Racial Differences in Erythrocyte Cation Transport

ALAN B. WEDER, M.D., BARBARA A. TORRETTI, A.B., AND STEVO JULIUS, M.D.

SUMMARY  Erythrocyte contents and ouabain-insensitive transport pathways were measured in 120 white and black normotensives and hypertensives. Mean maximal sodium-stimulated lithium-sodium countertransport rate was higher in white hypertensives than in white normotensives, and countertransport was significantly positively correlated with mean arterial pressure in whites. Values similar to those in white normotensives were found in both black normotensives and hypertensives, and countertransport was not significantly correlated with blood pressure in blacks. The rate constant for passive lithium efflux was greater in whites as compared to blacks, and the difference was not related to blood pressure level or sex. Ouabain-insensitive, furosemide-sensitive sodium and potassium effluxes were not found to be altered in hypertension. Furosemide-sensitive sodium efflux rate was lower in blacks but furosemide-sensitive potassium efflux was not similarly depressed. While white subjects demonstrated a close correlation between sodium and potassium effluxes, blacks did not. Further study of these differences in the cellular metabolism of sodium and potassium may provide clues to the pathogenesis of racial dissimilarities in total body sodium handling.

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KEY WORDS  • race • countertransport • cotransport • erythrocyte

Erythrocyte lithium-sodium countertransport and sodium-potassium cotransport have been proposed as markers for human essential hypertension.1,2 Virtually all reports have included only white subjects. For lithium-sodium countertransport, Canessa and colleagues1–3 have consistently demonstrated enhanced maximal activity in white hypertensives and others4–8 have confirmed the observation, although agreement is not universal.9 Canessa et al.10 reported that black hypertensives had values similar to those of black normotensives. Etkin et al.11 observed increases in tracer sodium influx rates in the erythrocytes of white essential hypertensives but not in blacks and suggested that tracer influx rate is closely correlated with the activity of the lithium-sodium countertransport system.12 However, Trevisan et al.13 found a significant correlation between lithium-sodium countertransport and blood pressure in black schoolchildren, and Woods et al.14 found higher countertransport rates in blacks by comparing the normotensive sons of two hypertensive parents and the normotensive sons of normotensive parents.

Regarding cotransport measures, Garay and co-workers15,16 have repeatedly found lower cotransport activity in white hypertensives as compared to normotensives but decreased cotransport activity in both normotensive and hypertensive black Africans.17 Davidson et al.18 did not confirm these observations in the South African population, noting no differences for blacks and whites, although within each race, hypertensives tended to be lower than normotensives. Canessa et al.19 have suggested in a preliminary report that hypertension is associated with lower cotransport activity in American blacks but not in whites. Most recently, Tuck et al.20 observed a similar decrease in sodium cotransport in black hypertensives but failed to find a defect in potassium cotransport in the same subjects.

The fragmentary characterization of transport systems in these studies3,9,21–24 and recent unpublished observations (A. Weder) regarding the interrelationships of lithium-sodium countertransport and sodium-potassium cotransport led us to investigate both functions in a mixed population of blacks and whites. Our findings indicate that lithium-sodium countertransport activity is positively correlated with blood pressure in whites but not in blacks. Furosemide-sensitive sodium efflux is markedly depressed in both black normotensives and hypertensives but is not reliably associated with hypertension. Furosemide-sensitive potassium efflux is not similarly affected by race. A relationship between lithium-sodium countertransport and sodium-potassium cotransport is present in whites but not in blacks.
**Materials and Methods**

Paid normotensive control subjects of both races were recruited by public advertisement. Untreated hypertensive subjects were recruited in the University of Michigan Hypertension Clinic and the Student Health Service. All were deemed to have essential hypertension on the basis of history, physical examination, blood chemistries and, when appropriate, plasma renin activity or radiologic evaluation. No subjects or patients were known to be related. After consent was obtained and the purpose of the study explained, a brief data base, consisting of age, sex, race, duration of prior history of hypertension, family history of hypertension, presence of other illness, alcohol and drug use, was recorded. Height and weight were determined, and blood pressure, with Phase I taken as the systolic and Phase V as the diastolic, was established as the average of three determinations taken with cuff and stethoscope after 5 minutes in the sitting position. Heart rate was recorded by counting the radial pulse at the end of the blood pressure recordings. Finally, a 30 ml sample of whole blood was drawn by venipuncture into a heparinized syringe, iced, and delivered immediately to the laboratory where the determinations described below were undertaken.

**Erythrocyte Cation and Water Contents**

For determination of cell water, two 0.4 ml aliquots of unwashed packed cells were transferred into pre-weighed 0.4 ml Beckman miicrofuge tubes and centrifuged in a Beckman Microfuge B for 5 minutes at 9000 g. The supernatant was completely aspirated, and the remaining cell pellets and tubes weighed, dried 48 hours in an oven at 90°C, cooled in a dessicator, and reweighed; the difference in wet and dry weights was taken as the total water in the sample. No correction was made for trapped extracellular plasma.

The remaining cells were prepared for subsequent analysis by transferring the blood into 50 ml plastic centrifuge tubes and adding approximately 30 ml of an ice-cold washing solution (WS) consisting of (mM) 75 MgCl₂, 85 sucrose, 10 Tris-MOPS (pH 7.4 at 37°C), mixing thoroughly and centrifuging for 5 minutes at 1000 g. The supernatants were aspirated and discarded and the process repeated three times, yielding suspensions of washed cells for the remaining determinations. Then 200 µl of the washed cells were lysed by addition to 10 ml distilled water and the hemoglobin content of the hemolysate determined by the cyanohemoglobin method. Cation content of the hemolysate was measured on a Perkin-Elmer Model 2380 AA spectrophotometer (Perkin-Elmer Corporation, Norwalk, Connecticut) using appropriate dilusions. AA standards were obtained commercially (Fisher Scientific Company, Fair Lawn, New Jersey) and diluted in water. Results are expressed as millimoles of cation per liter cells.

**Sodium-Lithium Countertransport Activity**

The following was based on a modification of the method of Canessa et al. as described by Smith et al. Five ml of washed cells were transferred to a 250 ml Erlenmeyer flask containing 20 ml of a lithium-loading solution (LLS) of (mM) 150 LiCl, 10 Tris-MOPS (pH 7.4 at 37°C), 10 glucose, and incubated at 37°C for 3 hours in a shaking bath. Following incubation, the cell suspension was transferred to a 50 ml centrifuge tube and centrifuged at 1000 g for 15 minutes. The supernatant was discarded and the cells washed free of external lithium with WS to which 0.1 mM ouabain was added (WSO). The cells, now loaded with lithium, were suspended in WSO to a final volume of approximately 4 ml and the hematocrit of the suspension determined in duplicate. A 200 µl aliquot of the suspension was taken for determination of cell cation contents (sodium, potassium, and lithium) as above. From the remaining suspension, two 1.6 ml aliquots were added to tubes containing 10 ml of either magnesium chloride solution (MS) of (mM) 75 MgCl₂, 85 sucrose, 10 Tris-MOPS (pH 7.4 at 37°C), 0.1 ouabain, 10 glucose or sodium chloride solution (SS) containing (mM) 150 NaCl, 10 Tris-MOPS (pH 7.4 at 37°C), 0.1 ouabain, 10 glucose. Following thorough mixing, 1.5 ml aliquots of the MS and SS suspensions were pipetted into two sets of six tubes. All tubes were incubated at 37°C in a water bath with constant shaking. Duplicates were removed at 20, 40, and 60 minutes, placed on ice for 2 minutes, and then immediately centrifuged at 1000 g for 5 minutes. Supernatants were removed and assayed for lithium content by atomic absorption spectrophotometry using standards prepared in MS or SS, as appropriate. Regression lines were fitted by linear regression and the slope of lithium concentration vs time taken as the rate of lithium efflux. The difference between the efflux rates in MS and SS is the rate of sodium-stimulated lithium countertransport and is expressed as millimoles of lithium per liter of cells per hour. The coefficient of variation for this assay is 14.2% (A. Weder, unpublished data) as calculated from the formula

\[ \sqrt{\frac{\Sigma d^2}{2N}} \]

(d = difference for each pair, N = number of pairs) and expressed as a percentage of the mean for 40 pairs of samples assayed in a blinded fashion.

**Furosemide-Sensitive Sodium-Potassium Cotransport**

The following method was derived from the report of Canessa et al. using the nystatin loading procedure first described by Cass and Dalmark.

The erythrocytes, washed as above in WS, were suspended at approximately 2% hematocrit in a sodium-loading solution (SLS) consisting of (mM) 75 NaCl, 75 KCl, 32 sucrose, 5 Hepes, 1 EGTA pH 7.4 at 4°C. Nystatin (Sigma Chemical Company, St. Louis, Missouri), dissolved in methanol just prior to each assay, was added to a final concentration of 30 µg/ml. The suspension was gently stirred for 20 minutes, then transferred to plastic centrifuge tubes at room temperature, centrifuged at 1000 g for 5 minutes, the supernatant discarded, and the cells washed twice with room temperature SLS to which 0.5% bovine albumin was...
added. Finally, the sodium-loaded red cells were washed six times in MS at room temperature, and the final wash supernatant sodium concentration checked to ensure that it was below 30 μM. If supernatant sodium concentration exceeded 30 μM, cells were washed until a lower supernatant sodium concentration was achieved. The washed cells were suspended in MS at an approximate hematocrit of 50%, and the cell concentration determined in duplicate. A 50 μl aliquot of the suspension was taken for determination of intra-cellular cation composition, as above, and in all samples, water content was assessed. From the remaining suspension, two 2 ml aliquots were removed and transferred to tubes containing 15 ml ice-cold MS with and without 1 mM furosemide HCl (Hoechst-Roussel Pharmaceutical Company, Somerville, New Jersey), titrated with Tris to pH 7.4. The resulting suspensions were pipetted into six tubes each (2.5 ml/tube) and incubated for 1.5 hours, with duplicates removed, iced for 2 minutes, and centrifuged for 5 minutes at 1000 g for 30, 60, and 90 minutes. The supernatants were recovered and analyzed for sodium and potassium concentrations by AA spectrophotometry with standards prepared in MS. Efflux lines were fitted by linear regression, and the difference in the presence and absence of furosemide taken as the furosemide-sensitive cotransport of sodium and potassium in units of millimoles per liter cells per hour. Coefficients of variation are 23.6% and 20.0% for furosemide-sensitive sodium and potassium effluxes, respectively (A. Weder, unpublished data).

Data Analysis

Not every subject underwent both countertransport and cotransport measurements, but all available data were included in the analysis. Simple group comparisons were made by Student's t test. Multiple group comparisons analyzing the effects of both race and sex were made by analysis of variance utilizing Scheffe allowances to determine significance levels. For the blood pressure data, group comparisons were made utilizing a mean arterial pressure (MAP) of 105 mm Hg as an arbitrary boundary between normotension and hypertension, but when appropriate, blood pressure was analyzed as a continuous variable by linear regression and correlation techniques. Family history was considered positive if subjects reported any known hypertension in either parent or any sibling. All data below are given as means ± se.

Results

A total of 120 subjects had at least one flux measurement. A summary of the clinical characteristics and cell contents is shown in Table 1.

| Table 1. Clinical Characteristics and Erythrocyte Cell Contents of the Study Population (Mean ± se) |
|---|---|---|---|
| | Whites | | Blacks |
| | Males | Females | Males | Females |
| No. | 56 | 30 | 19 | 15 |
| Age (yrs) | 35.3 ± 1.5 (18-64) | 34.2 ± 2.4 (19-74) | 31.8 ± 2.6 (20-68) | 33.4 ± 3.2 (19-59) |
| Height (cm) | 177.9 ± 0.9* (162.6-194.0) | 164.4 ± 1.0 (154.9-177.8) | 180.6 ± 1.9* (167.6-193.0) | 165.1 ± 2.0 (150.0-178.0) |
| Weight (kg) | 80.1 ± 1.8* (53.1-114.8) | 64.7 ± 2.0 (47.2-92.1) | 84.1 ± 2.5* (67.1-112.9) | 72.2 ± 2.8 (54-111.6) |
| Family history (+/-) | 28/28 | 10/20 | 11/8 | 6/9 |
| Sitting blood pressure (mm Hg) | | | | |
| Systolic | 137.1 ± 2.8* (106-197) | 121.5 ± 3.3 (90-155) | 130.7 ± 3.9 (100-172) | 122.1 ± 6.7 (86-182) |
| Diastolic | 89.5 ± 2.3* (60-132) | 77.9 ± 2.6 (60-106) | 78.7 ± 3.7 (54-108) | 79.1 ± 3.9 (58-100) |
| Mean | 105.4 ± 2.4* (78.0-153.7) | 92.5 ± 2.6 (73.3-117.0) | 96.0 ± 3.6 (73.3-129.3) | 93.5 ± 4.5 (70.0-119.3) |
| Heart rate (bpm) | 73.4 ± 1.5 (52-92) | 80.8 ± 2.1 (60-100) | 71.3 ± 2.5 (52-92) | 76.6 ± 2.7 (60-100) |
| Cell content | | | | |
| Sodium (mmol/liter cells) | 8.0 ± 0.3 (2.3-18.3) | 5.9 ± 0.6 (2.7-15.1) | 8.3 ± 0.7 (3.7-13.5) | 7.3 ± 0.8 (2.8-13.4) |
| Potassium (mmol/liter cells) | 92.7 ± 0.6 (79.8-101.3) | 96.8 ± 1.0 (83.6-114.2) | 95.1 ± 0.9 (87.6-100.4) | 94.2 ± 1.9 (82.1-107.2) |
| Water (%) | 64.83 ± 0.15 (62.14-67.17) | 65.90 ± 0.15 (64.42-68.12) | 66.38 ± 0.23 (64.66-68.73) | 66.73 ± 0.24 (65.42-68.83) |

*Males > females, p < 0.05 by analysis of variance.
TABLE 2. Initial Cell Contents and Lithium Efflux Rates from Lithium-Loaded Erythrocytes (Mean ± se)

<table>
<thead>
<tr>
<th>No.</th>
<th>Cell content (mmol/liter cells)</th>
<th>Ouabain-insensitive effluxes (mmol/liter cells•hr)</th>
<th>Rate constant, kLi (hr⁻¹) (mg medium)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Li</td>
<td>Na</td>
<td>K</td>
</tr>
<tr>
<td>57</td>
<td>5.9 ± 0.2</td>
<td>2.8 ± 0.1</td>
<td>91.8 ± 0.7</td>
</tr>
<tr>
<td>29</td>
<td>6.3 ± 0.1</td>
<td>2.3 ± 0.1</td>
<td>89.7 ± 0.8</td>
</tr>
<tr>
<td>23</td>
<td>6.1 ± 0.1</td>
<td>3.6 ± 0.3</td>
<td>95.9 ± 0.7</td>
</tr>
<tr>
<td>11</td>
<td>6.1 ± 0.3</td>
<td>3.0 ± 0.4</td>
<td>94.7 ± 1.2</td>
</tr>
</tbody>
</table>

*p < 0.05 vs all other groups by analysis of variance.
†p < 0.001 by Student’s t test.

Cell Contents

There were no significant differences related to sex, race, or blood pressure for cell sodium, potassium, and water contents.

Lithium-Sodium Countertransport

As shown in Table 2, maximal sodium-stimulated lithium-sodium countertransport rate was lower in white normotensives compared to white hypertensives (0.27 ± 0.01 vs 0.37 ± 0.02 mmol/liter cells • hr, p < 0.05 by analysis of variance, ANOVA). There was no difference for the same groups in the black subset (0.21 ± 0.03 vs 0.27 ± 0.03 mmol/liter • hr, respectively, p > 0.10), and neither black normotensives nor black hypertensives were significantly different from white normotensives (p > 0.10 for both). Individual values are displayed in Figure 1. Analysis of variance revealed no significant differences related to sex.

Division into normotensive and hypertensive groups required an arbitrary cutpoint, as the blood pressure distribution was continuous. Linear correlation analysis revealed a significant positive relationship between MAP and lithium-sodium countertransport rate in whites, r = 0.375, p < 0.001, but no significant correlation in blacks, r = 0.103, p > 0.1 (Figure 2, left and right).

The rate constant for lithium efflux (kLi) was calculated from the cell content of lithium and the rate of efflux into the magnesium medium. There was no significant effect of blood pressure level on the efflux rate constant for either whites or blacks (p > 0.1 by ANOVA), but whites as a group demonstrated a consistently higher efflux rate constant when compared to blacks (p < 0.001 by Student’s t test).

Furosemide-Sensitive Cation Transport

With the above blood pressure criteria for normotension and hypertension, neither whites nor blacks demonstrated group differences for the different levels of blood pressure for either sodium or potassium furosemide-sensitive effluxes (Figures 3 and 4). Furosemide-sensitive sodium efflux was (mmol/liter cells • hr, mean ± se) 0.30 ± 0.03 vs 0.32 ± 0.04 in white normotensives vs white hypertensives and 0.10 ± 0.03 vs 0.08 ± 0.02 in black normotensives and hypertensives. Furosemide-sensitive potassium efflux was 0.37 ± 0.04 vs 0.38 ± 0.05 in white normoten-
sives and hypertensives and 0.27 ± 0.04 vs 0.28 ± 0.05 in black normotensives and hypertensives, respectively. There were no significant correlations for either sodium or potassium efflux rates with blood pressure (r for MAP vs Na rate = 0.085 for whites, = -0.021 for blacks; vs K rate = 0.094 for whites, = 0.101 for blacks; p > 0.1 for all correlations). For furosemide-sensitive effluxes, the important differences were related to racial classification (Table 3). Although males generally had higher rates, male-female differences were not significant. Furosemide-sensitive sodium efflux was significantly higher for white males compared to black males (0.34 ± 0.03 vs 0.14 ± 0.04, p < 0.05), and for white females compared to black females (0.24 ± 0.04 vs 0.04 ± 0.01, p < 0.05). Furosemide-sensitive potassium efflux was not similarly affected, and there were no significant differences among the groups.

Rate constants for post-nystatin sodium and potassium effluxes into a magnesium chloride medium in the presence of ouabain and furosemide are shown in Table 3. No significant differences were apparent.

**Relationship of Co- to Countertransport**

A difference between the races was noted for the correlation of simultaneously determined countertransport and cotransport rates. Whites demonstrated a weak but significant positive relationship for lithium-

![Figure 2](image2.png)

**Figure 2.** There was a positive correlation of blood pressure and lithium-sodium countertransport rate in whites (left) but not in blacks (right).

![Figure 3](image3.png)

**Figure 3.** Ouabain-insensitive, furosemide-sensitive sodium cotransport was not different in hypertensives compared to normotensives in either whites or blacks.
sodium countertransport and both sodium ($r = 0.390$, $p < 0.01$ for 72 D.F.) and potassium ($r = 0.249$, $p < 0.05$ for 72 D.F.) furosemide-sensitive effluxes, whereas blacks demonstrated no significant relationship. In addition, while sodium and potassium cotransports were highly correlated in whites ($r = 0.902$, $p < 0.0001$), a similar relationship was not observed in blacks ($r = 0.149$, $p > 0.10$). Finally, a relationship previously noted by Adragna et al.$^3$ between the rate constant of lithium efflux into a magnesium medium (Table 2) and maximal furosemide-sensitive sodium and potassium effluxes (Table 3) was investigated and found to be significant in whites ($r = 0.426$ for sodium, $p < 0.01$; $r = 0.264$ for potassium, $p < 0.05$, 72 D.F.), but not in blacks.

**Other Measured Characteristics**

Age, weight, and height were not related to blood pressure or erythrocyte transport phenomena. The fraction of subjects claiming a positive family history

![Figure 4](image-url) **Figure 4.** Ouabain-insensitive, furosemide-sensitive potassium cotransport was not related to blood pressure level in either whites or blacks.

**Table 3.** Initial Cell Contents and Sodium and Potassium Efflux Rates From Sodium-Loaded, Potassium-Depleted Erythrocytes Prepared by the Nystatin Technique (Mean ± se)

<table>
<thead>
<tr>
<th></th>
<th>Whites</th>
<th></th>
<th>Blacks</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>No.</td>
<td>51</td>
<td>23</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Cell content (mmol/liter cells)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>55.2 ± 0.9</td>
<td>57.7 ± 1.9</td>
<td>55.0 ± 1.3</td>
<td>55.5 ± 1.1</td>
</tr>
<tr>
<td>Potassium</td>
<td>56.2 ± 0.6</td>
<td>57.3 ± 0.7</td>
<td>57.4 ± 0.7</td>
<td>57.1 ± 0.6</td>
</tr>
<tr>
<td>Ouabain-insensitive effluxes (mmol/liter cells-hr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide sensitive:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>0.34 ± 0.03</td>
<td>0.24 ± 0.04</td>
<td>0.14 ± 0.04*</td>
<td>0.04 ± 0.01*</td>
</tr>
<tr>
<td>Potassium</td>
<td>0.42 ± 0.04</td>
<td>0.31 ± 0.05</td>
<td>0.24 ± 0.05</td>
<td>0.31 ± 0.03</td>
</tr>
<tr>
<td>Furosemide insensitive:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>1.20 ± 0.03</td>
<td>1.28 ± 0.08</td>
<td>1.37 ± 0.08</td>
<td>1.24 ± 0.10</td>
</tr>
<tr>
<td>Potassium</td>
<td>1.03 ± 0.05</td>
<td>1.09 ± 0.08</td>
<td>1.27 ± 0.10</td>
<td>1.09 ± 0.02</td>
</tr>
<tr>
<td>Rate constants (hr⁻¹):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (kNa)</td>
<td>0.022 ± 0.001</td>
<td>0.022 ± 0.001</td>
<td>0.025 ± 0.001</td>
<td>0.024 ± 0.001</td>
</tr>
<tr>
<td>Potassium (kK)</td>
<td>0.018 ± 0.001</td>
<td>0.019 ± 0.002</td>
<td>0.022 ± 0.002</td>
<td>0.019 ± 0.001</td>
</tr>
</tbody>
</table>

*p < 0.05 vs white males, by analysis of variance.

*tp < 0.05 vs white females, by analysis of variance.
A potentially important membrane difference noted between the races was the lower rate constant for lithium efflux into the magnesium chloride medium seen in blacks. We did not find a relationship of passive lithium rate constant to blood pressure in either race, as has been suggested by Adragna and colleagues. 

The previous suggestion by Canessa et al. that hypertensive blacks do not manifest increased rates of lithium-sodium countertransport is supported by the present study. Although there is a difference in mean countertransport function in the black group when an arbitrary division between normotension and hypertension is applied, the difference is not significant. The failure to demonstrate a significant difference might be due to the small sample size, but more important, when countertransport and blood pressure were analyzed as continuous variables, there was no significant relationship in blacks, while a weak but highly significant positive correlation existed in whites. In all groups there was considerable overlap of individual values, as demonstrated in Figure 1.

Table 4. Influence of Family History on Ouabain-Insensitive Erythrocyte Cation Transport (Mean ± se)

<table>
<thead>
<tr>
<th></th>
<th>Lithium-sodium countertransport (mmol/liter cells·hr)</th>
<th>Furosemide-sensitive efflux (mmol/liter cells·hr)</th>
<th>Sodium</th>
<th>Potassium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>− FH</td>
<td>0.27 ± 0.02 (36)</td>
<td>0.37 ± 0.03 (12)</td>
<td>0.28 ± 0.03 (40)</td>
<td>0.37 ± 0.04 (40)</td>
</tr>
<tr>
<td>+ FH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blacks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>− FH</td>
<td>0.29 ± 0.02 (21)</td>
<td>0.38 ± 0.03 (17)</td>
<td>0.34 ± 0.05 (34)</td>
<td>0.40 ± 0.06 (34)</td>
</tr>
<tr>
<td>+ FH</td>
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</tr>
</tbody>
</table>

White hypertensives had significantly greater countertransport rates than white normotensives, regardless of family history status. Blacks demonstrated no significant differences. There was no consistent relationship of ouabain-insensitive, furosemide-sensitive sodium or potassium effluxes and family history. Numbers in parentheses indicate number of subjects.

* p < 0.05 by analysis of variance.

Discussion

The present study confirms the existence of a quantitative disorder of lithium-sodium countertransport in essential hypertension in whites, as previously described by others. Furthermore, whereas others have often included both treated and untreated hypertensives, our use of an exclusively untreated population permits a demonstration of the continuous nature of the relationship between blood pressure and sodium-stimulated lithium-sodium countertransport. Caution must therefore be exercised in studies treating blood pressure as a categorical variable as the magnitude of differences in mean countertransport rates can be expected to depend on the cut points established to define the hypertensive state.

The previous suggestion by Canessa et al. that hypertensive blacks do not manifest increased rates of lithium-sodium countertransport is supported by the present study. Although there is a difference in mean countertransport function in the black group when an arbitrary division between normotension and hypertension is applied, the difference is not significant. The failure to demonstrate a significant difference might be due to the small sample size, but more important, when countertransport and blood pressure were analyzed as continuous variables, there was no significant relationship in blacks, while a weak but highly significant positive correlation existed in whites. In all groups there was considerable overlap of individual values, as demonstrated in Figure 1.

Age, sex, weight, height, and family history do not seem to be important determinants for countertransport in any group. Others, including Woods et al., Canali et al., and Clegg et al. have described higher countertransport activities in both normotensive and hypertensive subjects with a positive family history of hypertension, although Canessa et al. Adragna et al., Cooper et al., and Ibsen et al. could not detect any influence. Our study does not demonstrate any effect of family history, but we did not have access to family members to directly assess blood pressures and trans-
port functions. A definitive answer will have to await a more exhaustive analysis.

The demonstration of racial differences in the relationship of blood pressure and lithium-sodium countertransport suggests the possibility that other genetic factors may be important constraints on the activity of the system. The population described by Duhm et al. 3 may represent another group in which the countertransport-blood pressure relationship is disordered.

The erythrocyte furosemide-sensitive sodium-potassium cotransport system is apparently subject to considerable geographic variability and has an inconsistent relationship to blood pressure, being variably reported as increased, 2 decreased, 2,14 or normal 9 in hypertension. We failed to demonstrate a difference when the racial groups were split at a MAP of 105 mm Hg and, furthermore, found no relationship on correlation and analysis between either furosemide-sensitive sodium or potassium effluxes and blood pressure. Major racial differences, however, did exist. Furosemide-sensitive sodium efflux was markedly lower in blacks compared to whites, independent of the level of blood pressure or of other factors such as sex, age, weight, or family history of hypertension.

The present study describes an intriguing qualitative difference between blacks and whites that has been previously commented upon by Tuck et al. 20 Whereas in whites the ratio of sodium and potassium furosemide-sensitive effluxes from sodium-loaded cells is near 1.0 and the effluxes are highly correlated, the decrease in furosemide-sensitive transport is more marked for sodium as compared to potassium in blacks, and there is no relationship between sodium and potassium rates. Such a dissociation has no obvious mechanistic basis since the cotransport system in human erythrocytes is thought to operate with tight 1:1 stoichiometry for sodium and potassium. However, controversy exists because some workers have 27 while others have not 28 demonstrated furosemide-sensitive, ouabain-insensitive fluxes of potassium in the absence of sodium or lithium ions. The possibility that blacks possess a qualitatively different furosemide-sensitive potassium efflux system is currently under investigation in this laboratory.

Conclusions

This report unequivocally confirms the presence of heightened maximal lithium-sodium countertransport rates in white essential hypertensives but not in blacks, although the mechanistic basis of the relationship of this erythrocyte cation transport function and human essential hypertension is as yet unknown. Evidence for the importance of lithium-sodium countertransport in nonerythrocyte tissues has been recently reviewed 28 and continues to accumulate, 29-31 but a role for heightened countertransport capacity in the initiation or maintenance of human hypertension has not been elucidated. The suggestion that sodium-proton exchange via the lithium-sodium exchanger may represent an inciting force in the hypertensive process is intriguing but unproved. 32 Any theory relating lithium-sodium countertransport dysfunction to hypertension will have to account for the lack of a relationship in blacks.

Even greater difficulties surround studies of sodium-potassium cotransport, as no general agreement exists on whether disorders of cotransport are present in hypertension. We cannot support previous contentions of a relationship of altered cotransport function and elevated blood pressure, 2,3,6,15 but we do note the major racial differences previously described by Garay et al. 17 Abnormalities of renal and pressor responses to sodium loading have been described in black normotensives when compared to whites. 33 If it can be demonstrated that renal tubular or vascular smooth muscle cells share the transport systems studied here in erythrocytes, it might be possible to relate racial patterns of whole-body cation handling to cellular transport dysfunction.

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