Dexamethasone-Suppressible Hyperaldosteronism
Adrenal Transition Cell Hyperplasia?

JOHN M.C. CONNELL, CHRISTOPHER J. KENYON, JOHN E.T. CORRIE, ROBERT FRASER, RUBY WATT, AND ANTHONY F. LEVER

SUMMARY Dexamethasone-suppressible hyperaldosteronism is a rare familial syndrome in which hypokalemia, suppression of plasma renin concentration, and elevated aldosterone secretion are corrected by treatment with glucocorticoids. Regulation of adrenocortical function and body electrolytes was studied in two affected brothers. Both were hypertensive (210/128 and 160/106 mm Hg) with hypokalemia (3.3 and 3.5 mM) and low plasma renin concentrations. Aldosterone was elevated intermittently with levels as high as 45 ng/dl (normal range, 4-16 ng/dl). Cortisol concentrations were normal but were correlated with aldosterone levels (r = 0.9 and 0.7). Concentrations of 11-deoxycorticosterone (19 and 21 ng/dl; normal range, 4–16 ng/dl) and 18-hydroxycortisol (1000 and 950 ng/dl; normal range, 34–150 ng/dl) were elevated, and diurnal changes in both were the same as those seen with aldosterone. Infusion of adrenocorticotropic hormone, \( \Delta^2 \) (ACTH) caused exaggerated increases of aldosterone, 11-deoxycorticosterone, and 18-hydroxycortisol; cortisol response was normal. A 4-week trial of dexamethasone normalized blood pressure and caused a natriuresis, a fall in aldosterone, and a rise in plasma renin. Administration of ACTH after dexamethasone treatment again caused exaggerated increases of aldosterone. Aldosterone did not respond to angiotensin II before dexamethasone therapy (r = 0.01), but it showed a normal response after therapy (r = 0.8, p<0.01). Neither administration of dopamine (1 \( \mu \)g/kg/min) nor long-term therapy with bromocriptine (2.5 mg i.d. for 4 weeks) affected aldosterone biosynthesis. Thus, loss of dopaminergic inhibition of mineralocorticoid biosynthesis does not account for hyperaldosteronism in this condition. The abnormal pattern of steroid secretion in these brothers is consistent with a population of adrenocortical transition-type cells that secrete aldosterone in response to ACTH but not to angiotensin II and have biosynthetic characteristics of both zona glomerulosa and zona fasciculata cell types. These properties would explain the excess synthesis of 18-hydroxycortisol from a cell type that can uniquely hydroxylate steroid at both the 17 and 18 positions. (Hypertension 8: 669–676, 1986)

Key Words • hyperaldosteronism • cortisol • 18-hydroxycortisol • 11-deoxycorticosterone • corticosterone

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plasma levels of 18-hydroxycortisol were measured, since urinary levels of this steroid are known to be elevated in this condition.8,9

Subjects and Methods

Case Histories

Subject 1 presented with a blood pressure of 150/95 mm Hg at 8 years of age (1966). He was referred for further investigation in 1982; at that time blood pressure was poorly controlled by propranolol, 80 mg b.i.d. Basal blood pressure (no therapy having been given for 4 weeks) was 210/128 mm Hg. Adrenal computed tomographic scan was normal. Data summarized in Tables 1 and 2 led to the diagnosis of dexamethasone-suppressible hyperaldosteronism.

Subject 2, the brother of Subject 1, was found at 29 years of age (1982) to have hypertension (160/106 mm Hg). Investigation, the results of which are summarized in Tables 1 and 2, confirmed the diagnosis of dexamethasone-suppressible hyperaldosteronism.

Since these studies were completed, both subjects have been receiving dexamethasone, 0.25 mg/day, and have good control of blood pressure.

Protocol

All studies were performed in hospital while the subjects were maintained on a diet containing 150 mmol of sodium and 60 mmol of potassium per day. Hypotensive drugs were withdrawn at least 4 weeks before admission.

Basal plasma steroid concentrations were measured in each subject 1) without therapy, 2) after 4 weeks of dexamethasone treatment (0.5 mg q.i.d.), and 3) after 4 weeks of bromocriptine treatment (2.5 mg t.i.d.). Total body sodium and potassium were measured before and after 4 weeks of dexamethasone treatment. Adrenal responses to graded infusions of ACTH (Synacthen; 0.1, 1, and 10 ng/kg/min) or ANG II (Hypertensin; 1, 2, and 4 ng/kg/min) were studied on separate days. Details of the experimental infusion procedures are as follows:

1. Infusion of ACTH without long-term dexamethasone or bromocriptine treatment.
2. Infusion of ACTH with a concomitant infusion of dopamine (1 μg/kg/min) without long-term dexamethasone or bromocriptine treatment.
3. Infusion of ACTH after 4 weeks of dexamethasone (0.5 mg q.i.d.) therapy.
4. Infusion of ACTH after 4 weeks of bromocriptine (Parlodol; 2.5 mg t.i.d.) therapy.
5. Infusion of ANG II without long-term dexamethasone or bromocriptine treatment.
7. Administration of metoclopramide (10 mg i.v. bolus) before and after 4 weeks of dexamethasone treatment.

Dexamethasone (1 mg p.o.) was given 10 and 2 hours before the start of all ACTH infusions to suppress endogenous ACTH secretion. Infusions of ACTH and ANG II without long-term dexamethasone treatment were given at least 6 months after withdrawal of the steroid. The ANG II infusion studies were performed following overnight fast while the subjects were supine. Infused substances were delivered through an indwelling cannula into a forearm vein; serial blood samples were drawn from a heparinized intravenous cannula in the opposite forearm.

Analyses

Plasma samples from each experiment were frozen at −20°C and subsequently analyzed as a batch. Total body electrolyte composition was measured by neutron activation analysis, performance characteristics of which have been defined previously.10 Plasma electrolytes were measured by autoanalyzer. Plasma renin, ANG II, cortisol, aldosterone, and 18-hydroxycortisol were measured by radioimmunoassay methods that have been described elsewhere.11-14 Plasma 11-deoxy-

Table 1. Basal (0800) Blood Pressure, Plasma Renin and Electrolyte Concentrations and Total Body Electrolyte Content Before and After Treatment with Dexamethasone and Bromocriptine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subject 1</th>
<th>Subject 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated</td>
<td>Dexamethasone*</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>210/112</td>
<td>134/84</td>
</tr>
<tr>
<td>Plasma active renin concentration (μU/ml)</td>
<td>&lt;3</td>
<td>68</td>
</tr>
<tr>
<td>Serum potassium (mM)</td>
<td>3.3</td>
<td>4.2</td>
</tr>
<tr>
<td>Serum sodium (mM)</td>
<td>142</td>
<td>139</td>
</tr>
<tr>
<td>Total body sodium (mM)</td>
<td>4029 (108)</td>
<td>3656 (99)</td>
</tr>
<tr>
<td>Total body potassium (mM)</td>
<td>3995 (99)</td>
<td>4384 (109)</td>
</tr>
</tbody>
</table>

Values in parentheses represent percentage of predicted values based on data from normal subjects of comparable age and morphometry.

*Dexamethasone: 0.5 mg q.i.d. for 4 weeks.
†Bromocriptine: 2.5 mg t.i.d. for 4 weeks.
corticosterone and corticosterone also were measured by radioimmunoassay after paper chromatography of neutral extracts in Bush-type solvent systems. Antisera to these compounds were raised in rabbits using bovine serum albumin conjugated to the third position. Within-batch coefficients of variation for 11-deoxycorticosterone and corticosterone were 6.2% and 8.2%, respectively. Between-batch coefficients of variation were 9.7% and 12.0%, respectively. Plasma prolactin concentrations were measured by radioimmunoassay using a double-antibody method calibrated with international reference standards. The interassay and intraassay coefficients of variation for this assay are between 8 and 12%.

Results

Blood pressure was high and plasma renin and potassium concentrations low in both subjects (see Table 1). Dexamethasone (0.5 mg q.i.d. for 4 weeks) therapy lowered blood pressure and increased potassium and renin concentrations. Associated with these changes were substantial reductions in total body sodium (373 and 323 mmol in Subjects 1 and 2, respectively) and equivalent increases in total body potassium. Bromocriptine treatment caused a reduction in blood pressure without affecting plasma potassium or renin concentrations, thus indicating that no major changes in body sodium content or plasma volume had occurred.

Plasma concentrations of all steroids (cortisol, aldosterone, corticosterone, 11-deoxycorticosterone, and 18-hydroxycortisol) varied synchronously during a 24-hour period; peak levels occurred at 0800 (Figure 1). Aldosterone and 11-deoxycorticosterone concentrations were above the normal range at 0800, but not during the evening or night. Levels of 18-hydroxycortisol were high throughout the 24-hour period.

Dexamethasone transiently reduced aldosterone concentrations to subnormal values (0 and 1 ng/dl) within 24 hours, but after 4 weeks of treatment all values throughout the 24-hour period had risen to within the normal range (Figure 2). There was evidence of
an abnormal diurnal pattern of secretion, in that values were highest at midnight and lowest at 0800. Concentrations of cortisol, corticosterone, 11-deoxycorticosterone, and 18-hydroxycortisol were all reduced during dexamethasone treatment, as was urinary excretion of 18-hydroxycortisol (see Table 2).

Aldosterone and cortisol were measured in plasma removed at 30-minute intervals between 0400 and 1600 both in the untreated state and after bromocriptine therapy (Figure 3). The relationship between the two steroids was close ($r = 0.9$ and $0.7$, respectively); peak concentrations of aldosterone coincided with those of cortisol, and levels of both steroids were highest in the morning. In both subjects a rise in cortisol and aldosterone concentrations was noted around lunchtime. Bromocriptine treatment had no effect on the relationship between aldosterone and cortisol concentrations (see Figure 3).

Without long-term dexamethasone treatment, ACTH infusion caused large increases in aldosterone, 11-deoxycorticosterone, and 18-hydroxycortisol concentrations. For comparison, data derived from eight normal male subjects studied using an identical protocol are also shown in Figure 4. The sensitivity (slope of the response) and capacity (maximum response) of aldosterone and 11-deoxycorticosterone responses to ACTH were greater in two subjects with dexamethasone-suppressible hyperaldosteronism than in controls. Following long-term dexamethasone treatment, the aldosterone response remained greater than normal in both subjects. The cortisol and corticosterone responses to ACTH were normal without treatment, and

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**Figure 2.** Diurnal rhythm of aldosterone concentrations in two subjects after treatment with dexamethasone, 0.5 mg q.i.d., for 4 weeks. Subjects were recumbent from 2400 to 0800 and ambulant thereafter. Cortisol concentrations were undetectable throughout.

**Figure 3.** Relationship between plasma aldosterone and cortisol concentrations in two subjects before treatment (left-hand panels) and after 4 weeks of treatment with bromocriptine, 2.5 mg t.i.d. (right-hand panels). Subjects were recumbent from 2400 to 0800 and ambulant thereafter. Samples were obtained every 30 minutes.
the cortisol response was attenuated by dexamethasone treatment.

In the untreated state, plasma ANG II concentrations during infusion of the octapeptide (1, 2, and 4 ng/kg/min) did not correlate with plasma aldosterone concentrations (Figure 5). In contrast, after dexamethasone treatment, the correlation between plasma ANG II and aldosterone concentrations was highly significant (r = 0.8, p < 0.001).

Long-term treatment with the dopamine agonist bromocriptine did not affect the aldosterone response to ACTH. Similarly, no effect on basal steroid concentrations was noted (see Table 2). The acute effects of the dopamine antagonist metoclopramide (10 mg i.v.) were assessed in each subject both with and without dexamethasone treatment (Table 3). In the first subject, 30 minutes after injection of metoclopramide, plasma aldosterone concentrations increased from 4 to 24 ng/dl without dexamethasone treatment, and from 4 to 19 ng/dl with dexamethasone treatment. The larger increase noted without dexamethasone therapy was associated with a subjective sensation of unease, and plasma cortisol also rose from 6 to 19 μg/dl. An increase in aldosterone in the second subject following metoclopramide injection was noted before (from 10 to 20 ng/dl) and after (from 5 to 8 ng/dl) 4 weeks of dexamethasone treatment; neither response was associated with a rise in plasma cortisol concentrations.

Infusions of dopamine (1 μg/kg/min) did not affect aldosterone, corticosterone, 18-hydroxycortisol, or cortisol responses to ACTH but markedly enhanced those of 11-deoxycorticosterone (see Figure 4). A similar effect has been described in normal subjects.13 Plasma prolactin concentrations were below the limit of reliable estimation (<60 mU/L) during bromocriptine therapy and during dopamine infusions. Basal prolactin concentrations at other times were normal, as were prolactin responses to metoclopramide (data not shown).

Discussion

Both subjects had hyperaldosteronism with hypertension, hypokalemia, and suppression of plasma active renin concentration. Dexamethasone treatment caused a sustained reduction in aldosterone, normalized blood pressure, and was associated with a pro-

![Figure 4. Corticosteroid responses to ACTH (0.1, 1, and 10 ng/kg/min) in Subjects 1 (---) and 2 (---) before treatment (A), after 4 weeks of dexamethasone, 0.5 mg q.i.d., treatment (B), after 4 weeks of bromocriptine, 2.5 mg t.i.d., treatment (C), and during concurrent dopamine (1.0 μg/kg/min) infusion (D). Shaded areas in A and D represent corticosteroid responses to ACTH in eight normal subjects studied using identical protocols. Values are means ± SD.](http://hyper.ahajournals.org/cover)
found fall in total body sodium and a rise in total body potassium. These electrolyte changes over a 4-week period are greater than those reported in subjects with tumors hyperaldosteronism following surgical removal of the tumor. Thus, increased body sodium as a consequence of renal mineralocorticoid action may be sufficient to explain the hypertension of dexamethasone-suppressible hyperaldosteronism. However, administration of exogenous aldosterone together with dexamethasone treatment in patients with this disorder caused sodium retention without raising blood pressure, suggesting that other "hypertensinogenic" steroids may also be involved in the pathogenesis of the hypertension. It is perhaps important that plasma 11-deoxycorticosterone levels also were elevated in these subjects and intermittently elevated concentrations of aldosterone and 11-deoxycorticosterone, along with normal levels of cortisol, may be sufficient to explain all metabolic and hemodynamic abnormalities in the condition. However, Gomez-Sanchez has suggested that the mineralocorticoid activity of 18-oxocortisol, which is elevated in patients with this condition, may also contribute to the development of hypertension.

Apart from the finding of hyperaldosteronism, the present study also found that plasma 18-hydroxycortisol concentrations are increased, which is in accordance with reports of high urinary levels of the steroid in this condition. Elevated plasma 11-deoxycorticosterone levels also were noted, as in a proportion of the patients studied by Oberfield et al. The marked diurnal variation of aldosterone and 11-deoxycorticosterone probably accounts for the finding that plasma concentrations of these steroids may be normal in subjects with dexamethasone-suppressible hyperaldosteronism. Changes in aldosterone concentration correlated closely with those of cortisol. Interestingly, levels of both steroids were increased simultaneously at around lunchtime. Recent careful studies of the periodicity of ACTH secretion have demonstrated a rise in ACTH around mealtimes that is superimposed on the well-established diurnal pattern of hormone secretion. Synchronous changes of aldosterone and cortisol strongly support the suggestion that ACTH is the principal regulator of aldosterone secretion in this condition. Since plasma aldosterone, but not cortisol or corticosterone, levels are elevated in these patients, the abnormality appears to concern an aspect of adrenocortical function other than the pituitary- (ACTH) adrenal (cortisol) axis.

Further evidence of the abnormal pattern of steroids secreted in response to ACTH was provided by infusion studies. The finding that aldosterone responses to ACTH were much greater than normal confirmed observations by Ganguly et al. In addition, we have shown that responses of 11-deoxycorticosterone and 18-hydroxycortisol were increased, whereas those of cortisol and corticosterone were normal. Again,

<table>
<thead>
<tr>
<th>Subject 1</th>
<th>Subject 2</th>
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<tbody>
<tr>
<td>Time (min)</td>
<td>Time (min)</td>
</tr>
<tr>
<td>Variable</td>
<td>-15</td>
</tr>
<tr>
<td>No treatment</td>
<td></td>
</tr>
<tr>
<td>Aldosterone (ng/dl)</td>
<td>5</td>
</tr>
<tr>
<td>Cortisol (µg/dl)</td>
<td>7</td>
</tr>
<tr>
<td>Dexamethasone, 0.5 mg q.i.d. for 4 wk</td>
<td></td>
</tr>
<tr>
<td>Aldosterone (ng/dl)</td>
<td>2</td>
</tr>
<tr>
<td>Cortisol (µg/dl)</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
these data suggest that the abnormal aldosterone, 11-deoxycorticosterone, and 18-hydroxycortisol synthesis is distinct from the normal zona fasciculata response to ACTH, as assessed by changes in cortisol concentrations.

As has been observed previously, aldosterone did not respond to ANG II infusion in untreated subjects. With dexamethasone treatment, however, plasma aldosterone did rise as a function of plasma ANG II levels. The lack of response without dexamethasone treatment is compatible with indirect evidence that aldosterone does not rise during ambulation in subjects with dexamethasone-suppressible hyperaldosteronism and is explained by down-regulation of adrenal ANG II receptor number as a consequence of suppression of renin and angiotensin II by sodium retention. After dexamethasone treatment, when total body sodium is decreased and renin no longer depressed, adoption of upright posture or infusion of ANG II causes a normal increase in aldosterone levels. Thus, the mechanisms regulating zona glomerulosa cell function appear to be intact in this condition.

Recent studies have indicated that dopamine might normally control adrenocortical function by tonically inhibiting aldosterone secretion. Ganguly et al. have suggested that dopaminergic control of mineralocorticoid synthesis is impaired in patients with dexamethasone-suppressible hyperaldosteronism, since administration of the dopamine (D2) receptor antagonist metoclopramide failed to cause an increase in aldosterone levels in untreated subjects during short-term suppression of ACTH with dexamethasone. In the present study, in the untreated state, the effects of metoclopramide were equivocal; one subject showed a marked increase in aldosterone associated with a rise in plasma cortisol. Similar stress-related changes have been described by Ganguly et al. in patients with this disorder and by others in normal subjects. After 4 weeks of dexamethasone treatment, however, metoclopramide caused a rise in aldosterone in both subjects without changing plasma cortisol concentrations. Since the aldosterone response to metoclopramide is directly proportional to the degree of activation of the renin-angiotensin system, the failure of aldosterone to rise in untreated dexamethasone-suppressible hyperaldosteronism may reflect the effects of sodium excess on renin secretion rather than an intrinsic adrenal abnormality.

Intravenous infusion of dopamine in the current study did not correct the exaggerated aldosterone response to ACTH, nor did long-term treatment with the dopamine (D2) receptor agonist bromocriptine affect basal or stimulated aldosterone levels. The marked effects of dopamine on 11-deoxycorticosterone responses to ACTH are also seen in normal subjects and may reflect an extra-adrenal effect of dopamine on 11-deoxycorticosterone synthesis. It seems unlikely that deficiency of dopaminergic control could account for the abnormalities of mineralocorticoid secretion in these subjects.

The cortisol-producing zona fasciculata cells of the human adrenal cortex are characterized by an ability to hydroxylate steroids in the 17 position, an inability to convert corticosterone to aldosterone, and physiological regulation by ACTH rather than ANG II or plasma potassium. Hydroxylation of corticosterone at the 18 position, a putative intermediate step in aldosterone biosynthesis, does not normally occur in the zona fasciculata.

In contrast to zona fasciculata function, aldosterone-producing zona glomerulosa tissue rapidly converts corticosterone to aldosterone, is unable to carry out 17-hydroxylations, and is primarily regulated by ANG II rather than ACTH. It is unlikely, however, that functional separation of the two zones is complete, since zona fasciculata morphology and function are thought to arise from centripetal migration of zona glomerulosa cells. A transitional intermediate zone may exist in which cells display biochemical features of both zones. Such cells might be capable of 1) 18-hydroxylating a 17-hydroxy steroid such as cortisol to produce 18-hydroxycortisol and, more importantly, 18-oxocortisol, 2) synthesizing aldosterone in response to ACTH rather than ANG II, and 3) secreting 11-deoxycorticosterone. Although this transitional zone would contribute little to overall adrenocortical output in normal subjects, we suggest that dexamethasone-suppressible hyperaldosteronism may arise as a result of its hypertrophy or hyperplasia. A similar hypothesis based on measurement of 18-oxocortisol in this condition has been proposed by Gomez-Sanchez. Thus, it may be of importance that the initial work by Sutherland et al. described nodules of abnormal tissue within the zona fasciculata of the adrenal in a patient with dexamethasone-suppressible hyperaldosteronism.

The origin of this genetic abnormality is unclear. In the current study, dexamethasone treatment reduced basal aldosterone concentration but had no effect on the aldosterone response to acutely administered ACTH. This finding may imply that the underlying adrenal abnormality is not dependent on ACTH stimulation but that expression of the abnormality in terms of increased aldosterone levels is. Since changes in adrenocortical cell function during migration may be due to high intra-adrenal glucocorticoid levels or to changes in the redox state, with increasing depth within the gland, one possible cause of this condition might be minor abnormalities in adrenocortical vascularization.

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