation in all but 2 patients. In hypopituitarism, median cortisol values were 1.45 µg/100 ml (range: <1-14.9) at 30 min, 9.00 µg/100 ml (range: <1-17.2) at 60 min and 11.75 µg/100 ml (range: <1-23) at 120 min.

Fig. 1.

Response to stimulation by upright posture in 10 hypopituitary patients. The shadowed area indicates the results (mean ± SEM) obtained in 12 healthy controls. The numbers on the right correspond to the numbers of the patients in Table 1.
3. Stimulation by angiotensin II (Fig. 3, Table 2)

In healthy controls, infusion of angiotensin II (7 ng/kg/min) induced an increase of 15–30 mmHg in diastolic blood pressure (Birkhäuser et al. 1973). In the hypopituitary patients, the rise of diastolic BP was 10–25 mmHg. Plasma aldosterone increase was smaller in all but 3 hypopituitary patients when compared with the rise in controls (Table 2). Median plasma aldosterone values in the patients were 1.6 ng/100 ml (range: < 1–19.1) at 0 min, 10.3 ng/100 ml (range: < 1.1–15.6) at 30 min, 13.5 ng/100 ml (range: < 1.5–34.0) at 60 min, 9.3 ng/100 ml (range: < 1.8–32.3) at 90 min and 10.3 ng/100 ml (range: < 1.1–36.2) at 120 min.

There was no difference in plasma renin activity which decreased steadily in controls (Table 2) and in hypopituitary patients until the end of the angiotensin II infusion. Median values of plasma renin activity measured in 6 patients were 0.83 ng/ml/h (range: 0.5–3.07) at 0 min and 0.46 ng/ml/h (range: < 0.25–1.13) at 120 min. The highest value of plasma renin activity at 0 min was observed in the only patient (No. 7) with no residual posterior pituitary function.

Plasma cortisol value fell significantly between 0 to 120 min in controls (P < 0.01, Table 2). As expected, in hypopituitary patients, both values were low and statistically not different (P > 0.05). Median levels were 1.20 µg/100 ml (range < 1–4.5) at 0 min and 1.45 µg/100 ml (range < 1–4.5) at 120 min.

In all hypopituitary patients tested, the pattern of aldosterone response following infusion of angiotensin II and assumption of upright posture was identical, as in all but 2 patients stimulated by angiotensin II and ACTH infusion. The 3 patients with the 3 highest plasma aldosterone increases in at least 2 of the 3 types of stimulation had low plasma cortisol levels as observed in the other patients, and had no response in the metyrapone test.
Discussion

The importance of intact pituitary function for adequate aldosterone regulation in man is still controversial (Muller et al. 1956, 1957; Raiti et al. 1968; Williams et al. 1971; Dluhy et al. 1974; McCaa et al. 1980). In the present study the plasma aldosterone response to 3 acute stimuli (upright posture, ACTH and angiotensin II) was examined in 12 patients with longstanding hypopituitarism. Replacement therapy had been withdrawn before the study. The mean age of the patients (52.6 ± 9.4 years, mean ± SD), although higher than the mean age of the controls (27.2 ± 3.6 years), was still in the middle-aged range of Takeda et al. (1980) who observed normal basal values of plasma aldosterone and plasma renin activity in this group and lower values only in the elderly group (69 ± 2 years). Thus age should not have influenced these parameters in our group of patients. In fact, basal levels of plasma aldosterone and plasma renin activity were similar in the hypopituitary patients and in controls, whereas plasma cortisol values were extremely low in the patients. This finding is consistent with the hypothesis that basal aldosterone levels are not significantly affected by the loss of anterior pituitary function and is supported by the generally accepted observation that, in contrast to the inner zones, zona glomerulosa function is conserved in longstanding hypopituitarism.

Following ACTH stimulation, a very similar response of plasma aldosterone to ACTH was observed in normal controls and in all but two hypopituitary patients. This confirms that response of the zona glomerulosa to ACTH remains intact in the absence of anterior pituitary hormones. This observation is consistent with the findings of López et al. (1980) and Merriam & Baer (1980) in glucocorticoid substituted hypopituitary man but it is in contradiction with the findings of Seifert & Oelkers (1980) and McCaa et al. (1980). It is interesting to note that patients with selective ACTH-suppression induced by chronic corticosteroid treatment had a normal response to ACTH infusion and sodium restriction (Williams et al. 1971; Thomas & El-Shaboury 1971). It might be postulated therefore that prior exposure to endogenous ACTH is not a prerequisite for plasma aldosterone response to exogenous ACTH as it is for plasma cortisol response. Also prior exposure to other hormones of the anterior pituitary does not seem mandatory for a normal plasma aldosterone response to exogenous ACTH.

On the other hand, the presence of an intact anterior pituitary seems to be important for a normal aldosterone response to stimulation by the renin-angiotensin system. In the present study, 7 out of 10 patients tested had an absent or extremely weak aldosterone response to assumption of upright posture. Under stimulation by angiotensin II, the plasma aldosterone increase was smaller, in all but 3 hypopituitary patients, than the increase observed in controls. There were no particular clinical (including BP) or biochemical feature to distinguish these 3 subjects from the other patients. They also had an exaggerated response of aldosterone in the posture test and although they did not respond to stimulation by metyrapone (Table 1) 2 of them showed the highest aldosterone increase during ACTH stimulation. It might be speculated that some residual ACTH secretion not detectable by the usual stimulation test was still present.

The observation of a diminished plasma aldosterone response to exogenous angiotensin II is in disagreement with the reports of López et al. (1980) and Merriam & Baer (1980) who demonstrated in glucocorticoid substituted hypopituitarism that aldosterone responsiveness to exogenous angiotensin II was similar to controls. It does, however, agree with the findings of McCaa et al. (1980) in hypopituitary patients and the report of Spark et al. (1968) who demonstrated in man, during dexamethasone-induced ACTH suppression, a reduced aldosterone response to exogenous angiotensin II.

Hyponorenia has been reported in untreated panhypopituitarism (Lefebvre et al. 1979) whereas plasma renin activity has been shown to be normal in patients receiving cortisol substitution (Williams et al. 1971; Murakami et al. 1972). These reports suggest that cortisol has a permissive role for proper functioning of the renin-angiotensin system.

In conclusion, the response of aldosterone to 3 different stimuli was studied in 12 hypopituitary patients. Stimulation by ACTH resulted in a plasma aldosterone increase similar to that observed in controls. Stimulation by assumption of upright posture and by exogenous angiotensin II induced a smaller plasma aldosterone response in most of the patients than in the controls. The latter observation suggests that either an anterior pituitary hormone, possibly ACTH itself, or a pituitary dependent non-hypophysal factor exerts a permissive action.
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References


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