Transepithelial Sodium Absorption Is Increased in People of African Origin

Emma H. Baker, Nicola J. Ireson, Christine Carney, Nirmala D. Markandu, Graham A. MacGregor

Abstract—Salt-sensitive hypertension is more common and has more severe consequences in urban black populations than in white populations. Increased renal sodium reabsorption through epithelial sodium channels may underlie the development of high blood pressure in black people. Increased sodium channel activity has been detected in subjects with Liddle’s syndrome by nasal potential difference measurements. Nasal potential difference measurements were made in 39 black normotensive, 106 black hypertensive, 51 white normotensive, and 61 white hypertensive subjects. Blood pressure, body mass index, and 24-hour urinary sodium excretion were also measured. Maximum potential difference was significantly higher in black subjects than in white subjects (P=0.009) but was not significantly different between normotensive and hypertensive subjects after adjustment for age, gender, current smoking status, body mass index, and 24-hour urinary sodium excretion (black normotensive, −21.6±1.0 mV; black hypertensive, −21.5±0.7 mV; white normotensive, −18.5±1.0 mV; and white hypertensive subjects, −18.9±0.9 mV). Nasal potential difference did not correlate with blood pressure or biochemical variables within ethnic and blood pressure groups. Nasal potential difference, an index of nasal sodium channel activity, is greater in black than in white people but does not differ between normotensive and hypertensive groups. Increased nasal potential difference measurements may reflect generalized upregulation of sodium transport in black people compared with white people, which may help to explain the high prevalence of hypertension in black people but would not explain differences in blood pressure within separate ethnic groups. (Hypertension. 2001;38:76-80.)

Key Words: blacks ■ whites ■ membrane potentials ■ nasal mucosa ■ sodium channels ■ hypertension, genetic

High blood pressure is common in black people living in urban societies, affecting nearly half of black adults between 40 and 59 years of age.1 Hypertensive end-organ damage is particularly severe in black subjects; prevalence of end-stage renal disease and stroke are 400% and 60% to 70% higher, respectively, in black than in white populations.2 Many clinical and biochemical features suggest that abnormalities of renal sodium handling may relate to the development of high blood pressure in black people. Black people with hypertension have suppressed plasma renin activity and angiotensin II levels, consistent with sodium retention and “corrected” volume expansion.3 Black people excrete a sodium load more slowly and less completely than white people,4 and in the majority, blood pressure is more salt sensitive.5,6 However, mechanisms underlying altered sodium handling in black people are incompletely understood.

The epithelial sodium channel is the final determinant of sodium reabsorption in the distal nephron. The importance of this channel in the control of blood pressure is illustrated by Liddle’s syndrome, a rare monogenic form of hypertension in which mutations in the sodium channel cause an increase in sodium reabsorption, resulting in sodium retention and thereby high blood pressure.7,8 Abnormalities of epithelial sodium channel function and regulation are also implicated in other “secondary” forms of hypertension. For example, increased levels or activity of mineralocorticoid and glucocorticoid hormones increase blood pressure at least in part by increasing sodium absorption through activation of renal epithelial sodium channels. It is possible, therefore, that activation of epithelial sodium channels, either due to structural variants of the channel subunits or to altered activity of regulatory processes, could underlie the rise in blood pressure in black people.

Renal sodium channel activity is inaccessible to clinical assessment. However, sodium channels with structural and physiological properties similar to renal channels are present in the nasal epithelium.9,10 Sodium absorption through epithelial sodium channels can be quantified in the nose by transmucosal electrical potential difference (PD) measurements before and after amiloride, a drug that blocks sodium channels. Recent studies have shown that nasal PD measurements are increased in Liddle’s syndrome11 and decreased in pseudohypoaldosteronism type 1, a syndrome of low blood pressure caused by inactivating mutations of the epithelial sodium channel.12 We therefore used measurement of nasal transmucosal PD to compare epithelial sodium channel ac-
tivity in black and white subjects with and without high blood pressure.

Methods

Subjects
Black and white hypertensive (HT) subjects were recruited from unselected referrals to the hypertension clinic by local general practitioners. Black and white normotensive (NT) controls were volunteers from the local population in the same area. All subjects had their blood pressure measured with a semiautomated ultrasound sphygmomanometer (Arteriosonde) on at least 2 separate occasions. On the day of the study, subjects rested for 5 minutes, after which blood pressure recordings were done in triplicate with the appropriate cuff size determined by upper midarm circumference. Blood pressure values given are the mean of these 3 recordings. HT subjects had systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or both. NT subjects had systolic blood pressure ≤140 mm Hg and diastolic blood pressure ≤90 mm Hg. HT subjects had not received previous treatment or had not taken drug treatment for at least 2 weeks and had not taken diuretics for 4 weeks. People with ischemic heart disease, cerebrovascular disease, renal impairment, or other concurrent illness, acute or chronic rhinitis, asthma, or atopy or people on nasal or other drugs were excluded from the study. Ethnicity was defined by skin color, place of birth, or parents’ birth and cultural identity. Where individuals were classified as “black,” African or Caribbean ancestry was also noted.

Written informed consent was obtained from all individuals before entry into the study, which was approved by the Local Research Ethics Committee of Merton, Sutton and Wandsworth. Procedures followed were in accordance with institutional guidelines.

Clinical Measurements
Subjects collected all urine for the 24 hours before nasal PD measurement, and this was analyzed for 24-hour urinary sodium and creatinine excretion. On the day of measurement, subjects attended the Blood Pressure Unit having had water but no food or other beverages from midnight onward. Blood pressure, weight, and height were recorded. Smoking history was taken to determine whether the subject had never smoked, was an ex-smoker, or was a current smoker. Serum sodium, potassium, creatinine, and urea were measured. Plasma was analyzed for plasma renin activity and aldosterone concentrations by radioimmunoassay.

Measurement of Nasal PD
All nasal PD measurements were made by one of 2 operators using the same set of equipment. Operators were not blinded to the blood pressure status of the subjects. Transmucosal nasal PD was measured by a technique previously established in our laboratory. In brief, transnasal PD was measured with a high-impedance voltmeter connected between an exploring electrode, inserted under the inferior surface of the inferior turbinate of the right nostril, and a reference electrode, sited in the subcutaneous tissue of the forearm. Two baseline measurements of PD were made, and the mean of these 2 values was taken as the maximum PD for analysis. Amiloride (10⁻⁴ mol/L in Ringer’s solution) was then perfused onto the nasal mucosa, and after 4 minutes, nasal PD was remeasured during continued application of 10⁻⁴ mol/L amiloride in Ringer’s solution (residual PD). The change in potential in response to amiloride (amiloride-sensitive PD) was determined by calculation of the difference between maximum PD and residual PD and was expressed both in millivolts and as a percentage of the maximum PD.

Statistical Analysis
Group values are given as mean±SEM for normally distributed data and as median and interquartile range for plasma renin activity and aldosterone concentration, which are not normally distributed. Differences between groups were tested by 2-sample t tests for normally distributed variables and χ² tests for categorical variables. Two-way ANOVA was used to compare PD measurements between black and white and between NT and HT subjects before and after adjustment for age, gender, body mass index, smoking status, and 24-hour urinary sodium excretion. Pearson correlation coefficients were calculated to examine relationships between PD measurements and biochemical variables within black and white NT and HT groups. Two-tailed probability values of <0.05 were considered significant.

Results
Thirty-nine black NT subjects, 106 black HT subjects, 51 white NT subjects, and 61 white HT subjects were studied. Demographic characteristics of subjects are shown in Table 1, and biochemical measurements are shown in Table 2.

Nasal PD Measurements in Black and White NT and HT Subjects
Maximum PD was greater in black than in white subjects (black NT, −21.6±1.0 mV; black HT, −21.5±0.7 mV; white NT, −18.5±1.0 mV; white HT, −18.9±0.9 mV). Two-way ANOVA showed that maximum PD was significantly higher in black than in white subjects (P=0.002) but was not significantly different between NT and HT subjects (P=0.848). The difference in maximum PD between black and white subjects remained significant after adjustment for age, gender, current smoking status, body mass index, and 24-hour urinary sodium excretion (P=0.009). (See Table 3.)

Residual PD after amiloride application was greater in black than in white subjects but did not differ between HT and NT subjects (black NT, −14.7±0.9; black HT, −13.7±0.5; white NT, −10.9±0.6; white HT, −12.1±0.6). Two-way ANOVA showed that residual PD was significantly higher in black than in white subjects (P<0.0001) but was not significantly different between NT and HT subjects (P=0.844). The difference in residual PD between black and white subjects remained significant after adjustment for age, gender, smoking status, body mass index, and 24-hour urinary sodium excretion (P=0.009). The absolute and percentage changes in PD after amiloride application were not different between black and white or between NT and HT subjects (Table 3).

Nasal PD and Smoking Status
Smoking status differed between ethnic groups. Significantly more black than white subjects had never smoked (nonsmokers: black, 74.5%; white, 42.0%; P<0.0001). Similar proportions of black and white subjects were current smokers (Table 1).

Observed differences between black and white subjects were not accounted for by differences in smoking status. Maximum potential was higher in black than in white subjects when grouped by smoking history (Figure). Maximum PD remained significantly greater in black than in white subjects after adjustment for current smoking status, as well as for age, gender, body mass index, and 24-hour urinary sodium excretion (P=0.009; Table 3).

Nasal PD in Black People of African and Caribbean Origin
Maximum PD was similar in black subjects of African and Caribbean origin (maximum PD: African, −22.6±1.1 mV, n=49; Caribbean, −21.6±0.7 mV, n=83; P=0.439). Two-
way ANOVA showed that maximum PD was not significantly different in African and Caribbean subjects before or after adjustment for blood pressure status (NT or HT), age, gender, current smoking status, body mass index, and 24-hour urinary sodium excretion.

**Relationship Between Maximum PD and Biochemical Variables**

Within each of the 4 groups of black and white NT and HT subjects, maximum PD did not correlate with blood pressure, serum biochemistry, 24-hour urinary sodium excretion, or plasma hormone activity or concentration.

**Discussion**

We investigated the hypothesis that activity of epithelial sodium channels is greater in black than in white people by the measurement of nasal PD. In the present study, maximum nasal PD was significantly higher in black than in white subjects. Nasal PD is generated by active absorption of sodium ions from airway surface liquid across nasal epithelium. Na-K-ATPase pumps in the basolateral membrane of epithelial cells generate a sodium gradient by pumping sodium out of the cell in exchange for potassium. Sodium ions enter epithelial cells down this gradient through epithelial sodium channels in the apical cell membrane. The greater the sodium

<table>
<thead>
<tr>
<th>Variable</th>
<th>Black Ethnicity</th>
<th>White Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Na, mmol/L</td>
<td>NT (n=34)</td>
<td>139.2±0.3</td>
</tr>
<tr>
<td></td>
<td>HT (n=100)</td>
<td>139.4±0.2</td>
</tr>
<tr>
<td>Serum K, mmol/L</td>
<td>NT (n=32)</td>
<td>4.25±0.06</td>
</tr>
<tr>
<td></td>
<td>HT (n=98)</td>
<td>4.17±0.06</td>
</tr>
<tr>
<td>Urine creatinine, nmol/24 h</td>
<td>NT (n=29)</td>
<td>14.5±0.8</td>
</tr>
<tr>
<td></td>
<td>HT (n=94)</td>
<td>14.5±0.5</td>
</tr>
<tr>
<td>Urine Na, mmol/24 h</td>
<td>NT (n=29)</td>
<td>135.8±11.1</td>
</tr>
<tr>
<td></td>
<td>HT (n=95)</td>
<td>129.1±6.0</td>
</tr>
<tr>
<td>Plasma renin activity, ng·mL⁻¹·h⁻¹ (range)</td>
<td>NT (n=19)</td>
<td>0.39 (0.19–0.78)</td>
</tr>
<tr>
<td></td>
<td>HT (n=83)</td>
<td>0.25 (0.10–0.48)</td>
</tr>
<tr>
<td>Aldosterone, pmol/L (range)</td>
<td>NT (n=22)</td>
<td>281 (180–347.3)</td>
</tr>
<tr>
<td></td>
<td>HT (n=87)</td>
<td>347.0 (221–532)</td>
</tr>
</tbody>
</table>

Table 2. Biochemical Characteristics of Black and White Subjects With Normal and High Blood Pressure

BMI indicates body mass index; BP, blood pressure; and NA, not applicable.
Maximum potential difference in black and white subjects with different smoking histories.

**TABLE 3. Nasal PD Measurements in Black and White Subjects With Normal and High Blood Pressure**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Black Ethnicity</th>
<th>White Ethnicity</th>
<th>Two-Way ANOVA, P for Adjusted Differences Between</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NT</td>
<td>HT</td>
<td>Ethnic Groups</td>
</tr>
<tr>
<td>Max PD, mV</td>
<td>−21.6±1.0</td>
<td>−21.5±0.7</td>
<td></td>
</tr>
<tr>
<td>Residual PD, mV</td>
<td>−14.7±0.9</td>
<td>−13.7±0.5</td>
<td></td>
</tr>
<tr>
<td>Amiloride-sensitive PD, mV</td>
<td>7.0±0.6</td>
<td>7.9±0.5</td>
<td></td>
</tr>
<tr>
<td>Amiloride-sensitive PD, %</td>
<td>32.8±2.4</td>
<td>35.9±1.7</td>
<td></td>
</tr>
</tbody>
</table>

*Significant difference.

absorption through epithelial sodium channels, the higher the transepithelial PD. Increased maximum PD in black compared with white subjects suggests that transnasal sodium absorption through epithelial sodium channels is greater in black subjects. The interpretation of nasal PD measurements after the application of amiloride is more complicated. Amiloride blocks sodium absorption through sodium channels, causing the epithelium to depolarize. However, this change in PD induces secretion of chloride ions through the cystic fibrosis transmembrane regulator (CFTR) chloride channels. Residual PD, but not amiloride-sensitive PD, was greater in black than in white subjects, perhaps reflecting a greater induction of chloride secretion generated by a greater amiloride-induced inhibition of sodium channel activity. Alternatively, increased maximum but not amiloride-sensitive PD could be explained either by increased activity of Na-K-ATPase pumps or by increased amiloride-insensitive transepithelial sodium absorption in black people. The lack of amiloride-resistant sodium absorption in human airway in ion flux studies suggests that the latter explanation is unlikely.\(^{16-18}\)

Nasal PD can only be generated by active ion transport across the epithelium if the epithelium has resistance as stated by Ohm’s law (V = IR). Epithelial resistance is maintained by tight junctions between cells and can be lost where the epithelium is abraded\(^{19}\) or damaged, e.g., by colds\(^{19}\) or cigarette smoke.\(^{20,21}\) It is important to consider whether observed differences in nasal PD between ethnic groups could be due to differences in epithelial resistance. A standard nasal PD measurement protocol was used for both ethnic groups that caused little or no epithelial trauma and excluded subjects with recent rhinitis, asthma, or atopy. Although black subjects were far less likely to have smoked cigarettes than white subjects, differences in smoking history did not account for ethnic differences in nasal PD. Maximum potential was higher in black than in white nonsmokers, ex-smokers, and current smokers (Figure), and the difference in PD between ethnic groups remained highly statistically significant after adjustment for current smoking status.

Although sodium channel activity as measured by nasal PD was greater in black than in white people, there was no difference in nasal PD between HT and NT people within ethnic groups and no correlation between nasal PD and blood pressure. The lack of relationship between the apparent upregulation of sodium absorption and blood pressure status in black people may be explained if the majority of black people are predisposed to hypertension. In a study of systolic hypertension in the elderly,\(^{22}\) 76% of black Americans between the ages of 65 and 74 years were found to have high blood pressure. Observed differences in blood pressure in people predisposed to hypertension may be accounted for by individual differences in exposure to environmental factors that increase blood pressure, such as high dietary sodium and increased body mass index. In the present study, the black HT group did not appear to eat more salt than the NT group, because black NT and HT subjects had similar measured 24-hour urinary sodium excretion (Table 2). Black HT subjects had a significantly greater body mass index (\(P=0.035\)) and were older than black NT subjects.

The lack of relationship between increased nasal sodium absorption and blood pressure status in black people could also be explained if increased nasal sodium absorption does not reflect sodium channel activity in the renal tubules. In the present study, we made the assumption that nasal epithelial sodium channels can be used as a model for renal sodium channels, because previous studies found altered nasal PD measurements in patients with sodium channel mutations that increase or decrease blood pressure. Nasal PD measurements were increased in 3 brothers with Liddle’s syndrome, who had activating mutations of the sodium channel \(\beta\)-subunit, compared with their unaffected sister and unrelated NT controls.\(^{11}\) Nasal PD was very low in a patient with pseudohypoaldosteronism type 1 who had inactivating sodium channel mutations.\(^{12}\) These findings suggest that nasal PD measure-
ments can detect abnormalities of sodium channel activity that affect blood pressure levels, at least when these are caused by structural changes in channel subunits. However, nasal and renal channels are regulated differently. For example, nasal channels are activated by aldosterone, which has no effect on nasal sodium channels.23 Sodium channel activity in respiratory epithelium is downregulated (decreased) by interactions with CFTR,24 but it is not clear whether CFTR has any influence on sodium channels in the renal tubule. Alteration of sodium channel regulation in the respiratory epithelium could lead to changes in sodium channel activity and nasal PD without altering renal sodium channel function.

Ethnic variation in nasal PD may be of direct relevance in the pathogenesis of airway disease. Black adults are 37% more likely than white adults to have active asthma and are nearly 3 times more likely to die of their asthma.25,26 The pathogenesis of airway disease. Black adults are 37% more likely than white adults to have active asthma and are nearly 3 times more likely to die of their asthma.25,26 The composition of liquid at airway surfaces has an important influence on bronchial reactivity. Hypotonic and hypertonic aerosols are thought to precipitate bronchospasm by altering the osmolarity of the periciliary fluid, invoking an intermediate event, possibly release of mediators from mast cells.27 Altered ion transport across airway epithelium in black people could predispose them to asthma by altering osmolarity of airway surface liquid.

We have shown that epithelial sodium channel activity is greater in black than in white people as assessed by nasal PD measurements. Generalized upregulation of sodium channel activity may account for the high prevalence of salt-sensitive hypertension in the black population.

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References

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