Adrenal Steroid Responses to ACTH in Glucocorticoid-Suppressible Aldosteronism

Arunabha Ganguly, Myron H. Weinberger, Gordon P. Guthrie, and Naomi S. Fineberg

SUMMARY To investigate adrenal responses to adrenocorticotrophin (ACTH), we infused graded doses of ACTH (1.25 to 20.0 mIU/30 minutes) in normal subjects, patients with low-renin essential hypertension (LREH), primary aldosteronism (PA), and glucocorticoid-suppressible hyperaldosteronism (GSH). Plasma aldosterone, cortisol, corticosterone, and 18-hydroxycorticosterone were measured. The results revealed a greater increase in the plasma aldosterone and 18-hydroxycorticosterone levels evoked by ACTH in the GSH group than in any other group, which suggested enhanced responsiveness of the aldosterone-producing cells to ACTH and a probable adrenal abnormality. (Hypertension 6: 563-567 1984)

KEY WORDS • adrenal hyperfunction • aldosterone • hypertension • pituitary • renin

G lucocorticoid-suppressible hyperaldosteronism (GSH), first reported by Suther-land and colleagues,1 is a unique form of aldosteronism.2 It is familial, and glucocorticoid treatment ameliorates all of its manifestations. In view of its excellent response to the glucocorticoids, adrenocorticotropic (ACTH) or some other pituitary factor is suspected to play an important role in the regulation of aldosterone secretion in this disorder. Such an impression has been strengthened further by other observations recently.3-6 Even though ACTH is seemingly responsible for the aldosteronism, there has been no evidence of excessive cortisol or androgen secretion in this disorder, which suggests a possible selective abnormality of the aldosterone-producing cells. Therefore, the responses of other adrenal steroids to ACTH stimulation in this disorder are of interest. In this study, we have examined the adrenal responses of corticosterone, 18-hydroxycorticosterone, aldosterone, and cortisol to graded doses of ACTH infusion in patients with GSH. We have compared their responses with those of normal subjects and patients with other forms of hyperaldosteronism.

Subjects and Methods

Subjects
We studied six normal subjects, six patients with primary aldosteronism (PA) (four with adrenal adenoma and two with adrenal hyperplasia), six patients with GSH, and five patients with low-renin essential hypertension (LREH). The diagnosis of hyperaldosteronism was made if findings showed the combination of non-suppressible plasma aldosterone levels after saline infusion and of persistently low plasma renin activity after furosemide administration, as previously described.7 8 The diagnosis of GSH was established in all six patients by the familial nature of the aldosteronism and its response to glucocorticoid therapy. The clinical characteristics, genetic aspects, and the diagnostic studies in the two GSH families have been described previously.9 10

Localization of the adrenal lesion was undertaken in all patients with PA by adrenal venography and adrenal venous blood sampling.8 All but one patient with PA were operated on, and the diagnosis was confirmed by the pathological examination of the extirpated adrenal gland. Preoperatively, all patients were treated with either spironolactone or a thiazide-triamterene combination.11 Blood pressure and plasma potassium became normal after the operation in all four patients with adrenal adenoma. One patient with hyperplasia has
remained hypertensive after unilateral adrenalectomy. The other patient with hyperplasia regained normal blood pressure after treatment with spironolactone. The patients with GSH were initially treated with a glucocorticoid but later with a triamterene-thiazide combination.11

**Study Protocol**

Informed consent was obtained from all subjects. None of the hypertensive subjects had taken any medication for 2 weeks preceding the study, and all subjects were on a normal sodium diet (150 mEq sodium a day) before the study. Dexamethasone was given 1 mg at midnight and 0.5 mg orally at 6 a.m. on the morning of the study to inhibit endogenous ACTH secretion. An indwelling catheter was inserted into a vein in each forearm 1 hour prior to the initiation of the study and kept in place with heparinized saline in a syringe. The patient remained recumbent throughout, and breakfast was withheld. At the time of the study a control blood sample was obtained, and the infusion of ACTH24 (Organon, Inc., West Orange, New Jersey) was initiated at graded doses of 1.25, 2.5, 5.0, 10.0, and 20.0 mIU/30 minutes. Blood samples were obtained for plasma electrolytes, renin activity, and steroids at the end of each infusion period.

Plasma renin activity,12 cortisol,6 and aldosterone13 were measured by radioimmunoassays, as described previously. Plasma corticosterone and 18-hydroxy cortisol were measured by radioimmunoassays after chromatographic separation with LH-20 columns.14 The last two steroids were not measured in the LREH patients. The sensitivities of the corticosterone and 18-hydroxy cortisol assays were 10 ng/dl and 2 ng/dl, respectively. The inter- and intraassay coefficients of variation were 5% and 10.5%, and 10.9% and 15%, respectively. The characteristics of the plasma aldosterone and cortisol assays have been previously described.6

Statistical analysis of the data involved standard linear regression analysis, fitted for each individual with the incremental dosage of ACTH as the independent variable and the plasma steroid concentrations as the dependent variable. Slopes and intercepts for the groups were compared by analysis of variance with respect to each steroid response. Because of non-normality of distribution, nonparametric tests were used for group comparisons of control plasma steroids and peak increases of the steroids; these were the Kruskal-Wallis (K-W) one way analysis of variance and Friedman one-way repeated measures analysis.

**Results**

The plasma steroid measurements are shown in Table 1. Before ACTH was given, the mean control plasma aldosterone concentration of 13.9 ± 3.1 (SEM)

### Table 1. Plasma Steroid Responses to Adrenocorticotrophin (ACTH)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Control</th>
<th>1.25</th>
<th>2.5</th>
<th>5.0</th>
<th>10.0</th>
<th>20.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n = 6)</td>
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<tr>
<td>Plasma cortisol (µg/dl)</td>
<td>1.7±0.2</td>
<td>1.7±0.2</td>
<td>1.7±0.2</td>
<td>5.2±2.4</td>
<td>7.6±1.4</td>
<td>12.7±1.2</td>
</tr>
<tr>
<td>Plasma corticosterone (ng/dl)</td>
<td>35.6±8.9</td>
<td>14.9±3.3</td>
<td>31.3±13.5</td>
<td>103.3±17.7</td>
<td>471.3±78.0</td>
<td>883.5±133.6</td>
</tr>
<tr>
<td>Plasma 18-hydroxy corticosterone (ng/dl)</td>
<td>3.8±1.4</td>
<td>4.6±2.0</td>
<td>7.8±3.0</td>
<td>20.9±6.8</td>
<td>31.6±6.6</td>
<td>47.7±8.2</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td>3.9±0.4</td>
<td>4.4±0.7</td>
<td>5.3±1.1</td>
<td>10.6±2.7</td>
<td>14.3±3.2</td>
<td>16.8±4.0</td>
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<tr>
<td>Low-renin essential hypertension. (n = 6)</td>
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<tr>
<td>Plasma cortisol (µg/dl)</td>
<td>1.4±0.2</td>
<td>1.4±0.2</td>
<td>1.5±0.3</td>
<td>2.7±0.8</td>
<td>7.0±1.9</td>
<td>13.9±2.6</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td>7.2±1.5</td>
<td>6.8±1.1</td>
<td>8.2±1.6</td>
<td>11.8±3.3</td>
<td>17.1±5.3</td>
<td>21.0±0.6</td>
</tr>
<tr>
<td>Primary aldosteronism (n = 6)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Plasma cortisol (µg/dl)</td>
<td>2.2±0.4</td>
<td>2.3±0.5</td>
<td>3.1±0.7</td>
<td>4.8±1.5</td>
<td>11.0±3.1</td>
<td>18.0±3.4</td>
</tr>
<tr>
<td>Plasma corticosterone (ng/dl)</td>
<td>42.1±18.0</td>
<td>31.8±9.6</td>
<td>61.8±27.2</td>
<td>171.5±66.2</td>
<td>351.6±94.0</td>
<td>952.5±142.2</td>
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<tr>
<td>Plasma 18-hydroxy corticosterone (ng/dl)</td>
<td>16.7±4.4</td>
<td>18.0 ±4.9</td>
<td>21.2±6.7</td>
<td>26.4±6.3</td>
<td>42.9±7.5</td>
<td>72.5±12.3</td>
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<tr>
<td>Plasma aldosterone* (ng/dl)</td>
<td>13.9±3.1</td>
<td>13.4±3.3</td>
<td>17.2±5.8</td>
<td>20.1±5.8</td>
<td>24.9±4.8</td>
<td>30.9±3.7</td>
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<td>Glucocorticoid-suppressible hyperaldosteronism (n = 6)</td>
<td></td>
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<tr>
<td>Plasma cortisol (µg/dl)</td>
<td>1.0±0.0</td>
<td>1.0±0.0</td>
<td>1.1±0.1</td>
<td>1.5±0.4</td>
<td>5.8±2.2</td>
<td>12.2±3.0</td>
</tr>
<tr>
<td>Plasma corticosterone (ng/dl)</td>
<td>46.3±14.4</td>
<td>45.4±22.3</td>
<td>31.8±13.9</td>
<td>48.6±35.4</td>
<td>351.6±159.0</td>
<td>913.0±312.5</td>
</tr>
<tr>
<td>Plasma 18-hydroxy corticosterone (ng/dl)</td>
<td>1.9±0.9</td>
<td>1.5±0.5</td>
<td>5.3±3.9</td>
<td>15.8±9.5</td>
<td>72.4±27.3</td>
<td>121.6±44.4</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td>2.7±0.4</td>
<td>2.6±0.4</td>
<td>2.8±0.6</td>
<td>14.0±5.3</td>
<td>42.7±13.5</td>
<td>60.3±18.3</td>
</tr>
</tbody>
</table>

*Because of nonlinearity of response, one patient excluded from analysis.

Values are means ± SEM. Increases in response to ACTH for all steroids were significant (p < 0.001).
ng/dl in PA was significantly greater than in all other groups \( (p < 0.001) \). The lowest aldosterone concentration was seen in the GSH group. There was a progressive rise of plasma aldosterone concentration in all groups \( (p < 0.001) \) at ACTH infusion rates of 5.0 mIU/30 minutes or greater (Table 1). The increment was the greatest in the GSH group. One patient with PA showed a nonlinear rise in the plasma aldosterone concentration, and that patient was excluded from analysis. Linear regression analysis revealed that the slope of the rise of plasma aldosterone concentration in relation to ACTH infusion rates was significantly steeper \( (p < 0.002) \) in the GSH group than all other groups (Figure 1). There was no difference in the intercepts for plasma aldosterone responses between any groups, which suggested that the thresholds of response were similar. Dexamethasone pretreatment markedly reduced the control plasma cortisol levels, and the ACTH-mediated increases in plasma cortisol did not significantly differ between the groups (Table 1).

The mean control plasma 18-hydroxycorticosterone of 16.7 ± 4.4 (SEM) ng/dl was higher \( (p < 0.005) \) in the PA group than that in the normal subjects or in the patients with GSH (Table 1). ACTH infusion evoked increases in all groups \( (p < 0.001) \), but the greatest rise was seen in the GSH, although it was not significantly different from the other two groups \( (p < 0.10) \). The mean control corticosterone concentration and its response to ACTH were not different between the groups. Regression analysis showed that the intercept in the PA group was slightly higher \( (p < 0.03) \) than that of the GSH group for plasma 18-hydroxycorticosterone. Plasma sodium, potassium, and renin activity did not change significantly in any group during the ACTH infusion. Plasma renin activity remained suppressed \( (<0.5 \text{ ng/ml/3 hr}) \) in the PA and GSH groups.

**Discussion**

The pathogenesis of the rare genetic disorder, GSH\(^1,4,9,10,15-18\) is of considerable interest. ACTH is thought to be involved in the aldosteronism in this disorder in view of the glucocorticoid-induced reversal of aldosteronism and its manifestations.\(^2\) In the other forms of aldosteronism, glucocorticoid treatment has only a short-term effect on the aldosterone secretion,\(^19,23\) even though ACTH appears to influence the day-to-day secretion of aldosterone, as shown by a number of investigators.\(^24\) The reason for this difference between GSH and other types of aldosteronism remains unclear and may be related to a specific adrenal abnormality of GSH. A possible role for another ACTH-like peptide in the pathogenesis of GSH has also been suggested.\(^25\) Limited measurements of the plasma levels of the various pro-opiomelanocortin-derived peptides, however, have not supported such a contention thus far.\(^26,27\) The reports of normal levels of plasma ACTH in the patients with this disorder\(^26,27\) seem to absolve further any pituitary abnormality involving the ACTH family and tend to implicate an
adrenal defect. It is not known, however, if the ACTH secreted in the patients with GSH is chemically similar to the ACTH circulating in normal humans. In such a perspective, adrenal responsiveness to exogenous ACTH in the patients with GSH is of special interest.

In the present study, ACTH infusion evoked a greater plasma aldosterone response in the patients with GSH than in either normal subjects, patients with LREH, or those with primary aldosteronism due to adenoma or hyperplasia. At the low doses of ACTH used in this study, no differences were observed in the plasma aldosterone responses between normal subjects, the PA group, and LREH group. The 18-hydroxycorticosterone responses in the patients with GSH also tended to be higher than those in the other groups. Plasma corticosterone and cortisol changes during ACTH infusion were similar in all groups. Since most of the corticosterone and virtually all of the cortisol originate from the zona fasciculata of the adrenal glands, except perhaps in the patients with primary aldosteronism (especially those associated with an adrenal adenoma), these results suggest further that the abnormality in GSH is confined to the aldosterone-producing cells.

The basal plasma aldosterone and 18-hydroxycorticosterone concentrations in the dexamethasone-pre-treated patients with primary aldosteronism, most of whom had an adenoma, were greater than those in the patients with GSH and in the normal subjects. Thus, it is clear that aldosterone and 18-hydroxycorticosterone secretion can only be partially reduced by acute inhibition of ACTH secretion by dexamethasone administration, even though the secretion of cortisol and corticosterone was lowered markedly. Elevated levels of plasma 18-hydroxycorticosterone, especially in the adenomatous form, have been reported. These results seem to indicate that the late pathway of aldosterone synthesis in the zona glomerulosa is very active in this disorder. This finding is also supported by in vitro studies of adrenal adenomas from patients with primary aldosteronism. It is not known what factors sustain the zona glomerulosa steroid secretion beyond the step of corticosterone in PA under these conditions of suppressed renin-angiotensin system, ACTH, and low extracellular potassium concentrations. Possibly under these conditions the secretion from this zone is autonomous.

By contrast, in the patients with GSH, dexamethasone pretreatment caused a virtual cessation of steroid secretion including that from the aldosterone-producing cells, as judged from the plasma levels of the steroids. This is a unique situation in which all steroid production from the adrenal gland is apparently dependent on ACTH.

Normally, aldosterone secretion does not seem to be influenced in a significant way by the endogenous variations of ACTH and appears to be modulated principally by angiotensin and to some extent by the ambient potassium concentration. In this context, the clear-cut demonstration of modulation of aldosterone secretion in different degrees in the various forms of aldosteronism by ACTH is an intriguing finding. Morphological similarities between the normal zona fasciculata cells, the cells of aldosteronoma, and perhaps the cells in the hyperplastic adrenal gland in GSH (since information is rather sketchy on the latter) may explain the unusual ACTH responsiveness of the latter two disorders. Despite these similarities, it is even more puzzling why the aldosterone secretion in those two disorders responds differently to chronic glucocorticoid treatment and to chronic ACTH administration. These contrasting characteristics strongly suggest that the aldosterone-producing cells in the two disorders are qualitatively different or that there is a lack of a normal inhibitory influence on these cells in GSH.

Recently, Ulick and his colleagues have reported the isolation of two unique steroids present in large quantities in the urine of patients with GSH. Excessive amounts of these steroids have also been found in the urine of patients with aldosterone-producing adenoma. The significance of these findings is not entirely clear. Further studies are needed to clarify the nature of the adrenal aberration.

Acknowledgments

The authors thank Dr. Clarence E. Grim for permitting these investigations to be carried out with some of his patients, and Catherine Guin for preparing the manuscript.

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Adrenal steroid responses to ACTH in glucocorticoid-suppressible aldosteronism.
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Hypertension. 1984;6:563-567
doi: 10.1161/01.HYP.6.4.563

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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