Improvement in Blood Pressure With Inhibition of the Epithelial Sodium Channel in Blacks With Hypertension

Chandan Saha, George J. Eckert, Walter T. Ambrosius, Tae-Yon Chun, Mary Anne Wagner, Qianqian Zhao, J. Howard Pratt

Abstract—Hypertension in blacks is more prevalent and less often controlled than the hypertension of other ethnic groups. We sought to explore the benefit of adding inhibitors of the epithelial sodium channel (ENaC), an aldosterone-regulated site of sodium reabsorption in the distal nephron, to the antihypertensive regimen of black hypertensive patients. In a prospective, randomized, placebo-controlled, double-blind clinical trial, we used a 2-by-2 factorial design with 4 treatment groups: amiloride (a direct inhibitor of ENaC), spironolactone (an aldosterone receptor antagonist), the combination of both drugs, and placebo. The subjects (n=98) had an elevated blood pressure despite treatment that included a diuretic and a calcium channel blocker; the level of plasma renin activity was ≤0.56 ng/L per second. The primary end points were changes from baseline in systolic and diastolic blood pressure over a 9-week period of treatment. The reductions in systolic and diastolic blood pressures (mm Hg) were, respectively, 9.8±1.6 (SE) and 3.4±1.0 for amiloride (P<0.001) and 4.6±1.6 (P=0.006) and 1.8±1.0 for spironolactone (P=0.07). Treatment with either amiloride or spironolactone or the combination was well tolerated; no patient experienced hyperkalemia. In a substudy, plasma endothelin-1 levels were observed to decrease after 3 weeks of treatment with spironolactone (P<0.001), consistent with a non–ENaC-related potential benefit of spironolactone. In conclusion, treatment with either amiloride or spironolactone can provide an additional reduction in blood pressure in blacks already receiving conventional antihypertensive therapy. (Hypertension. 2005;46:481-487.)

Key Words: sodium channels  ■  aldosterone  ■  ethnicity  ■  endothelin

In the United States, hypertension among blacks is a major public health problem. According to the 1999 to 2000 National Health and Nutrition Evaluation Survey, ≈60% of black men 50 to 59 years of age and ≈50% of black women 40 to 59 years of age were hypertensive.1 In addition, fewer than half of all black hypertensives had a blood pressure controlled to <140/90 mm Hg. When compared with hypertensive whites, black hypertensives have an increased incidence of complications such as stroke2 and end-stage renal disease.3 Improved strategies for treatment of hypertension could favorably influence health outcomes in blacks in particular.

An increase in renal reabsorption of sodium is thought to underlie much of the pathophysiology of hypertension.4 Blacks appear to retain more sodium than whites,5,6 an ethnic difference that may contribute to the high prevalence of hypertension in blacks. A principal determinant of net sodium retention is the epithelial sodium channel (ENaC) in the collecting duct of the distal nephron,7 a highly regulated transport system in which aldosterone is a principal stimulus. ENaC plays a pivotal role in the development of hypertension in instances in which there are sustained increases in its activity level, specifically primary aldosteronism and most of the monogenic forms of hypertension.8 Treatment that results in inhibition of ENaC could serve as an adjunct to the antihypertensive therapy of blacks by reducing reabsorption of sodium beyond what can be achieved using diuretics that act more proximally in the nephron. In a previous observational study, spironolactone, an antagonist of the aldosterone receptor, significantly reduced blood pressure in blacks and whites with resistant hypertension.9 Amiloride, a direct inhibitor of ENaC, was shown in previous studies to have antihypertensive properties;10 and, more recently, the effectiveness of amiloride in combination with a diuretic was demonstrated in patients with treatment-resistant, low-renin hypertension.11 We report here on a prospective, randomized, double-blind, placebo-controlled clinical trial that examined the effectiveness of inhibiting ENaC function with spironolactone or amiloride for improving blood pressure control. Participants were black hypertensives with elevated blood pressures while receiving treatment that included a diuretic targeted to the proximal nephron and a calcium channel blocker. Because aldosterone levels secondarily increase with amiloride treatment12-13 but are antagonized by spironolacto-
tone treatment, we also explored the relationship of both drugs to the effects of aldosterone on nonepithelial tissues by measuring endothelin-1 (ET-1), a potent vasopressor that was shown in vitro to be stimulated by aldosterone.14

Methods

Study Design
The study was a randomized, placebo-controlled, double-blind, parallel-group trial that used a 2-by-2 factorial design consisting of 4 treatment groups: amiloride (10 mg per day), spironolactone (25 mg per day), the combination of both drugs, and placebo. Patients were screened ≥3 weeks before randomization, and those who were eligible received 2 placebo capsules to take each morning for 3 weeks. This was followed by a 9-week period of active treatment during which patients received 2 capsules each morning that were identical in appearance, the first being either spironolactone or placebo, the second being either amiloride or placebo. The study protocol was approved by the Indiana University-Purdue University at Indianapolis institutional review board. All patients gave written informed consent. Blood pressure was measured 3×/while patients were in the sitting position (in the morning before taking the study medication), and the average of the last 2 readings was used in the analyses. Measurements were made and blood samples collected at baseline and at weeks 1, 3, 5, 7, and 9.

Serum levels of electrolytes and creatinine were measured using a Vitros 950 instrument (Ortho Clinical Diagnostics). Plasma renin activity (PRA) was measured using a radioimmunoassay for angiotensin I (Clinical Assays GammaCoat kit); the intra-assay coefficient of variation (CV) was 4.6%, and the interassay CV was 7.6%. Aldosterone was also measured by radioimmunoassay (Diagnostic Products Corporation), and the intra-assay and interassay CVs were, respectively, 5.4% and 13.1%. Plasma ET-1 was measured using a competitive enzyme immunoassay kit (S-1156) from Peninsula Laboratories, Inc; the intra-assay and interassay CV were, respectively, 5% and 14%.

Patients
Patients were eligible for enrollment if they were self-identified as black (defined as of African decent), between 18 and 75 years of age, with a systolic blood pressure >140 and $\leq 175$ mm Hg or a diastolic blood pressure $>90$ and $\leq 105$ mm Hg while receiving hydrochlorothiazide (minimum dose of 25 mg) or furosemide (minimum dose of 40 mg) or equivalent doses of similar diuretics and amldipine 5 or 10 mg or equivalent doses of a similar calcium channel blocker. Any use of triamterene, an angiotensin-converting enzyme (ACE) inhibitor, or an angiotensin receptor blocker was discontinued for 1 month before starting the study. Exclusion criteria were a serum creatinine $>1.5$ mg/dL in males and $>1.4$ mg/dL in females, a serum potassium $>5.0$ mmol/L ($>4.5$ mmol/L in diabetic patients), a history of hyperkalemia, or clinical evidence suggesting a secondary form of hypertension. Patients were excluded if the PRA exceeded 0.56 ng/L per second (2.0 ng/mL per hour) to restrict enrollment to patients with hypertension that was more volume dependent. Additional exclusion criteria included pregnancy, a history of poor compliance with taking medications, drug or alcohol abuse, or the use of spironolactone within 3 months. For measurements of ET-1 levels, 15 subjects from each treatment group were randomly selected.

Randomization Procedure
Randomization was stratified by gender using a block-randomization scheme to equalize treatment assignments. Participants were randomly assigned to 1 of the 4 treatment groups after the eligibility criteria were verified. The treatment assignment was blinded to patients and study personnel until all participants had completed the study.

Outcome Measures
The study was designed with the primary end points being the changes from baseline in systolic and diastolic blood pressures at weeks 1, 3, 5, 7, and 9. The secondary end points were the serum levels of potassium and creatinine and the plasma levels of renin activity and aldosterone.

Sample Size and Power
Using data from a pilot study, we estimated a difference in reduction of diastolic blood pressure of $8.4 \pm 12.0$ (SD) mm Hg between the placebo and the spironolactone groups. With a sample size of 22 in each of the 4 treatment groups, the study was estimated to have 90% power to detect the main effect of spironolactone of $\geq 8.4$ mm Hg with a type 1 error rate of 5%.

Statistical Analysis
The intention-to-treat principle was used for all the analyses. For continuous variables, descriptive statistics are presented as the mean±SD, and differences between the 4 groups at baseline were evaluated by ANOVA or the nonparametric Kruskal–Wallis test. For discrete variables, comparisons were made using Fisher’s exact test. A mixed-model ANOVA was used to assess the effects of amiloride and spironolactone on systolic and diastolic blood pressures. Subject was treated as a random effect, and a Toeplitz covariance matrix was used. Treatment effects were adjusted for the baseline blood pressure and age of onset of hypertension, the only significant predictors of the blood pressure response. We also adjusted for gender, although it was not a significant predictor. Primary analysis for outcomes included all patients who had ≥1 measurement after baseline. Tukey’s adjustment for multiple comparisons was used for pairwise comparisons. The Kruskal–Wallis test was used to compare compliance from pill counts among the 4 groups.

Figure 1. A summary flowchart depicting the numbers of subjects recruited, found to be eligible, randomized, and ultimately studied.
Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=27)</th>
<th>Spironolactone (n=23)</th>
<th>Amiloride (n=28)</th>
<th>Both (n=22)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.4±9.4</td>
<td>48.5±8.9</td>
<td>44.5±9.4</td>
<td>46.3±9.2</td>
<td>0.52</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>35.7±10.1</td>
<td>32.0±6.4</td>
<td>34.6±5.6</td>
<td>34.8±6.7</td>
<td>0.43</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>14 (51.9)</td>
<td>11 (47.8)</td>
<td>14 (53.8)</td>
<td>13 (59.1)</td>
<td>0.92</td>
</tr>
<tr>
<td>Age of onset of hypertension (years)</td>
<td>35.3±8.1</td>
<td>38.2±8.7</td>
<td>32.4±8.8</td>
<td>35.7±8.5</td>
<td>0.13</td>
</tr>
<tr>
<td>Diabetic n (%)</td>
<td>3 (11.1)</td>
<td>5 (21.7)</td>
<td>5 (19.2)</td>
<td>3 (13.6)</td>
<td>0.71</td>
</tr>
<tr>
<td>No. of blood pressure medications (%)</td>
<td>2</td>
<td>23 (85.2)</td>
<td>17 (73.9)</td>
<td>21 (80.8)</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4 (14.8)</td>
<td>6 (26.1)</td>
<td>3 (11.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>141.4±10.3</td>
<td>141.5±14.5</td>
<td>140.7±9.8</td>
<td>143.4±12.1</td>
<td>0.58</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>91.1±6.6</td>
<td>92.3±6.1</td>
<td>91.5±8.9</td>
<td>91.2±9.2</td>
<td>0.98</td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>141.8±2.2</td>
<td>142.2±2.3</td>
<td>141.5±2.6</td>
<td>141.8±1.8</td>
<td>0.77</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>3.6±0.3</td>
<td>3.7±0.4</td>
<td>3.6±0.3</td>
<td>3.6±0.4</td>
<td>0.67</td>
</tr>
<tr>
<td>Serum creatinine (mmol/L)</td>
<td>90.0±23.9</td>
<td>89.2±15.7</td>
<td>94.2±21.8</td>
<td>90.0±21.9</td>
<td>0.84</td>
</tr>
<tr>
<td>PRA (ng/L per second)</td>
<td>0.2±0.3</td>
<td>0.3±0.5</td>
<td>0.2±0.6</td>
<td>0.1±0.2</td>
<td>0.54</td>
</tr>
<tr>
<td>Plasma aldosterone (pmol/L)</td>
<td>386.4±173.4</td>
<td>398.7±135.1</td>
<td>475.1±271.3</td>
<td>420.3±182.2</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Analysis of covariance (ANCOVA) was used to assess the plasma ET-1 level responses to treatment. Adjustments were made for demographic and clinical covariates that were found to be significant; adjustments were also made for sex and age, although neither by itself was a significant predictor. SAS version 8 (SAS Institute Inc.) statistical software was used for all analyses.

Results

Participants

Patient recruitment, randomization, and follow-up history are shown in Figure 1. Between May 2001 and April 2004, 341 patients were screened and 199 were determined to be eligible. Of these, 107 were randomized and 98 were included in the final analyses. Those who dropped out of the study had similar baseline characteristics as the nondropouts.

Patient Characteristics

Baseline patient characteristics are shown in the Table. The 4 study groups were comparable at baseline with respect to the variables examined. With respect to the baseline antihypertensive treatment that was continued throughout the intervention phase, 89 patients took hydrochlorothiazide (84 at a dose of 25 mg per day and 5 at a dose of 50 mg per day); 8 patients took furosemide, and 1 patient took torsemide. Twenty patients took a β-adrenergic receptor blocker (atenolol or metoprolol): 4 in the placebo group, 5 in the amiloride group, 6 in the spironolactone group, and 5 in the combination group. One patient took terazosin and another took minoxidil; both were in the combination group.

Primary Outcomes

There was no significant interaction of amiloride with spironolactone, and thus the response to the combination therapy was considered additive. The main effects for the reductions in systolic and diastolic blood pressure (mm Hg; mean±SE) were, respectively, 9.8±1.6 and 3.4±1.0 for amiloride, and 4.6±1.6 and 1.8±1.0 for spironolactone. Amiloride significantly reduced systolic and diastolic blood pressures (P<0.001). Spironolactone produced a significant reduction in systolic blood pressure (P=0.006) and a marginally significant reduction in diastolic blood pressure (P=0.07).

Pairwise comparisons between each of the 3 active treatment groups and placebo produced similar results. The adjusted mean (±SE) decreases in systolic and diastolic blood pressures compared with treatment with placebo (mm Hg) were, respectively, 12.2±2.2 (P<0.001) and 4.8±1.3 (P=0.003) for the amiloride group, 7.3±2.3 (P=0.010) and 3.3±1.4 (P=0.082) for the spironolactone group, and 14.1±2.3 (P<0.001) and 5.1±1.4 (P=0.002) for the amiloride–spironolactone combination group.

Figure 2 depicts the adjusted mean changes from baseline in blood pressure. The greatest decrements in blood pressure occurred within 3 weeks. Blood pressures continued to decline until week 7, at which point values stabilized for each of the treatment groups. The amiloride–spironolactone combination group showed the greatest reduction in blood pressure followed by the amiloride-alone and the spironolactone-alone treatment groups.

Secondary Outcomes

Levels of PRA and aldosterone increased substantially in the amiloride and in the combination groups (P<0.001 for aldosterone and P<0.01 for PRA compared with placebo; Figure 3). The plasma aldosterone level increased more than the level of PRA, probably because of additional stimulation of aldosterone secretion by the increase in the potassium concentration. The mean increments in serum potassium levels were 0.35±0.06, 0.17±0.06, and 0.51±0.06 mmol/L for amiloride, spironolactone, and combined treatment groups, respectively (P values ranged from <0.0001 to 0.035 when compared with the placebo group). A significant increase in the serum creatinine concentration (≈5.30 μmol/L) occurred only in the combined treatment group (P<0.001).
Figure 4 depicts the ET-1 measurement at baseline and week 3 for subjects in each of the 4 groups. Treatment with placebo, the combination, or amiloride resulted in no significant change in ET-1 levels. One patient treated with amiloride showed an increase in ET-1 that was >3 SDs from the mean change (Figure 4) and was therefore left out of the analysis. Treatment with spironolactone resulted in a decrease in ET-1 levels. Using the ANCOVA model, there was a significant interaction effect between baseline the ET-1 level and the response to treatment. None of the other covariates were significant in predicting the changes in ET-1 levels. The adjusted mean (±SE) changes from baseline in ET-1 levels (ng/L) were, respectively, 2.2±8.2 (P=0.79) for the placebo group, 9.3±9.1 (P=0.31) for the amiloride group, -28.8±7.1 (P<0.001) for the spironolactone group, and 2.4±7.0 (P=0.74) for the amiloride–spironolactone combination group. When the outlier value for the amiloride group was included in the analysis, the mean change from baseline was 32.8±10.6 (P=0.003).

Compliance
There was no evidence that compliance, expressed as percentage of pills that were used, differed by treatment group. The overall average compliance was 95% for the placebo group, 94% for the amiloride group, 96% for the spironolactone group, and 94% for the combination group (P=0.52).

Adverse Events
The frequencies of adverse events (primarily headache, muscle cramps, gastrointestinal symptoms, and sexual dysfunction) were low and not different in the active treatment groups when compared with the placebo group. The number of reported adverse events per treatment group was 4 for the amiloride group, 5 for the spironolactone group, 5 for both drugs combined, and 8 for the placebo group. There were no serious adverse events. The highest measured serum potassium concentration was 5.1 mmol/L (at week 3 in a nondiabetic patient treated with the combination of amiloride and spironolactone).

Discussion
In the present study, the addition of either spironolactone or amiloride resulted in a substantial further lowering of blood pressure in black hypertensive patients who were being treated with a diuretic and a calcium channel blocker and, in some cases, additional drugs. The findings suggest that an increase in sodium reabsorption mediated by ENaC can interfere with the control of blood pressure in patients already receiving antihypertensive therapy.

Although the blood pressure–lowering response was greater for amiloride than for spironolactone, this may have resulted from unequal dosing of the 2 drugs: a response similar to that seen with amiloride might have occurred had we used a larger dose of spironolactone. In the previous study in which spironolactone was used to treat patients with resistant hypertension,9 significant reductions in blood pressure occurred with a dose that averaged 30 mg per day. In the group that received the combination of amiloride and spironolactone, spironolactone might have been expected to block some of the effects of the increase in the aldosterone level that resulted from the amiloride treatment, thus potentially providing for a more favorable blood pressure response. However, no synergism of the 2 drugs used in combination was observed, and thus there appeared to be no benefit to using both drugs. The exception would be the development of dose-dependent side effects and where the lower doses of the combined regimen would be better tolerated.

Because the response to amiloride was, if anything, superior to that of spironolactone, the observed reduction in blood pressure appeared to specifically result from inhibition of ENaC, although aldosterone has been shown to affect sodium reabsorption at other sites in the distal nephron.16,17

We elected to exclude the use of ACE inhibitors or angiotensin receptor blockers because of the potential for hyperkalemia, especially in patients assigned to receive both amiloride and spironolactone. However, their concomitant use could conceivably improve blood pressure control even further by reducing the secondary increase in aldosterone secretion that accompanies inhibition of ENaC. The increase in renin secretion that accompanies treatment with amiloride13 (or triamterene12) may be greater than would be predicted from the degree of volume contraction.18 In the present study, after 1 week, the levels of
PRA in the amiloride-treated patients exceeded those in the spironolactone-treated patients by several-fold, although with time, the levels became similar. Although not apparent in the present study, it would seem reasonable that the ensuing secondary hyperaldosteronism might compromise a blood pressure–lowering response.

Although an increase in ENaC function could stem from common molecular variations in the channel,19,20 we feel a more compelling explanation is that an increase in aldosterone was driving ENaC activity. In the Framingham Family Offspring Study, higher but nonetheless normal aldosterone levels were associated with a future increase in blood pressure and a greater risk for becoming hypertensive.21 The authors suggested that aldosterone levels that are considered to be in the physiological range may, in some instances, be inappropriately increased. Regulation of aldosterone secretion probably evolved to accommodate the scarcity of dietary sodium during a much earlier ancestral period, there being a less complete downward adjustment to the modern day diet that is replete with sodium. With respect to black hypertensives in particular, plasma aldosterone levels were shown to be increased in relation to the prevailing level of PRA when comparisons were made with white hypertensives,22 as if there were some autonomy in aldosterone secretion. The reported high prevalence of primary aldosteronism in general23 and in patients with resistant hypertension in particular24 makes it almost certain that such patients were represented by the hypertensives we selected for study. However, we reasoned that an excess of aldosterone may exist even if the criteria for primary aldosteronism were not fully met. Overrepresentation by patients having primary aldosteronism in any of the treatment groups would not necessarily be expected to favorably influence the treatment response; indeed, if anything, it might lead to an underestimation of the effectiveness of treatment because patients with primary aldosteronism have been shown to require additional spironolactone to normalize the blood pressure.9 Finally, it should be noted that thiazide and loop diuretics produce a compensatory increase in angiotensin II–stimulated aldosterone secretion that could also augment ENaC function and potentially interfere with the intended natriuresis.

The unique location of ENaC in the nephron was probably important to the favorable blood pressure response observed. Increases in sodium reabsorption that occur at sites situated more proximally in the nephron are countered by reciprocal declines in reabsorption at sites located more distally if required for purposes of sodium balance. On the other hand, ENaC is the most distal site for sodium reabsorption, and therefore it lacks a downstream site where a compensatory adjustment can occur. Thus, it is conceivable that even small increments in ENaC activity could, over time, interfere with maintenance of a normal blood pressure. In a previous study of young normotensive subjects, we observed that ENaC activity as judged from the blood pressure response to amiloride was lower in blacks than in whites.25 We speculated that the blacks more than the whites retained additional sodium in proximal nephron regions that then suppressed aldosterone levels and, in turn, ENaC activity. Certain individuals may have increased proximal nephron sodium reabsorption without an appropriate reduction in ENaC activity, leaving them at risk for a higher blood pressure.

The patients in the present study were, on average, obese (body mass index $\approx 34$ kg/m$^2$). Although body mass index was not predictive of the blood pressure response to treatment, the high insulin levels that accompany the insensitivity to insulin in obesity could conceptually at least elevate ENaC function because insulin has been shown in vitro to stimulate sodium transport by ENaC.26 It may be less than correct to narrow the focus of the benefit achieved with ENaC inhibition to the distal nephron. There is growing evidence that ENaC facilitates vascular function through influences on the endothelium27 and the vascular smooth muscle.28 The central nervous system is a known site of blood pressure regulation, and centrally administered inhibitors of ENaC lower blood pressure in salt-sensitive animal models of...
hypertension;29,30 although with respect to the current study, it is unclear whether either amiloride or spironolactone crosses the blood–brain barrier.

Although the current study was restricted to black hypertensives with a lower level of renin activity, the findings are probably generalizable to other population groups. Blacks and whites have been shown to respond to spironolactone9 and eplerenone,31 a newer aldosterone receptor antagonist, with similar reductions in blood pressure. Thus, ethnicity per se may not predict which hypertensives are more likely to respond to ENaC inhibition. We would suggest that ENaC inhibition be considered in patients with lower PRA levels who show a failure to reach an acceptable blood pressure level with more standard therapies that include a diuretic.

Treatment directed at inhibition of ENaC places certain patients at risk for hyperkalemia. This was underscored in a recent report of an increased incidence of hyperkalemia-associated hospital admissions as well as deaths after the published account of the benefit of providing spironolactone for the treatment of congestive heart failure.32 Clearly, there should be avoidance of ENaC-suppressing drugs in patients who might be predisposed to increased potassium retention such as those with a reduced glomerular filtration rate, especially in diabetics or those taking medications that may interfere with potassium disposal such as ACE inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, and heparin. Careful monitoring of potassium levels will be required for higher-risk patients. All of the patients in the present study were taking diuretics that lower potassium levels, thereby reducing the risk for hyperkalemia, and of course, adding a drug that reduces ENaC function can prevent hypokalemia.

Finally, there is a large body of evidence that aldosterone has nonepithelial (non–ENaC-mediated) actions that adversely affect the cardiovascular system.33,34 In the present study, treatment with spironolactone significantly lowered plasma ET-1 levels. Aldosterone was shown previously to increase expression of ET-1 in a renal cell line,35 but to our knowledge, the present results are the first demonstration of an aldosterone receptor antagonist to lower ET-1 levels. For example, there was no noticeable effect of spironolactone to reduce ET-1 levels in the Randomized Aldactone Evaluation Study of patients with congestive heart failure.36 It was not entirely clear in the present study whether amiloride, which increased aldosterone levels, had, at the same time, an effect to increase ET-1 levels. We were also unable to determine whether the decline in ET-1 levels in response to spironolactone contributed to the improvement in blood pressure. That this could have been the case is suggested by a recent report showing that black hypertensives had greater ET-1–dependent vasoconstriction than white hypertensives.35 Spironolactone was shown to increase endothelium-dependent flow-mediated arterial dilatation in patients with chronic heart failure37 and in hypertensive subjects with hyperaldosteronism,38 responses that could also have been related to a reduction in ET-1 levels. The findings thus point out potential additional advantages to using aldosterone receptor antagonists.

**Perspectives**

ENaC inhibition was an effective means for reducing blood pressure in blacks with hypertension that was not controlled with standard doses of proximally acting diuretics and a calcium channel blocker. The findings point to an underappreciated and possibly frequent increase in ENaC activity that is important for the maintenance if not the development of hypertension. It may result mostly from an inappropriately increased level of aldosterone. Antihypertensive treatment that targets ENaC for inhibition may be effective for a large segment of the hypertensive population, probably regardless of ethnicity. Furthermore, an antagonist of aldosterone may provide the additional benefit of reducing exposure to ET-1.
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References

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