Levels of Mineralocorticoids in Whites and Blacks


Abstract—Blacks appear, on average, to retain more Na than whites. A higher production rate of mineralocorticoids could explain the greater Na retention in blacks. Although production of aldosterone has been shown to be lower in blacks, the level of another mineralocorticoid may be increased. Plasma levels of deoxycorticosterone and cortisol were measured in young whites (n=23; age=16.4±3.1[SD] years) and young blacks (n=25; age=13.8±1.3 years). Blacks had lower plasma levels of renin activity and aldosterone and lower urinary aldosterone excretion rates; thus, they appeared to be representative of blacks that retain additional Na. Plasma deoxycorticosterone levels were lower in blacks than in whites both at baseline (247±161 versus 381±270 pmol/L, P=0.048) and after stimulation with adrenocorticotropin hormone (822±294 versus 1127±628 pmol/L at 30 minutes, P=0.047; 925±366 versus 1440±834 pmol/L at 60 minutes, P=0.013). Cortisol levels were also lower in blacks at baseline (P=0.014) but were not significantly different from levels in whites after stimulation with adrenocorticotropin hormone. In a larger cohort of 407 whites (age=12.0±2.9 years) and 247 blacks (age=12.9±3.1 years), 18-hydroxycortisol excretion rates were also lower in blacks (P=0.021). In conclusion, increased Na retention in blacks does not appear to be secondary to increased production of either aldosterone, deoxycorticosterone, cortisol, or 18-hydroxy cortisol. A primary renal mechanism may mediate the increase in Na reabsorption in blacks. (Hypertension. 1999;34:315-319.)

Key Words: deoxycorticosterone ■ cortisol ■ 18-hydroxy cortisol ■ aldosterone ■ renin

Fluid homeostasis and blood pressure are integrally related to Na reabsorption by the kidneys. Blacks appear to retain more Na than whites, because blood pressure is typically more “salt-sensitive”1-2 and plasma renin activity (PRA) is usually lower in blacks than in whites.3-5 The greater Na reabsorption may underlie the increased susceptibility to hypertension of blacks.6-7 Why blacks might retain Na more than whites is unknown. Aldosterone does not appear to mediate the increased Na retention, because in studies that we performed in children, plasma aldosterone levels and urinary aldosterone excretion rates were actually lower in blacks than in whites.6.8 In the present study, we addressed the question of whether another mineralocorticoid might be produced in excess in blacks to account for the increase in Na reabsorption. We chose to study deoxycorticosterone (DOC) because, although it is less potent than aldosterone,10 an increase in DOC secretion, such as occurs with adrenal deficiency of 11-hydroxylase11 or 17-hydroxylase,12 can result in hypertension. There is also evidence that a partial deficiency of 11-hydroxylase contributes to common forms of hypertension.13 Cortisol was also measured because it, too, has mineralocorticoid activity14 and because an increase in the plasma cortisol level15 as well as urinary excretion of cortisol16 has been associated with higher blood pressure. Levels of DOC and cortisol were measured in whites and blacks before and after stimulation with adrenocorticotropin hormone (ACTH). Finally, we also measured urinary excretion of 18-hydroxycortisol, which reflects production of 18-oxocortisol,17 a mineralocorticoid with activity in the range of that of DOC.18,19 Levels of 18-hydroxy cortisol and 18-oxocortisol are elevated in glucocorticoid-remediable aldosteronism20-22 and with adrenal tumors that result in primary aldosteronism.23

Methods

Subjects

Subjects were recruited from a young cohort that is followed longitudinally in a study of blood pressure regulation.24 We randomly selected subjects by sending them letters requesting their participation in the study; there was no selection based on previously observed levels of renin activity, aldosterone, or blood pressure. Of those who were sent letters, ~30% agreed to participate. Their characteristics are described in Table 1. All subjects were in good health, and none were taking medication, including oral contraceptives. All female subjects had a negative result on a pregnancy test before starting the study. In these subjects, the renin-aldosterone axis was assessed and plasma levels of DOC and cortisol were measured. In a much larger, additional group of subjects, consisting of most of the members of the original cohort, the level of 18-hydroxy cortisol in overnight urine samples was measured. The studies were approved by the institutional review board of Indiana University–Purdue University of Indianapolis.
TABLE 1. Characteristics of Subjects in Whom Plasma DOC and Cortisol Were Measured

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Whites</th>
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<tbody>
<tr>
<td>Gender, n</td>
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<td>1.00</td>
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<tr>
<td>Male</td>
<td>10</td>
<td>11</td>
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</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>14</td>
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<tr>
<td>Age, y</td>
<td>16.4±3.1</td>
<td>13.8±1.3</td>
<td>0.0007</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.0±4.2</td>
<td>23.8±6.4</td>
<td>0.59</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>110.0±11.9</td>
<td>108.0±9.0</td>
<td>0.50</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>67.9±8.4</td>
<td>68.9±8.1</td>
<td>0.70</td>
</tr>
<tr>
<td>PRA, Supine ng/L · s⁻¹</td>
<td>0.42±0.27</td>
<td>0.26±0.21</td>
<td>0.026</td>
</tr>
<tr>
<td>After 2 h of standing</td>
<td>1.98±0.99</td>
<td>1.47±0.89</td>
<td>0.074</td>
</tr>
</tbody>
</table>

Plasma aldosterone concentration, pmol/L

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<tbody>
<tr>
<td>Supine</td>
<td>256.5±176.8</td>
<td>172.7±159.7</td>
<td>0.099</td>
</tr>
<tr>
<td>After 2 h of standing</td>
<td>926.2±443.5</td>
<td>669.5±414.5</td>
<td>0.049</td>
</tr>
</tbody>
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Urinary aldosterone excretion, nmol/12 h

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<tbody>
<tr>
<td>1.78±1.45</td>
<td>0.90±0.80</td>
<td>0.012</td>
<td></td>
</tr>
</tbody>
</table>

*Values are mean±SD.

Procedure

The first group of subjects was admitted to the General Clinical Research Center in the afternoon. The renin-aldosterone axis in each subject was studied by first collecting a 12-hour overnight urine sample (from 7 PM to 7 AM) for measurement of the aldosterone excretion rate. Blood samples were collected the next morning (at 7 AM) while subjects were supine and again after 2 hours of standing (at 9 AM) for measurement of the levels of renin activity and aldosterone. Plasma samples were also collected at 9 AM (baseline) and 30 and 60 minutes after an intravenous bolus injection of ACTH (Cortrosyn, 25 U) for measurement of cortisol and DOC.

An assay for 18-hydroxycortisol was available for urine but not plasma. Therefore, overnight urine samples were collected on an outpatient basis from the larger cohort for measurement of 18-hydroxycortisol excretion rate. Aldosterone excretion rate was determined from the same samples to assess the relationship of 18-hydroxycortisol excretion to aldosterone excretion. Results were expressed per unit of excreted creatinine.

Assay Procedures

Aldosterone in blood was measured by radioimmunoassay (RIA) with antiserum from Diagnostic Products Corporation. Aldosterone excretion was assessed by hydrolyzing aldosterone-18-glucuronide overnight at pH 1 to generate free aldosterone, which was measured by RIA. PRA was measured with the Clinical Assays GammaCoat RIA kit. DOC and cortisol were determined in the laboratory at Endocrine Sciences. DOC was measured by RIA after extraction and purification by paper chromatography. Recovery through the procedure ranged from 70% to 85% and was monitored in all samples with a ³H DOC tracer. Cortisol was measured by RIA in diluted serum with a specific antibody and ¹²⁵I cortisol label. The interassay coefficients of variation for aldosterone, PRA, DOC, and cortisol were 10%, 10%, 9%, and 5%, respectively.

Urinary 18-hydroxycortisol was measured with an ELISA modified from a previously published direct RIA that uses 0.5 µL of urine. The polyclonal antibody was stripped of cross-reacting antibodies by incubation with aminosilanes controlled-pore glass beads, to which cortisol-3-carboxymethoxime had been conjugated. The antibody showed very little cross-reactivity with cortisol (<0.0034%), corticosterone (0.0079%), cortisone (<0.003%), 18-hydroxycorticosterone (0.013%), and tetrahydrocortisol (<0.003%). The assay had an intraassay coefficient of variation of 8% and an interassay coefficient of variation of 12%.

Statistical Analyses

Means and SDs of the variables of interest were calculated and are presented in Table 1. All descriptive statistics for continuous data are reported as mean±SD. Comparisons of the variables, unadjusted for the other covariates, were made by 2-sample t tests. Fisher’s exact test was used to compare the proportion of female subjects in the black and white samples. Plasma levels of cortisol and DOC were modeled with ANCOVA. Included as predictors were age and race. Pearson’s correlation was used to describe the relationships among PRA, plasma aldosterone, plasma cortisol, and plasma DOC levels. Excretion rates of 18-hydroxycortisol were also examined by use of ANCOVA with race, gender, age, and body mass index (BMI) (weight divided by height squared) as predictors. Because the data were not normally distributed, we used a log transformation of the data. Adjusted means were calculated on the log scale and back-transformed to the original scale. The correlation of the log of 18-hydroxycortisol excretion and the log of aldosterone excretion was also calculated.

Results

Characteristics of Subjects

Characteristics of the subjects are presented in Table 1. Whites were, on average, 3.2 years older than blacks (P=0.0007), whereas BMI and blood pressure were not significantly different in the 2 groups. PRA was lower in blacks, a difference that was significant when subjects were supine (P=0.026) but only marginally significant after they had been standing for 2 hours (P=0.074). Although plasma aldosterone levels were lower in blacks than in whites, this racial difference was only marginally significant both in the supine position (P=0.099) and after being upright (P=0.049). Levels of PRA and plasma aldosterone were significantly related both when subjects were supine (P=0.0012) and after they were standing (P=0.035). The overnight urinary excretion rate of aldosterone in blacks was about half the value observed in whites (P=0.012). Thus, the blacks who participated in the study had a suppressed renin-aldosterone axis when compared with the whites.

Plasma Cortisol and DOC Levels

Plasma levels of cortisol and DOC before and 30 and 60 minutes after administration of ACTH are shown in Figure 1. Cortisol increased by ~2-fold and DOC by ~4-fold in response to ACTH. At baseline, the mean cortisol level was...
Table 2. Urinary Excretion of 18-Hydroxycortisol and Aldosterone*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Whites</th>
<th>Blacks</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males (n=213)</td>
<td>Females (n=194)</td>
<td>Males (n=118)</td>
</tr>
<tr>
<td>Age, y</td>
<td>13.0±3.2</td>
<td>12.9±3.1</td>
<td>12.3±2.7</td>
</tr>
<tr>
<td>18-Hydroxycortisol, nmol/mmol creatinine†</td>
<td>−1.628±0.653 (0.242±0.176)</td>
<td>−1.773±0.570 (0.202±0.146)</td>
<td>−1.825±0.703 (0.205±0.158)</td>
</tr>
<tr>
<td>Aldosterone, nmol/mmol creatinine†</td>
<td>0.277±0.830 (1.89±2.28)</td>
<td>0.226±0.793 (1.69±1.50)</td>
<td>−0.236±0.895 (1.15±1.09)</td>
</tr>
</tbody>
</table>

*Values are mean±SD.
†Derived from t test.
‡Nonlog values.

Discussion
Blacks appear to retain more Na than whites, a condition that may predispose blacks more than whites to hypertension. We showed previously that production of aldosterone was lower in blacks than whites and thus that an increase in aldosterone did not explain the increase in Na reabsorption in blacks. In this study, we showed that the blood level of DOC, a mineralocorticoid with less activity than aldosterone10 but with the potential to produce hypertension,11–13 was also not increased in blacks, and in fact, like aldosterone, DOC production appeared to be lower in blacks. The level of cortisol was also not higher in blacks. Urinary excretion of the cortisol level at baseline (P=0.037), whereas age was not (P=0.88); neither race nor age was a significant predictor of the cortisol level at either time point after administration of ACTH. Race was a significant predictor of the DOC level both before and after treatment with ACTH, with P values of 0.015, 0.0031, and 0.0019 at baseline and 30 and 60 minutes after ACTH treatment, respectively. When age was used as a predictor of DOC level, the P values were 0.14, 0.017, and 0.071, respectively.

18-Hydroxycortisol Excretion Rates
Excretion rates of 18-hydroxycortisol were also measured in the larger cohort of whites and blacks. Aldosterone excretion was also determined to examine its relation to 18-hydroxycortisol excretion. By use of ANCOVA, race (P<0.0001), gender (P=0.026), age (P<0.0001), and BMI (P=0.015) were significant predictors of the 18-hydroxycortisol excretion rate, with lower levels occurring in blacks than in whites (0.154 versus 0.189 nmol/mmol creatinine) and lower levels in the female subjects than in the male subjects (0.162 versus 0.180 nmol/mmol creatinine). As BMI and age increased, excretion of 18-hydroxycortisol increased and decreased, respectively (slopes were 0.013 and −0.085 using a log scale). The t test, which used unadjusted values, produced similar results (Table 2): for race, P=0.017, and for gender, P=0.065. Aldosterone excretion rates were significantly related only to race (P<0.0001), again with lower levels in blacks. A similar result for a racial difference in aldosterone excretion rate was observed when the t test was used (Table 2). 18-Hydroxycortisol and aldosterone excretion rates were highly related, with a correlation coefficient of 0.36 (P<0.0001).

The results were similar. Race was a significant predictor of

Plasma levels of cortisol and DOC at baseline and 30 and 60 minutes after acute administration of ACTH to whites (○) and blacks (●).

Significantly higher in whites than in blacks (580±178 [SD] versus 457±146 nmol/L, P=0.014). The mean baseline DOC level was also significantly higher in whites (381±270 versus 247±161 pmol/L, P=0.048). After treatment with ACTH, cortisol levels were no longer significantly different in the 2 groups: mean cortisol levels were 840±150 versus 782±137 nmol/L (P=0.18) at 30 minutes and 933±172 versus 877±158 nmol/L (P=0.26) at 60 minutes in whites and blacks, respectively. Conversely, after ACTH treatment, DOC levels remained higher in whites at 30 minutes (1127±628 versus 822±294 pmol/L, P=0.047) and at 60 minutes (1440±834 versus 925±366 pmol/L, P=0.013). Because the blacks were older, the data were also examined with linear regression analysis with age and race in the model. The results were similar. Race was a significant predictor of

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Although DOC secretion appears to be driven primarily by mineralocorticoid, another mineralocorticoid, was also lower in blacks. Our results are consistent with a primary renal mechanism for Na reabsorption that functions at a higher level in blacks or, alternatively, with overproduction in blacks of still another mineralocorticoid.

Although DOC levels were lower in blacks, like aldosterone levels, may be responding to suppression of the renin-angiotensin system. To explore this potential mechanism, we examined the relation of the 2-hour upright PRA to the DOC level (Table 3). For purposes of comparison, the relationships of PRA to the aldosterone and cortisol levels were also studied. Similar to aldosterone, DOC (but not cortisol) showed at the least a trend for a significant association with PRA (at 30 and 60 minutes after ACTH; values for the DOC/PRA relationship were 0.027 and 0.097, respectively). The lower 18-hydroxycortisol excretion rate in blacks may also reflect less stimulation by the renin-angiotensin system. Although 18-hydroxycortisol production is known to respond to ACTH, as occurs in glucocorticoid-suppressible aldosteronism, Na restriction also increases it.

An increase in the normal production of cortisol has been associated with a higher blood pressure in several studies. Litchfield et al found higher urinary free cortisol excretion rates in hypertensive than in normotensive subjects, and, by use of the “four corners” model for identifying factors that contribute to development of hypertension, Watt et al found the highest plasma cortisol levels in subjects who were normotensive but had the highest blood pressures and in a parent who was hypertensive. A higher cortisol level was not observed in the blacks in our study; thus, we believe that a role of cortisol in increasing the risk of hypertension in blacks is unlikely.

In summary, plasma levels of DOC and cortisol, both at baseline and after stimulation with ACTH, were not higher, and in the case of DOC were actually lower, in blacks than in whites. 18-Hydroxycortisol excretion rates were also lower in blacks. These findings, in conjunction with previous observations that aldosterone production is lower in blacks, suggest that greater Na reabsorption in blacks is not mediated by higher levels of these mineralocorticoids but rather may result from a more active primary renal mechanism.

### TABLE 3. Correlation Coefficients for Relationships of DOC, Aldosterone, and Cortisol Levels to Level of PRA*

<table>
<thead>
<tr>
<th>Adrenal Steroid</th>
<th>Baseline</th>
<th>30 min after ACTH</th>
<th>60 min after ACTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doc</td>
<td>0.013 (P = 0.93)</td>
<td>0.33 (P = 0.027)</td>
<td>0.25 (P = 0.097)</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>0.31 (P = 0.034)</td>
<td>0.32 (P = 0.029)</td>
<td>0.29 (P = 0.056)</td>
</tr>
<tr>
<td>Cortisol</td>
<td>−0.12 (P = 0.44)</td>
<td>0.14 (P = 0.37)</td>
<td>0.04 (P = 0.78)</td>
</tr>
</tbody>
</table>

*PRA was drawn after the subject had stood for 2 h.

18-hydroxycortisol, which is reflective of 18-oxocortisol, another mineralocorticoid, was also lower in blacks. Our results are consistent with a primary renal mechanism for Na reabsorption that functions at a higher level in blacks or, alternatively, with overproduction in blacks of still another mineralocorticoid.

### Acknowledgments

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### References


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