Renin-Angiotensin-Aldosterone System

Racial Differences in Sensitivity of Blood Pressure to Aldosterone

Wanzhu Tu, George J. Eckert, Tamara S. Hannon, Hai Liu, Linda M. Pratt, Mary Anne Wagner, Linda A. DiMeglio, Jeesun Jung, J. Howard Pratt

See Editorial Commentary, pp 1168–1170

Abstract—Blacks in comparison with whites are at risk for a more serious form of hypertension with high rates of complications. Greater sodium retention is thought to underlie the blood pressure (BP)-determining physiology of blacks, but specific mechanisms have not been identified. In a prospective observational study of BP, 226 black children and 314 white children (mean age, 10.6 years) were enrolled initially. Assessments were repeated in 85 blacks and 136 whites after reaching adulthood (mean age, 31 years). The relationship of BP to plasma aldosterone concentration in the context of the prevailing level of plasma renin activity was studied in blacks and whites. In a secondary interventional study, 9-α-fludrocortisone was administered for 2 weeks to healthy adult blacks and whites to simulate hyperaldosteronism. BP responses in the 2 race groups were then compared. Although black children had lower levels of plasma renin activity and plasma aldosterone, their BP was positively associated with the plasma aldosterone concentration, an effect that increased as plasma renin activity decreased ($P=0.004$). Data from black adults yielded similar results. No similar relationship was observed in whites. In the interventional study, 9-α-fludrocortisone increased BP in blacks but not in whites. In conclusion, aldosterone sensitivity is a significant determinant of BP in young blacks. Although its role in establishing the risk of hypertension is not known, it could be as relevant as the actual level of aldosterone. (Hypertension. 2014;63:1212-1218.) • Online Data Supplement

Key Words: aldosterone ■ blood pressure ■ child ■ continental population groups ■ renin ■ sodium

Blacks in comparisons with whites have disproportionately more hypertension¹ and suffer hypertensive complications at higher rates.² The cause of the hypertension seems to center on overly efficient sodium reabsorption by the kidney. The renin–angiotensin system, for example, is more likely to be suppressed in blacks than in whites, consistent with greater volume expansion from sodium accumulation and water retention.³,⁴ In addition, blood pressure (BP) in blacks in contrast to BP in whites typically increases in response to an increase in sodium intake (there is greater salt sensitivity).⁵ Whether blacks have a unique renal physiology that puts them at risk for a more aggressive form of hypertension is unclear. A more complete understanding of how BP is regulated in blacks could revise the current approaches for treatment should hypertension develop.

A higher production rate of aldosterone, the principal sodium-retaining hormone, is becoming increasingly appreciated as a contributor to the pathophysiology of hypertension. Primary hyperaldosteronism, for example, accounts for ≈10% of cases of essential hypertension⁶ and ≈20% of cases of resistant hypertension.⁷ In the Framingham Offspring Study, normotensive individuals with levels of plasma aldosterone in the upper quartile of the normal range compared with those in the lower quartile when studied 4 years later had significantly higher BP and were more likely to be hypertensive.¹⁰ In blacks, BP has been shown in several studies to be positively related to the level of plasma aldosterone.¹¹–¹₅ BP,¹⁴,¹⁵ presence of hypertension,¹¹–¹₃ and left ventricular mass¹²,¹₅ have all been shown to be positively associated with the aldosterone/renin ratio. Despite evidence that aldosterone has the potential to affect BP, blacks often have an elevated BP in the absence of any noticeable increase in the aldosterone level.

More than 20 years ago, we initiated a cohort study of BP regulation where enrollees were children, blacks and whites, from Indianapolis, IN.¹⁶ We found that black children had lower plasma aldosterone levels and urinary aldosterone excretion rates than white children, whereas there was little if any race difference in BP. Other investigative groups have also found lower aldosterone production in blacks.¹⁵,¹₇,¹₈ The presumptive explanation was a suppressed renin–angiotensin axis from greater sodium retention in blacks. On a background of more positive sodium balance and lower aldosterone production rates, the role of aldosterone in determining BP could be diminished in blacks.
Alternatively, preexisting sodium retention might enhance an effect of aldosterone on BP—just as blacks are more salt-sensitive, they may also be more sensitive to aldosterone.

The present study sought to determine the extent of aldosterone’s influence on BP in blacks in comparison to whites. We undertook a new assessment of the Indianapolis cohort data collected in childhood as well as an assessment of data collected recently with subjects now adults. Employing a novel analyses, BP in blacks was found to increase as plasma aldosterone concentration (PAC) increased and the level of plasma renin activity (PRA) decreased, a relationship that was largely absent in whites. The results from observational data led us to perform a second study, an intervention where blacks and whites were treated with the synthetic mineralocorticoid 9-α-fludrocortisone to simulate modest hyperaldosteronism. BP responses in the 2 race groups were then compared.

Methods
Observational Cohort Study

Subjects and Study Design
Data for the main analysis were collected from a prospective observational cohort study that was started in 1986. The characteristics of the study participants and the data collection process were described in detail previously. Briefly, however, healthy black children and white children between 5 and 17 years of age were recruited from schools in Indianapolis selected to provide a range of socioeconomic levels. Renal or cardiac disease, hypertension, diabetes mellitus, and use of medications that could affect BP excluded subjects from participation. Subjects were seen twice a year. BP was measured in the right arm while in the seated position after resting for ~5 minutes.

Three BP readings were taken 2 minutes apart. The average of the last 2 readings was used as the final BP measurement. Height and weight were also measured. Blood samples were drawn in most subjects only once and between 0800 and 1000 hours after sitting for 15 minutes. Urine samples were collected overnight.

In 2008, we invited those who had participated as children to return for further evaluations as adults. The data collection protocol and procedures followed for the adults remained unchanged from the child study with the exception that blood sampling was performed at each visit. To eliminate the possible influences of antihypertensive medication on BP and biochemical measurements, the current analysis excluded 32 visits from 14 individuals (7 blacks and 7 whites) who were receiving antihypertensive medications. The study protocol was approved by the Institutional Review Board of Indiana University. Consent was obtained from all adult participants and from parents of children <18 years; assent was obtained from children as appropriate.

9-α Fludrocortisone Interventional Study

In a secondary study, we tested the hypothesis that the administration of a synthetic mineralocorticoid similar to aldosterone, 9-α-fludrocortisone, would raise BP more in blacks than in whites. In addition, parameters reflective of the state of sodium balance, including the levels of PRA, PAC, and B-type natriuretic peptide, were measured at baseline and after 2 weeks of treatment. Healthy subjects were recruited from local medical center facilities. The study was approved by the Indiana University and the Department of Veterans Affairs Institutional Review Board. Each subject gave informed consent.

Measurements made at baseline and after 2 weeks of treatment with 9-α-fludrocortisone were used in the analysis. Subjects were also seen at 1 week as part of an overall assessment. Ambulatory BP monitoring (ABPM) was performed at baseline and after 2 weeks of treatment (Spacelab 90207, Redmond, WA). BP was automatically measured every 30 minutes during the day and every 60 minutes overnight (2200 to 0800 hours) for 24 hours. After the first set of measurements, subjects were given 9-α-fludrocortisone (0.2 mg as tablets each morning, which was approximately twice the replacement dose of aldosterone) for 2 weeks. Compliance was determined from pill counts at 1 and 2 weeks; no difference between groups was observed.

Assay Procedures
See online-only Data Supplement.

Statistical Analysis
Demographic and clinical characteristics of study participants were summarized by self-reported black and white categories. Continuous variables were compared by t test and categorical variables by χ² test. To assess the accuracy of self-identified race information, we performed a principle component analysis. Specifically, we compared the self-reported race identified in the collected samples to 7 ethnic groups in HapMap phase 3 data. Analysis (Figure S1 in the online-only Data Supplement) revealed close genetic resemblance between self-identified blacks in our cohort and individuals of African ancestry in Southwest United States, and between self-identified whites and Utah residents of Northern and Western European ancestry.

For the childhood data, we converted all BP values into age-, sex-, and height-adjusted percentile values. We then used varying coefficient regression models to examine the influences of aldosterone on BP percentile at different renin levels. Unlike traditional linear regression analysis, varying coefficient regression characterizes the effect of aldosterone on BP as a smooth function of renin. In this analysis, regression analysis was performed using systolic BP percentile as the response variable, and the regression coefficient of aldosterone was modeled as a function of renin. Separate analyses were performed for blacks and whites. Estimated aldosterone effects on BP were displayed graphically with corresponding 95% confidence intervals. We analyzed the adult data similarly using systolic BP values instead of
percentiles as the response variable. The same analytic approach was used to examine the effects of urinary aldosterone excretion rate (per milligram of urinary creatinine) on systolic BP percentile in children and systolic BP in adults at different levels of PRA.

In the interventional study, we determined changes in clinic BP, ABPM (daytime, nighttime, and 24 hours), and body weight, as well as changes in plasma levels of B-type natriuretic peptide, renin activity, and aldosterone. The responses of the aldosterone/renin ratio were also calculated over the 2 weeks. The magnitudes of within-subject changes were examined using a paired *t* test; changes between race groups were compared using ANOVA adjusted for the effects of age, body mass index, and sex. The analysis was implemented by using R software (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). Throughout the analysis, *P* values <0.05 were considered statistically significant.

## Results

### Subjects

Characteristics of children at initial enrollment and of adults when re-enrolled are presented in the Table. Characteristics of subjects in the interventional study are also presented. The levels of PRA and PAC in children (obtained at a visit that was subsequent to the enrollment visit) and in adults were significantly lower in blacks regardless of the age group (Figure 1); in black children, the PAC/PRA ratio was significantly lower. Mean values for plasma measurements and for urinary aldosterone and electrolyte excretion rates are available in Table S1.

### Aldosterone Sensitivity

Using varying coefficient regression analysis, we estimated the effect of PAC on systolic BP in blacks and whites in children as well as in adults. The effects of aldosterone on systolic BP percentiles are depicted in Figure 2 as smooth functions of PRA. The plots showed 2 distinctly dissimilar patterns of influences of PAC on systolic BP at various levels of PRA in the 2 race groups. In whites, the estimated PAC–BP association consisted of a barely discernable increase as PRA increased, the confidence interval overlapped with the zero effect, and thus this was not statistically significant. In blacks, the estimated BP effect of aldosterone was highly significant (*P*=0.004) and became stronger as the level of PRA declined. For example, in children with PRA of 1.0 ng/mL per hour, there was on average a 2% increase in systolic BP percentile for each nanogram per deciliter increase in PAC. Importantly, the PAC effect on systolic BP in adults showed similar patterns: the BP responded strongly to aldosterone in the blacks, especially in those with lower PRA. A similar pattern was once again not evident in the whites. The relation of urinary aldosterone excretion to BP at different PRA levels was also examined. The analysis showed a similar race difference (see Figure S2).

### 9-α Fludrocortisone

The BP responses to 9-α fludrocortisone administered over 2 weeks were clearly different in blacks and whites (Figure 3).

![Figure 1](http://hyper.ahajournals.org) The mean levels of plasma renin activity (PRA; A, D), plasma aldosterone concentration (PAC; B, E), and aldosterone/renin ratio (ARR; C, F) with corresponding 95% confidence intervals in blacks and in whites, in children, and in adults.
Whereas in whites BP did not change, in blacks systolic BP increased by 5 to 6 mm Hg ($P=0.034$ for clinic BP; $P<0.001$ for daytime ABPM; $P=0.006$ for nighttime ABPM; and $P<0.001$ for ABPM over 24 hours). Weight increased in blacks ($P=0.028$) and not in whites ($P=0.11$). Similarly, levels of BNT increased only in blacks ($P=0.012$), PRA decreased in blacks ($P=0.002$) and in whites ($P<0.001$). Although PAC decreased significantly in both race groups ($P=0.010$ for blacks and $P<0.001$ for whites), the magnitude of the decrease was significantly greater for whites ($P=0.014$). The aldosterone/renin ratio increased in response to 9-$\alpha$ fludrocortisone in whites ($P=0.036$) and showed a marginally significant decrease in blacks ($P=0.09$). In blacks only, the serum potassium concentration decreased by 0.2 mmol/L with treatment ($P=0.0008$).

**Discussion**

In the current study, we assessed the role of aldosterone in regulating BP in young blacks and whites. We used an analytic approach that took into account the prevailing state of sodium retention as reflected in the level of PRA. In the blacks, BP showed a significant association with PAC. This effect of aldosterone on BP or aldosterone sensitivity intensified as PRA decreased. The findings were evident in both children and adults. A similar effect pattern was not observed in whites. In a separate study, the 24-hour ambulatory BP response of young blacks and whites to administrated 9-$\alpha$ fludrocortisone was determined, an intervention that in effect directly tested for aldosterone sensitivity. BP increased significantly in the blacks but not in the whites. The results corroborated the
finding in the association study. The sensitivity of BP to the circulating level of aldosterone may be an integral component of the BP-determining physiology in young blacks.

A mechanism for why young blacks have a heightened sensitivity to aldosterone may reside with a preexisting state of increased sodium retention. This was implied by the lower level of PRA that inversely correlated with aldosterone’s positive influence on BP, pointing to an expansion of fluid volume. In blacks, less additional sodium uptake by aldosterone would be required to reach a threshold where BP might increase. The response by blacks to treatment with 9-α-fludrocortisone was also consistent with having greater baseline sodium stores. In contrast to whites, blacks experienced significant weight gain and an increase in their level of B-type natriuretic peptide, a marker of volume and which would be expected to increase as extracellular fluid volume expanded.20 It was as if the capacity for taking on any additional sodium had already been fully realized in the blacks, and achieving sodium balance would rely more on a natriuresis from an increase in BP.24,25 On the other hand, the whites seemed to adjust to additional sodium or an increase in volume without resorting to an increase in BP. Indeed, the whites responded with a significant decrease in the levels of PRA and PAC, whereas the blacks did not, suggesting that whites have a greater capacity for accommodating additional sodium. Urinary excretion rates of sodium and potassium were not measured in the interventional study. Although a potential shortcoming, race differences in what was consumed would likely have affected the findings at baseline more than response to 9-α-fludrocortisone, and it was these results that were most noteworthy.

Aldosterone sensitivity was delineated in the blacks using analyses that simultaneously took into account the dual influences of plasma aldosterone and PRA on BP. If we had relied only on the aldosterone/renin ratio, which is used commonly as a clinical tool to assist in diagnosing primary hyperaldosteronism,8 it could have led to our having missed recognizing aldosterone sensitivity in the blacks. Various combinations of the levels of aldosterone and renin activity can give identical values for the aldosterone/renin ratio while at the same time quite different propensities for affecting BP. The black children in our study, for example, had significantly lower
aldosterone-renin ratios compared with the white children, yet ultimately we found that aldosterone was a principal determinant of the BP.

The present study did not lend itself to suggesting a better treatment for hypertensive blacks. However, in an earlier randomized, placebo-controlled study limited to blacks with poorly controlled low renin hypertension, adding small doses of spironolactone (a mineralocorticoid receptor antagonist) or amiloride (an inhibitor of the epithelial sodium channel, a principal target of aldosterone) lowered the average BP into the normal range. In a comparison between race groups of the antihypertensive properties of the mineralocorticoid receptor antagonist eplerenone, blacks and whites were found to respond equally. In the same study, however, the blacks showed a significantly better BP-lowering response to eplerenone than the angiotensin receptor blocker losartan, whereas in the whites, eplerenone as an antihypertensive was not superior to losartan.

The propensity to retain sodium and develop hypertension is very much age-dependent. As people become older, aldosterone sensitivity may also become more common and may occur regardless of race, but earlier and probably more often in blacks. The nonpressor effects of aldosterone might also be enhanced when sensitivity to aldosterone is increased. The present findings also raise the question of what constitutes a normal aldosterone level in blacks and at what level is it too high, especially for the level of PRA and thus amendable to a treatment that mitigates aldosterone’s actions. Answers to these questions could impact greatly on the management of hypertension.

Our findings suggest that the serious nature of hypertension in blacks is related to mechanisms specific for this population group. Genetic backgrounds selected for the survival advantages offered by highly developed renal sodium conservation mechanisms were likely contributors. We did not study hypertension per se but instead the normal physiology, although in so doing we avoided the confounders that can accompany the inclusion of hypertensives as such the effects of antihypertensive medications.

Perspective

Until now, aldosterone production has been the focus of studies for how aldosterone influences BP. We can now add aldosterone sensitivity to the equation for a more complete picture of aldosterone’s sodium-retaining properties that affect the risk for hypertension. The mechanisms that confer aldosterone sensitivity, which would seem to include increases in sodium retention, will be challenging to delineate. Treatment approaches that antagonize aldosterone’s actions or target mechanisms that instill sensitivity to aldosterone could have enormous relevance to the prevention of stroke, end-stage renal disease, and heart disease in blacks.

Sources of Funding

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Disclosures

None.

References


What Is New?

• Sensitivity of blood pressure (BP) to aldosterone is described for the first time.
• It was present in black children and in black young adults but not in whites of comparable age.
• Although blacks may have, on average, lower plasma aldosterone levels compared with whites, the level of aldosterone may nonetheless still impact on BP because of aldosterone sensitivity.

What Is Relevant?

• Although we did not study hypertension per se, the findings strongly imply a fundamental role of aldosterone in the development of hypertension in many blacks. A normal plasma aldosterone level in a black patient with hypertension may not rule out participation by aldosterone in the pathophysiology.

Novelty and Significance

Summary

A comparative study of young blacks and whites revealed contrasting pathways for determining BP, with blacks having BP that was more sensitive to aldosterone. This may have more than made up for the lower levels of aldosterone in blacks. Blacks are seemingly positioned to reach the hypertension threshold more easily and possibly with minimal additional sodium accumulation compared with whites.
Racial Differences in Sensitivity of Blood Pressure to Aldosterone

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SUPPLEMENT

Title: RACIAL DIFFERENCES IN SENSITIVITY OF BLOOD PRESSURE TO ALDOSTERONE

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**Assay Procedures**

PRA was measured using a Clinical Assays GammaCoat radioimmunoassay kit (Baxter Healthcare, Cambridge, MA); PAC and, following acid hydrolysis, urinary aldosterone concentration were measured by radioimmunoassay with antiserum from Diagnostic Products Corp. (Los Angeles, CA); and B-type natriuretic peptide was measured using a chemiluminescence assay from Siemens (Malvern, PA). Serum and urinary sodium and potassium were measured using flame photometry.
Table S1. Summary Statistics of Plasma and Urinary Measurements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Full sample</th>
<th>Black</th>
<th>White</th>
<th>P value</th>
</tr>
</thead>
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<tr>
<td><strong>Children: Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRA (ng/mL/h)</td>
<td>3.1 (2.2)</td>
<td>2.8 (2.1)</td>
<td>3.3 (2.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>PAC (ng/dL)</td>
<td>12 (9)</td>
<td>9 (7)</td>
<td>14 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARR (ng/dL per ng/mL/h)</td>
<td>5.2 (5.6)</td>
<td>4.8 (7.5)</td>
<td>5.4 (4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma K (mmol/L)</td>
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<td>4.3 (0.8)</td>
<td>4.2 (0.4)</td>
<td>0.555</td>
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<tr>
<td>Urine K (mmol/mg Creatinine)</td>
<td>0.024 (0.016)</td>
<td>0.023 (0.013)</td>
<td>0.025 (0.018)</td>
<td>0.413</td>
</tr>
<tr>
<td>Urine Na (mmol/mg Creatinine)</td>
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<td>0.093 (0.047)</td>
<td>0.099 (0.059)</td>
<td>0.601</td>
</tr>
<tr>
<td>Urine Aldosterone (ug/mg Creatinine)</td>
<td>34 (131)</td>
<td>25 (96)</td>
<td>38 (145)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Adults: Mean (SD)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRA (ng/mL/h)</td>
<td>1.3 (1.2)</td>
<td>1.0 (1.0)</td>
<td>1.5 (1.2)</td>
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<td>PAC (ng/dL)</td>
<td>8 (8)</td>
<td>5 (5)</td>
<td>9 (9)</td>
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<td>ARR (ng/dL per ng/mL/h)</td>
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<td>Plasma K (mmol/L)</td>
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<tr>
<td>Urine K (mmol/mg Creatinine)</td>
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<td>0.021 (0.015)</td>
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<tr>
<td>Urine Na (mmol/mg Creatinine)</td>
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<tr>
<td>Urine Aldosterone (ug/mg Creatinine)</td>
<td>4.7 (5.0)</td>
<td>3.8 (3.6)</td>
<td>5.2 (5.7)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

PRA: Plasma Renin Activity; PAC: Plasma Aldosterone Concentration; ARR: Aldosterone/Renin Ratio
Figure S1. A comparison of self-reported race classification and genotype-based race classification. A principle component analysis was performed to verify the accuracy of self-reported race identification in this study. (See Price et al. Principle component analysis corrects for stratification in genome-association studies. Nature Genetics, 2006, 38(8), 904-909). Specifically, we compared the self-identified blacks and whites in our sample to seven known ethnic groups in HAPMAP phase 3 data (ASW: African ancestry in Southwest USA, CEU: Utah residents of Northern and Western European ancestry from the CEPH collection, CHB: Han Chinese in Beijing, China, JPT: Japanese in Tokyo, Japan, MEX: Mexican ancestry in Los Angeles, California, TSI: Tuscans in Italy, YRI: Yoruba in Ibadan, Nigeria.) It is clear from the HAPMAP plot that the self-identified blacks in our study (HTN-AA: indicated by purple x) were genetically similar to ASW, and self-identified whites (HTN-EA, indicated by blue asterisk ) were similar to CEU. Although the groups exhibit some levels of heterogeneity, as expected in an American population, the black and white groups have a clear separation. The self-reported race categories in the current study appeared to be consistent with HAPMAP results.
Figure S2. Relationship of urinary aldosterone excretion and blood pressure at different renin levels in blacks and whites.

Associations between urinary aldosterone excretion and systolic blood pressure (SBP) were assessed at different levels of plasma renin activity (PRA), which was measured simultaneously with blood pressure. Urine samples were collected overnight with aldosterone excretion expressed per mg urinary creatinine. No relationship to SBP was observed in whites. In blacks there was a similar pattern to that of the relationship of plasma aldosterone concentration to SBP. In black children, however, the significance level was lower with p=0.28; in black adults p=0.021.