Adrenal Androgen Excretion During Adrenarche
Relation to Race and Blood Pressure

J. Howard Pratt, Amita K. Manatunga, Mary Anne Wagner, Jerrlyn J. Jones, and F. John Meaney

We have previously shown that black children have higher blood pressures than white children. In the present study, we examined whether a possible racial difference in adrenal androgen production during adrenarche might contribute to the racial disparity in blood pressure. Adrenal androgen production was estimated from urinary excretion of adrenal androgen metabolites that showed cross-reactivity with antisera to dehydroepiandrosterone sulfate (DHEA-S). Urine samples were collected overnight in 798 children, one third of whom were black. Analyses were performed for two different age groups, less than 10 years and 10 years or more of age. In children less than 10 years of age, adrenal androgen excretion rates were 17% higher in blacks than in whites ($p=0.0099$); adrenal androgen excretion rates tended to be higher in older black children as well, but differences here were not statistically significant. Adrenal androgen excretion rates were positively correlated with diastolic blood pressure in the older age group only ($p=0.014$). However, when the relation of race to blood pressure was examined along with adrenal androgen excretion adjusted for age, sex, and weight, race remained an independent contributor to the level of blood pressure, suggesting that a difference in adrenal androgens could not explain the racial differences in blood pressure. In summary, black children produced more adrenal androgen, but this did not explain their higher blood pressures. In older children, where adrenal androgen excretion rates were higher, diastolic blood pressure and adrenal androgen excretion were positively related, suggesting that adrenal androgens participate in establishing the level of blood pressure in young people. (Hypertension 1990;16:462-467)

Dehydroepiandrosterone sulfate (DHEA-S) and dehydroepiandrosterone (DHEA) are the major androgen secretory products arising from the adrenals. There is an acceleration of their production at about age 6-7 years, with peak values occurring early in the third decade, a phenomenon referred to as the adrenarche. In conjunction with the adrenarchal increase in adrenal androgen (AA) production, there is an increase in blood pressure. AA's could be contributing to the increase in blood pressure, possibly through anabolic effects on the cardiovascular system. Katz et al found that serum DHEA-S was higher in children with higher blood pressures. Reports on the relation of DHEA-S production to blood pressure in adults have been inconclusive.

In a biracial population, we found that black children without hypertension had significantly higher blood pressures than white children, and the adrenal's production of aldosterone was also lower in blacks. Whether AA production is different in blacks and whites is not known. The purpose of the present study was to examine AA production during adrenarche for racial differences, differences that might contribute to the racial disparity in blood pressures. We also studied the relation of AA production to body fat, as assessed by measuring skinfold thickness and arm circumference, to provide insight into mechanisms for regulating AA production.

Methods

Subjects

Children were recruited from 18 schools in Indianapolis. Seven hundred and ninety-eight subjects participated; about one third were black. All sub-
jects were in good health. Informed consent was obtained from each child as well as from his or her parents or a guardian.

**Procedures**

Each subject had weight and height measured. Blood pressures were measured with a random zero sphygmomanometer (Hawksley and Sons, Lancing, Sussex, England) while subjects were in the sitting position. The first and fifth Korotkoff sounds were used to designate systolic and diastolic blood pressures, respectively, and the average of the second and third readings was used as the final blood pressure. In subjects in whom the fifth Korotkoff sound was not audible, the fourth sound was designated as the diastolic blood pressure. Skinfold thickness was measured in the triceps and subscapular regions using a Lange Skinfold Caliper (Cambridge Scientific Industries, Inc., Cambridge, Md.), and arm circumference was measured at the midway point of the right upper arm. Urine samples were collected from bedtime to the following morning.

A second study was designed to validate findings from the initial set of observations. This group of subjects consisted of 43 black and 56 white children with a mean age of 10.3 ±2.1 (SEM) and 10.6 ±2.0 years in blacks and whites, respectively. Blood samples were collected between 9:00 AM and 1:00 PM.

AA production rates were estimated by measuring AA urinary metabolites with cross-reactivity to antisera that showed 100% cross-reactivity with DHEA-S (Radioassay Systems Laboratories, Inc., Carson, Calif.). The cross-reactivity of the DHEA-S antisera with DHEA was 58.5%. Urine samples were usually diluted 1:200 and serum samples 1:500 with phosphate buffer. The detection limit of the assay was 500 pg/ml of urine or serum. Urinary creatinine was measured using a Beckman-2 creatinine analyzer (Beckman Instruments, Inc., Fullerton, Calif.).

**Statistical Methods**

The data were analyzed separately for two age groups, less than 10 years old and 10 years or older, to avoid some of the heterogeneity associated with growth and development and to separate prepubertal from pubertal time periods. Statistical analyses of difference in group means were performed using the unpaired t test. To assess the effect of race, with allowance made for the other variables related to AA excretion, a series of multiple regressions was performed.9 First, with AA excretion rates as the dependent variable, the stepwise procedure was used to select an appropriate subset of predictor variables that might be confounded with race. Variables considered initially included age, sex, body mass index (BMI) (weight/height²), triceps and subscapular skinfold thicknesses, and arm circumference. These analyses were repeated for both age groups. In both analyses the variable race was excluded. Analyses were then repeated for both groups without the stepwise procedure, including in both analyses any variable that had previously been selected by either of the stepwise analyses.9 The effect of race was then assessed by including it in the model along with the other variables selected and noting the consequent decrease in mean squared error of the AA excretion rate. The multiple regression coefficients were used to present the association between the AA excretion rate and its predictors, which were selected by the above analyses.

To determine the degree to which AA excretion variation contributed to blood pressure variation, after making allowance for age, race, and weight, general linear models were fitted for the two groups (less than 10 and 10 or more years of age). Descriptive mean AA excretion rates together with standard errors for each age group were plotted for both groups, blacks and whites and boys and girls (Figures 1–3).

**Results**

Table 1 shows the characteristics of the population studied. Blacks and whites were of similar age, and the age distributions for blacks and whites were also similar. Black children were heavier than white children for age less than 10 years (p=0.0003) and age 10 years or more (p=0.043). The BMI was greater in
blacks in the younger age group \((p=0.0012)\) only. Subscapular skinfold thickness \((p=0.0001)\) and arm circumference \((p=0.009)\) were greater in blacks for ages less than 10 years.

AA excretion rates increased with age in girls and boys (Figure 1) and blacks and whites (Figures 2 and 3). Serum DHEA-S levels from a smaller sample size were plotted against AA excretion rates to examine the correlation of serum values with those in urine. Serum DHEA-S levels were found to be highly correlated with urinary excretion of AA \((r=0.82)\) (Figure 4).

To examine for racial differences in AA excretion, the stepwise regression procedure was performed for both age groups (less than 10 and 10 years or more) using the variables age, sex, BMI, triceps and subscapular skinfold thicknesses, and arm circumference. The intention was to find a subset of variables, excluding race, that would best explain AA excretion rates. The selected variables were age and subscapular skinfold thickness for the younger group and age, arm circumference, and sex for the older group. Triceps skinfold thickness, weight, and BMI were not selected for either group. For both groups, the general linear models were fitted for both groups with age, sex, subscapular skinfold thickness, and arm circumference as independent variables. The decrease in mean squared error after subsequently fitting the race variable was \(2.637\) (\(F_{1,46}=6.70, p=0.0099\)) for the younger group and \(0.765\) (\(F_{1,46}=1.78, p=0.183\)) for the older group. These results indicated that there was a racial difference in the AA excretion rate after adjusting for possible confounders such as age, subscapular skinfold thickness, sex, and arm circumference. The results are given in Table 2. In the younger groups, adjusted means for AA excretion rates means were \(0.2975\) and \(0.3480 \mu g/mg\) creatinine for whites and blacks, respectively; AA excretion rates were \(17\%\) higher in black children than white children \((p=0.0099)\). For the older children, the adjusted means for AA excretion rates were \(0.7274\) and \(0.8237 \mu g/mg\) creatinine in whites and blacks, respectively. AA excretion rates
were about 13% higher in blacks in the older age group, but here the difference was not statistically significant. The racial difference in AA production was also examined in a smaller group in whom serum DHEA-S levels were measured. Serum DHEA-S levels were highly associated with age (<0.001), and the variable race was found to be a significant predictor of serum DHEA-S levels (p=0.049), as it was with AA excretion. Similar to what was observed with measurements in urine, there was a 13% increase in serum DHEA-S levels in black children compared with white children.

To examine the association between AA excretion and other variables, the model shown in Table 2 was used. There was no significant difference in AA excretion rates between boys and girls in the younger age group, but for the older group, girls had higher AA excretion rates (p=0.018). Subscapular skinfold thickness was positively associated with AA excretion for the younger group (p=0.017) but not for the older group. For the older group, arm circumference was highly associated with AA excretion rates (p=0.007).

To determine if the racial difference in blood pressure is related to racial variation in AA excretion rates, general linear models were fitted in which AA excretion was included as an independent variable along with the variables age, sex, and weight. The results are presented in Table 3. After adjusting for the effect of AA excretion, age, sex, and weight, the variable race was significantly related to systolic blood pressure in the age group less than 10 years (n=558) (p=0.019), whereas diastolic blood pressure was not related to race (p=0.671). In the older age group (10 years or older, n=240), the relation of race to blood pressure was in the direction of significance (p=0.067 for systolic blood pressure and p=0.052 for diastolic blood pressure). Because the regression coefficients (effect sizes) were similar in the two age groups (2.072 for systolic blood pressure in the age group less than 10 years, and 2.875 and 2.786 for systolic and diastolic blood pressures, respectively, in the age group 10 years or more), the fewer number of subjects in the older group may have been the reason for slightly higher p values. The findings indicate that the racial difference in blood pressure cannot be explained by the racial difference in AA excretion. Systolic blood pressure after adjusting for the covariates was approximately 3 mm Hg higher in blacks than in whites for both age groups, whereas diastolic blood pressure was 3 mm Hg higher in blacks in the older age group. When BMI was substituted for weight, this same analysis resulted in similar results.

Discussion

The increase in AA production that characterizes the adrenarche was estimated in this study from the excretion of AAs during sleep. Sleep samples offer the advantage of simplicity of collection (usually the first voided morning sample is the only sample required), thus assuring completeness of collections better than with 24-hour samples. Androgens secreted by the adrenals are converted one to the other, and subsequently there is conversion to metabolites, which may be excreted in urine. There is no single urinary measurement that can provide more than an estimate of AA production. In blood, DHEA-S is the predominant AA; its plasma concentration is disproportionately high as a result of its very low metabolic clearance rate (15-20 l/day). A reliable urinary parameter of AA production would be expected to correlate with the concentration of DHEA-S in blood. Our values for AA excretion as estimated using an antiserum to DHEA-S were highly correlated with serum DHEA-S levels (r=0.82). Thus, the urinary measurement of AA

### Table 2. Relation of Adrenal Androgen Excretion to Age, Race, Sex, Subscapular Skinfold Thickness, and Arm Circumference Expressed as Regression Coefficients

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Age (yr)</th>
<th>Race*</th>
<th>Sex†</th>
<th>Subscapular skinfold (mm)</th>
<th>Arm circumference (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 yr</td>
<td>0.180±0.024</td>
<td>0.157±0.061</td>
<td>0.007±0.058</td>
<td>0.026±0.011</td>
<td>0.035±0.019</td>
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<tr>
<td>(p value)</td>
<td>(0.0001)</td>
<td>(0.0099)</td>
<td>(0.899)</td>
<td>(0.017)</td>
<td>(0.065)</td>
</tr>
<tr>
<td>≥10 yr</td>
<td>0.242±0.044</td>
<td>0.125±0.093</td>
<td>0.255±0.094</td>
<td>−0.001±0.011</td>
<td>0.056±0.021</td>
</tr>
<tr>
<td>(p value)</td>
<td>(0.0001)</td>
<td>(0.183)</td>
<td>(0.018)</td>
<td>(0.941)</td>
<td>(0.007)</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Adrenal androgen excretion is expressed in terms of the log.

*Whites=0, blacks=1.
†Boys=0, girls=1.
excretion used in the present study appeared to be an accurate index of AA production. In addition, AA excretion rates increased with age in a manner characteristic of the adrenarche. That samples could be easily collected and assayed directly made it feasible to examine AA production in a much larger population of children than had been studied previously. We found that AA excretion rates were higher in black than white children, at least in children under the age of 10 years. In a smaller sample size, serum DHEA-S levels were also higher in black children, corroborating findings from urinary measurements. In contrast to white children, black children had more truncal fat, which would be expected to increase AA excretion rates, but when adjustments were made for racial differences in body fat, black children had AA excretion rates that were still about 17% higher than in white children. In the older children, AA excretion rates were 13% higher in blacks than in whites, but this difference did not reach statistical significance, possibly because there were fewer children in the older group. A greater level of AA production in blacks during the adrenarche, or at any age, has not been described previously. This finding was not completely unexpected in that premature adrenarche, defined as the early growth of axillary or pubic hair, occurs more commonly in black girls than white girls. Recently, it was also shown that 20% of black girls with premature adrenarche have various degrees of nonclassical 3-β-hydroxy steroid dehydrogenase deficiency.

Androgens have been shown to augment blood pressure in hypertensive animals, possibly through anabolic actions that affect growth of cardiovascular tissues, or by affecting tissue levels of vasopressors or the responsiveness to vasopressor substances. In human subjects, an increase in AA production as estimated from measurements of DHEA-S has been associated with hypertension in some studies but not all. A role for AA to increase blood pressure in growing children is suggested by the observation that blood pressure and AA production increase in parallel during adrenarche. Katz et al. found in studies of black adolescents that those with higher serum DHEA-S levels had higher blood pressures, even after making appropriate adjustments for body fat. Conceivably, a greater increase in AA production by blacks during adrenarche might be relevant to the higher blood pressures of black children.

In the older age group, where AA excretion rates were higher, there was a positive relation of AA excretion with diastolic blood pressure. This finding is consistent with the observations of Katz et al. At ages less than 10 years, however, AA excretion rates were not related to blood pressure. When the relation of race to blood pressure was examined along with AA excretion (and age and weight), race remained a significant contributor to the level of blood pressure, suggesting that AAs were not contributing to the racial effect on blood pressure.

In the present study, AA excretion rates were positively correlated with truncal fat but not limb fat in subjects less than 10 years of age. A positive relation of truncal fat to serum DHEA-S has been observed previously. In older children, AA excretion rates were related to arm circumference, a relation that represents a new finding. Arm circumference reflects primarily muscle and may depict a response to the AA produced. Girls had higher AA excretion rates than boys. Because girls enter puberty at an earlier age than boys, ovarian hormones may have contributed somewhat to the higher AA excretion rates in girls. In addition, boys had higher urinary creatinines, and to some extent this would have overcorrected AA excretion rates expressed per milligram creatinine. No significant sexual difference was observed in serum levels of DHEA-S. At all ages, however, in both blood and urine, girls tended to have higher levels. In adults, serum DHEA-S levels have been shown to be higher in men.

In conclusion, AA production was higher in black children, particularly early in adrenarche, but this increase in AA production did not explain their higher blood pressures. In older children, AA excretion rates were positively related to diastolic blood pressure, suggesting that AAs may affect blood pres-
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sure at a later stage of adrenarche when AA production is higher. Truncal fat and arm circumference are strong predictors of AA production.

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References


KEY WORDS • androgens • dehydroepiandrosterone • race • blood pressure • adrenarche • body fat • skinfolds

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