Ethnic Differences in Renal Responses to Furosemide

Tae-Yon Chun, Lise Bankir, George J. Eckert, Daniel G. Bichet, Chandan Saha, Syed-Adeel Zaidi, Mary Anne Wagner, J. Howard Pratt

Abstract—Blacks have a greater tendency to retain Na than whites. The present study sought evidence for ethnic differences in parameters reflective of Na uptake by the Na,K,2Cl cotransporter in the thick ascending limb, namely, the urine concentration and urinary excretion of certain cations before and after furosemide administration (40 mg IV). Subjects were healthy (ages 18 to 36 years). During the preceding overnight period, urine volume was lower, and osmolality was higher in blacks than in whites, an ethnic difference that disappeared when water intake was restricted to infused normal saline (60 mL/h). Plasma vasopressin levels were higher in black males than in other sex/ethnic groups. Baseline urinary excretion rates of K, Ca, and Mg were significantly lower in blacks than in whites. After furosemide (0 to 1 hour), K and Ca excretion rates increased, but the proportionate ethnic difference decreased from 44% to 22% and from 22% to 10%, respectively, consistent with blacks having more basal Na,K,2Cl cotransporter activity to inhibit. During a later postfurosemide period (1 to 5 hours), urinary concentrations of Ca and Mg recovered more slowly in blacks, consistent with greater reuptake in the thick ascending limb. In summary, there were distinct ethnic differences in renal handling of Ca and Mg basally and in response to furosemide that were consistent with a more active Na,K,2Cl cotransporter in the thick ascending limb in blacks. An increase in vasopressin levels appeared to explain greater urine concentrations in black males but not black females. (Hypertension. 2008;52:241-248.)

Key Words: Na,K,2Cl cotransporter  ■  aldosterone  ■  thick ascending limb  ■  osmolality  ■  ethnicity  ■  furosemide  ■  calcium

Blacks, in comparison with whites, have lower levels of plasma renin activity (PRA) and aldosterone and are more likely to develop hypertension that is salt sensitive, findings consistent with blacks having greater renal reabsorption of Na. Where in the nephron the greater uptake of Na occurs is unknown. We showed previously that amiloride, an inhibitor of the epithelial Na channel in distal nephron, significantly lowered blood pressure in whites when compared with blacks, consistent with less Na uptake by the epithelial Na channel in blacks, probably because of lower aldosterone levels. Greater Na reabsorption in blacks appeared to take place at a more proximal nephron site. The thick ascending limb (TAL), a principal nephron region for reclamation of Na by way of the Na,K,2Cl cotransporter (NKCC2), is a potential site for increased Na reabsorption. Although NKCC2 in TAL is more active in the salt-sensitive hypertensive Dahl rat, NKCC2 has never been shown to cause hypertension in humans.

Ethnic differences suggesting that TAL could be a site for more active Na uptake in blacks are described here: (1) Blacks have, on average, lower urine volumes and higher urine concentrations than whites. Na taken up by NKCC2 in TAL is essential for maintaining the renal medullary osmotic gradient required for water reabsorption in the collecting duct. Greater Na reabsorption by NKCC2 could augment water uptake and lead to a more concentrated urine in blacks. (2) Urinary excretion of Ca is lower in blacks than in whites. The luminal transepithelial potential difference in TAL that promotes paracellular uptake of Ca and Mg is coupled to the activity level of NKCC2. (3) Urinary excretion of K is lower in blacks than in whites. Greater Na uptake anywhere in proximal nephron regions, including TAL, would result in suppression of aldosterone levels, as well delivery of less Na downstream, both causing a reduction in distal nephron function, which is coupled to K secretion. In the present study, these known ethnic differences were studied further by comparing water homeostasis and urinary cation excretion rates in whites and blacks, basally and in response to inhibition of NKCC2 with furosemide, to explore the hypothesis that NKCC2 in TAL is more active in blacks.

Methods

Subjects
Subjects were from a cohort study of blood pressure regulation where subjects were initially recruited from their schools and, more
recently, through advertisements posted on the university campus. Sampling was such that representation was from across the socioeconomic spectrum. Subjects were in excellent health. None were taking medication with the exception that some of the female subjects used hormone-based contraceptives. Subjects completed a questionnaire regarding family history of hypertension. The study protocol was approved by the Indiana University-Purdue University at Indianapolis Institutional Review Board. All of the subjects provided informed consent.

Protocol
Subjects were admitted to the General Clinical Research Center in the afternoon. They had a physical examination that included measurements of height and weight for calculation of body mass index and body surface area. A 12-hour urine sample was collected beginning at 7 PM. Subjects consumed a standard diet for dinner, evening snack, and breakfast with no restrictions on water consumption. After breakfast the next morning, no additional food or liquid was consumed, and normal saline was infused (60 mL/h) for the purpose of maintaining similar vasopressin secretion and fluid homeostasis between subjects. After an equilibration period of 1 hour, followed by a 2-hour baseline period, subjects were given 40 mg of furosemide IV and monitored for an additional 5 hours. Urine volumes were significantly less in blacks than in whites (P<0.047) were significantly different between groups (P=0.038). Blood pressures were similar across the black and white groups (P=0.74 systolic; P=0.95 diastolic). After administration of furosemide, blood pressures were again similar in black and white groups (data not shown).

Serum Osmolality and Electrolyte Excretion Rates When Consuming Food and Water Ad Libitum
From 7 PM until 7 AM, when subjects had free access to water, urine volumes were significantly less in blacks than in whites (P<0.001); the ethnic difference was stronger for males (P=0.001) but still significant for females (P=0.047; Table 2). Uosm was greater in blacks than in whites (P<0.001), a significant difference that was maintained within sex groups. The frequencies of subjects within each sex and ethnic group over the range of Uosm are shown in the Figure in the supplement (available online at http://hyper.ahajournals.org); blacks are predominantly represented at the upper end of the Uosm, whereas the whites predominate over the range of 250 to 499 mosmol/kg of water. Both urinary K (P<0.001) and Ca (P=0.001) excretion rates were lower in blacks than in whites (Table 2). Urinary creatinine excretion rates (P=0.005) and creatinine clearance rates (P=0.047) were significantly greater in black females than in white females. Urinary Na excretion rates were not significantly different between groups (P=0.37).

Table 1. Characteristics of Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Black Females</th>
<th>White Females</th>
<th>Black Males</th>
<th>White Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>59</td>
<td>49</td>
<td>52</td>
<td>39</td>
</tr>
<tr>
<td>Age, y</td>
<td>23.8 (0.6)</td>
<td>23.5 (0.6)</td>
<td>22.9 (0.6)</td>
<td>22.1 (0.6)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.7 (1.1)</td>
<td>25.7 (0.8)</td>
<td>27.2 (0.8)</td>
<td>25.0 (0.7)</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.85 (0.03)</td>
<td>1.75 (0.03)</td>
<td>2.01 (0.03)</td>
<td>2.00 (0.03)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>121.6 (1.3)</td>
<td>121.6 (1.5)</td>
<td>126.4 (1.4)</td>
<td>125.7 (1.6)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>68.9 (1.0)</td>
<td>69.5 (1.1)</td>
<td>69.9 (1.0)</td>
<td>69.7 (1.2)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; BSA, body surface area; BP, blood pressure. Data are mean (SE) unless otherwise specified.

Results
There were 111 blacks (59 females and 52 males) and 88 whites (49 females and 39 males) ages 18 to 36 years (mean: 23 years; Table 1). There were 23 sets of siblings (22 pairs, 1 set of 3). Information regarding maternal history of hypertension was available for 90% of the subjects, and paternal history was available for 75% of the subjects. The subjects’ mothers were hypertensive in 23% of blacks and 14% of whites (P=0.15), and fathers were hypertensive in 25% of blacks and 20% of whites (P=0.52).

The mean body mass index was 27 kg/m²; blacks had a significantly higher body mass index than whites (P=0.001). The mean body surface area was 1.9 m²; blacks had a significantly higher body surface area than whites (P=0.038). Blood pressures were similar across the black and white groups (P=0.74 systolic; P=0.95 diastolic). After administration of furosemide, blood pressures were again similar in black and white groups (data not shown).

Statistical Analyses
Baseline values were an average of measurements made during the two 1-hour periods that preceded furosemide administration. After furosemide, averages were calculated for the measurements taken at 30 minutes and 1.0 hour; for measurements made between 1.5 and 2.5 hours, and for measurements made between 3.0 and 5.0 hours. Analyses of different time periods were performed separately. The analyses used the ranks of the data, because many of the outcomes were not normally distributed.

Comparisons of outcomes between the 2 ethnic groups (or between the 4 sex-ethnic groups) were performed using ANCOVA controlling for sex, age, and body surface area. The analyses included a random-effects model to account for possible correlations between siblings. Spearman correlation coefficients were calculated to assess relationships with levels of PRA and aldosterone.

The black:white ratios of the means for urinary excretion rates of electrolytes were calculated and then compared between time periods using a resampling bootstrap method of Efron and Tibshirani. The bootstrap method involves resampling with replacement from the original data, keeping all of the data for a selected subject so that the number of observations selected from each sex-ethnic group matched the original data. The ratios were calculated within each sample, and the results from 1000 samples were combined to obtain distributions of the differences in the black:white ratios for different time periods for calculating P values.

Serum Osmolality and Electrolyte Excretion Rates When Consuming Food and Water Ad Libitum
From 7 PM until 7 AM, when subjects had free access to water, urine volumes were significantly less in blacks than in whites (P=0.001); the ethnic difference was stronger for males (P=0.001) but still significant for females (P=0.047; Table 2). Uosm was greater in blacks than in whites (P<0.001), a significant difference that was maintained within sex groups. The frequencies of subjects within each sex and ethnic group over the range of Uosm are shown in the Figure in the supplement (available online at http://hyper.ahajournals.org); blacks are predominantly represented at the upper end of the Uosm, whereas the whites predominate over the range of 250 to 499 mosmol/kg of water. Both urinary K (P<0.001) and Ca (P=0.001) excretion rates were lower in blacks than in whites (Table 2). Urinary creatinine excretion rates (P=0.005) and creatinine clearance rates (P=0.047) were significantly greater in black females than in white females. Urinary Na excretion rates were not significantly different between groups (P=0.37).
similar for blacks and whites \((P=0.78; \text{Table 3})\). At baseline, however, when subjects were food and water restricted, serum osmolality was significantly lower in blacks than in whites \((P=0.008)\), a difference that resided primarily with males. One hour after administration of furosemide, a similar ethnic difference was observed \((P=0.039)\), whereas subsequent levels of serum osmolality were not different between groups.

### Plasma Vasopressin Levels
A subset of subjects randomly selected from each sex and ethnic group \((13\ to\ 15\ subjects\ per\ group)\) had measurements of vasopressin concentrations \((\text{Figure 1})\). In response to furosemide, levels increased in all of the groups. Black males had significantly higher vasopressin levels than white males at baseline \((P=0.044)\), 1 hour after administration of furosemide \((P=0.022)\), and 3 hours after administration of furosemide \((P=0.013)\) but were not different at 5 hours. There were no significant differences in vasopressin levels between black and white females at any of the time points. Spearman rank correlations between vasopressin and \(U_{\text{osm}}\) revealed a weakly positive association at baseline \((r=0.22)\,\text{higher vasopressin was associated with higher } U_{\text{osm}}\) and a weakly negative association \((r=-0.29)\,\text{higher vasopressin was associated with lower } U_{\text{osm}}\) 3 to 5 hours after administration of furosemide.

### Levels of PRA and Aldosterone
The levels of both PRA and aldosterone were significantly lower in blacks than whites at baseline \((P<0.001; \text{Figure 2})\). After administration of furosemide, levels of PRA and aldosterone increased as expected, and the ethnic differences persisted \((P<0.001)\).

### Urine Flow Rates and Osmolality in Relation to the Administration of Furosemide
When infused saline was the only source of solute and water, the urine flow rate was significantly higher in whites than in blacks \((P=0.049)\), whereas \(U_{\text{osm}}\) was not significantly different \((P=0.22)\) at baseline \((\text{Figure 3})\). After administration of furosemide, the urine flow rate increased 8- to 10-fold, and the \(U_{\text{osm}}\) decreased to levels slightly \(<300\ \text{mosmol/kg of } H_2O\), approximately equal to plasma osmolality, in both blacks and whites, consistent with furosemide having inhibited NKCC2 completely for >1 hour. Despite marked increases in urine flow rates, creatinine excretion rates remained stable. Although there was no difference between any of the groups in these responses to furosemide, the subsequent recovery of \(U_{\text{osm}}\) was slightly but significantly slower in blacks \((P<0.001)\). \(U_{\text{osm}}\) during the recovery was significantly related to the concurrently measured levels of PRA \((r=0.15; P=0.033)\) and aldosterone \((r=0.15; P=0.042)\) for all of the groups combined.

### Table 3. Osmolality and Electrolyte Concentrations in Serum Samples

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time Period</th>
<th>Black Females</th>
<th>White Females</th>
<th>Black Males</th>
<th>White Males</th>
<th>Ethnicity (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum osmolality, mosmol/kg of (H_2O)</td>
<td>7 AM</td>
<td>59</td>
<td>49</td>
<td>52</td>
<td>39</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>BL</td>
<td>281.9 (0.8)</td>
<td>281.4 (0.9)</td>
<td>284.8 (0.8)</td>
<td>285.8 (1.0)</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>F+1 h</td>
<td>282.5 (1.0)</td>
<td>282.8 (1.2)</td>
<td>282.9 (1.1)</td>
<td>284.9 (1.3)</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td>F+2 h</td>
<td>281.6 (1.0)</td>
<td>281.6 (1.1)</td>
<td>284.0 (1.1)</td>
<td>284.9 (1.2)</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>F+5 h</td>
<td>281.9 (0.9)</td>
<td>282.6 (1.1)</td>
<td>285.4 (1.0)</td>
<td>284.7 (1.2)</td>
<td>0.59</td>
</tr>
<tr>
<td>Serum Na, mmol/L</td>
<td>BL</td>
<td>137.8 (0.3)</td>
<td>137.8 (0.3)</td>
<td>137.9 (0.3)</td>
<td>137.9 (0.3)</td>
<td>0.84</td>
</tr>
<tr>
<td>Serum K, mmol/L</td>
<td>BL</td>
<td>4.06 (0.04)</td>
<td>4.02 (0.05)</td>
<td>4.13 (0.05)</td>
<td>4.04 (0.05)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

BL indicates baseline; \(F+n\ h\), number of hours after furosemide administration. Data are mean \(\text{(SE)}\) unless otherwise specified.
Urinary Electrolyte Excretion Rates and Concentrations in Relation to Administration of Furosemide

Urinary excretion rates of Na were the same in both groups at baseline and remained similar after administration of furosemide (Figure 4). K excretion, on the other hand, at baseline in blacks was only approximately half that observed in whites (44% less). Although furosemide administration caused K excretion to increase several-fold over a period of 1 hour, the response was greater in blacks to the extent that the difference between blacks and whites was reduced to 22%. Similar observations were made for Ca: blacks excreted 22% less than whites over the baseline period but only 10% less after administration of furosemide. Furosemide-induced reductions in ethnic differences in both K and Ca excretion rates were significant at $P<0.05$. In the case of Mg, excretion rates were 12% less in blacks at baseline, a difference that increased to only 16% after furosemide (the increase in the ratio was not significant).

The time profiles for excretion rates of Na, Ca, and Mg after furosemide are depicted in Figure 5. After the initial rise, the excretion of all 3 of the cations returned to basal levels 3 hour postfurosemide. Their concentrations, on the other hand, showed a solute-specific pattern with distinct ethnic differences. The Na concentration remained stable over time after furosemide, as might be expected, because of the water reabsorption in downstream nephron regions. In contrast, the concentrations of Ca and Mg fell markedly after furosemide and then recovered slowly over several hours, although never returning to baseline. During the recovery period, 2 to 5 hours postfurosemide, the concentrations of Ca ($P<0.001$) and Mg ($P<0.001$) were lower in blacks consistent with a more intense reabsorption with the ethnic differences in Ca concentrations being particularly pronounced. Fractional excretion of Ca was calculated in the same subset of subjects in whom vasopressin was measured. Fractional excretion of Ca was lower in blacks than in whites at baseline ($P=0.002$), was
similar between groups after administration of furosemide ($P=0.89$), and was again lower in blacks during the recovery period ($P=0.039$; data not shown).

**Discussion**

As a group, blacks are highly susceptible to hypertension and its complications, and an understanding of mechanism for the greater Na retention in blacks is of great interest. We observed in the present study distinct differences between blacks and whites in the renal handling of water and certain electrolytes. Certain of the findings at baseline, during the period shortly after administration of furosemide, and during the postfurosemide recovery period provide separate and corroborative pieces of evidence suggesting the existence of an ethnic difference in NKCC2 activity.

**Baseline**

Before furosemide administration (including the overnight period), blacks, in comparison with whites, had lower urinary excretion rates of Ca and K, findings that confirm previous reports. Greater uptake of Ca in TAL could explain in part the reduced Ca excretion in blacks, whereas an increase of Na uptake by NKCC2 would lead to less K secretion because of lower aldosterone levels and less Na reaching the distal nephron.

We also examined the role played by NKCC2 in TAL to concentrate urine. Urine volume was less and U_osm was greater in blacks than in whites, consistent with previously reported observations, but only during the overnight period when subjects had free access to water. During the study protocol baseline period, when the sole source of water was infused normal saline, $U_{osm}$ was the same in blacks and whites. Vasopressin levels were significantly higher in black males than in white males at baseline when serum osmolality was significantly lower in black males than in white males (as would be expected if water intake was the same for both groups and vasopressin levels were higher in black males). Although higher vasopressin levels could explain the higher urinary concentrations in black males than in white males at baseline when serum osmolality was significantly lower in black males than in white males (as would be expected if water intake was the same for both groups and vasopressin levels were higher in black males). Results of the 2 previous studies, together with the current results, appear to be insufficient to conclude that vasopressin secretion in blacks and whites is significantly different and cannot with certainty explain the higher urine concentration observed in blacks. Thus, a role for increased Na reabsorption in TAL cannot be ruled out. Indeed, for a more active NKCC2 to affect water reabsorption, there would need to be a less than full downward adaptation of vasopressin secretion. In addition, if vasopressin is in fact higher in blacks, this in itself increases Na reabsorption in TAL, because vasopressin stimulates NKCC2 activity, and, in
humans, TAL receptors for vasopressin have been demonstrated.27

Early Responses to Furosemide (0 to 1 Hour)
Differences in excretion rates of K and Ca between blacks and whites under basal conditions were reduced after inhibition of NKCC2 with furosemide. At baseline, K excretion in blacks was 44% lower than in whites, a difference that was reduced by almost half after inhibition of NKCC2. A similar effect of furosemide was observed in studies of Luft et al.28 as pointed out by Aviv et al.29 The ethnic difference in urinary Ca excretion at baseline was, like K, reduced by approximately half with furosemide administration. Thus, with complete inhibition of NKCC2, both K and Ca excretion increased proportionately more in blacks, suggesting a greater basal level of NKCC2 activity in blacks. In addition, the lower fractional excretion of Ca in blacks at baseline disappeared immediately after furosemide and then recovered during the recovery period.

The majority of filtered Mg is also passively reabsorbed by the paracellular route in TAL.30 Mg excretion was 12% lower in blacks at baseline, a difference that did not significantly change after furosemide administration. However, the distal convoluted tubule (DCT) has a substantial capacity to take up Mg not extracted in TAL,31 and, thus, an ethnic difference could be maintained after furosemide inhibition through adjustments by the DCT.

Postfurosemide Recovery (1 to 5 Hours)
Findings also supportive of an ethnic difference in NKCC2 activity took place during the recovery from furosemide. After furosemide administration, concentrations of Ca and Mg declined in all of the groups to the same level. This was followed by a much slower restoration of their concentrations in blacks than in whites (Figure 5). A more rapid restoration of NKCC2 function in blacks could explain these ethnic differences. Although changes in urinary Ca and Mg excretion were used as markers of TAL reabsorptive activity, we cannot exclude a significant influence on their disposition by DCT, because both sites act to conserve Ca and Mg. Recent studies of mice deficient in TRPV5 in DCT revealed its importance as a mediator of Ca uptake,32 and conceivably there are differences in TRPV5 expression or level of activity that contributes to the ethnic difference in Ca excretion. Transport of Ca in DCT might also be affected by furosemide-induced increases in Ca excretion, as was shown in a mouse model where expression of TRPV5, TRP6, and an intracellular Ca binding protein all increased.33

Uosm depends on the renal medullary concentration gradient of which generation is influenced by multiple factors. Uosm was restored slightly (but significantly) more slowly in blacks
after furosemide administration. In studies reported previously, an identical pattern of slowed recovery of $U_{\text{osm}}$ after furosemide administration was observed in dogs when exposure to angiotensin II was reduced pharmacologically. The authors speculated that a reduction in angiotensin II–mediated resistance in the vasa recta that penetrates the renal medulla led to greater perfusion, thereby delaying restoration of the concentration gradient. We observed a significant relation of $U_{\text{osm}}$ during recovery with levels of PRA and aldosterone. Aldosterone has also been shown to increase renal vascular tone, and, thus, we consider it likely that reduced levels of angiotensin II and/or aldosterone in blacks account for the slower recovery.

A limitation to the current study is that we cannot be certain that there were not ethnic differences in the metabolism or disposition of furosemide that might explain our findings. We are, however, unaware of any reports of such an effect of ethnicity, and the responses to furosemide did not suggest any such ethnic difference to the extent that the dose of furosemide administered (40 mg IV) completely inhibited the activity of NKCC2, as evidenced by a decline in $U_{\text{osm}}$ to $\approx 300$ mosmol by 30 minutes, an effect that lasted for $>1$ hour and appeared to be identical in whites and blacks.

Finally, if in fact NKCC2 is more active in blacks than in whites, why then in blacks was Na excretion not lower and blood pressure not higher? This can be explained by the downregulation of Na uptake by the distal nephron. Such an adjustment could equalize Na homeostasis and blood pressure in the 2 groups. When blood pressure increases in blacks to hypertensive levels, the adjustment appears to break down.

In summary, clear ethnic differences in renal handling of electrolytes in response to furosemide were observed. The findings were consistent with there being greater NKCC2 activity in blacks than in whites, although a significant influence by DCT could not be excluded. A lower urine volume and higher $U_{\text{osm}}$ in blacks appeared at the least to be partially attributable to a higher vasopressin level in blacks, although a contribution from a more active NKCC2 could not be ruled out.

**Perspectives**

Most human studies (primarily genetic) of mechanisms of salt sensitivity of blood pressure have focused on the distal nephron. This is easily justified considering the pivotal role that the distal nephron plays in making the necessary adjustments to overall Na homeostasis. There may be instances, however, where Na reabsorption upstream in the nephron overwhelms the capacity of the kidney to adjust other than to invoke a pressure natriuresis. Although a variety of protocol designs can be proposed for the study of specific Na transport systems in humans, the comparison of 2 population groups with different levels of salt sensitivity appeared to be informative in the current study.

**Acknowledgments**

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