Epidemiological Studies of Sodium Transport and Hypertension

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SUMMARY Red blood cell membrane cation transport was measured in five population-based surveys and two randomized, controlled, dietary intervention studies to examine its associations with demographic, biological, and dietary variables in free-living individuals. A total of 508 individuals, 255 with high blood pressure, were studied. Both sexes, blacks and whites, and several age groups were represented. The intervention studies included short-term dietary sodium restriction in normotensive adolescents, and a 4-year multifactorial trial on weight, sodium, and alcohol in hypertensive adults. The findings from these surveys and intervention studies are summarized in this report. Sodium-stimulated lithium countertransport was significantly related to diastolic blood pressure in white adults ($r = 0.28, p < 0.001$), and to systolic blood pressure in black children ($r = 0.50, p < 0.005$) and white adolescents ($r = 0.31, p < 0.05$). Lithium countertransport was related to sex and race, but not age. Body mass index had an independent relationship with lithium countertransport in some age groups. Lithium countertransport was lower in normotensive adults than in both younger and older hypertensive adults. Lithium countertransport did not differ significantly between subjects with hypertension treated with antihypertensive medications and those with untreated hypertension. Short-term dietary sodium restriction did not influence lithium countertransport in normotensive adolescents. Long-term dietary intervention was associated with low lithium countertransport in hypertensive adults able to maintain blood pressure control without medication. These findings indicate that lithium countertransport is related to blood pressure and hypertension among free-living individuals. (Hypertension 10 [Suppl I]: I-42-I-47, 1987)

KEY WORDS hypertension • countertransport • epidemiology • intervention • diet

THE presence of abnormal cellular sodium metabolism in hypertension has been known for many years. Recent refinement of techniques to measure membrane cation transport in red blood cells, and the early findings that several of these transport systems may be altered in hypertension, has stimulated interest in the relationship between these alterations and the etiology of hypertension. Over the past several years, in a series of population-based surveys, our research group has examined red blood cell cation transport in various age, sex, and racial groups to explore the association between membrane cation transport and blood pressure (BP) among free-living individuals. A summary of the findings from these studies is given here.

Methods

Participants

Children

A total of 29 black and 41 white boys and girls (ages 11–15 years) were recruited from sixth- through eighth-grade science classes in two Chicago parochial schools. These children were participants in a larger study evaluating the relationship between urinary sodium excretion and BP.
Adolescents

Data were obtained in separate studies from 76 adolescents. The first study recruited 21 boys and 22 girls (mean age, 16 years) from a suburban Chicago public school to examine the influence of family history of hypertension on cation transport. Half had at least one parent with a current diagnosis of hypertension (n = 22). The second study recruited 21 boys and 12 girls (mean age, 16 years) from a larger group of 124 volunteers participating in an intervention study on dietary sodium and BP at a Seventh-Day Adventist boarding school. 

Young Adults

Participants were recruited through the student health service and from the ranks of students in the first 2 years of a 6-year medical school curriculum at Northwestern University, Evanston, Illinois. Volunteers were divided according to level of BP. Twenty-five men and 12 women were placed in the normal BP group; 15 men and 3 women in the high BP group.

Adults

One group of adults was made up of male employees of the Chicago People’s Gas Company recruited at the company-sponsored, periodic health examination. A total of 134 white men participated, 64 with normal BP and 70 with high BP. Twenty-three of the hypertensive subjects were receiving antihypertensive medications. Among the 47 with untreated hypertension, 24 were classified as having borderline disease based on BP readings of 140/90 through 160/95 mm Hg, and 23 as having definite hypertension with BP greater than 160/95 mm Hg.

A second group of adults was participating in a cooperative trial, in Chicago and Minneapolis, to investigate nonpharmacological control of hypertension. These men and women had hypertension, chiefly diastolic BP (DBP) averaging 90–104 mm Hg, which was controlled by medications during the previous years as part of the national cooperative Hypertension Detection and Follow-up Program (HDFP). Red blood cell cation transport was measured at the final 4-year examination in 167 of the 189 participants randomized into the trial.

Study Protocols

Surveys

All demographic and biological data were collected using standard questionnaires and procedures as described previously. BP were measured according to the HDFP protocol.

Dietary Intervention

Dietary sodium was moderately restricted through modifying cafeteria menus in 33 normotensive adolescents attending a Seventh-Day Adventist boarding school. Half the volunteers were randomized into Group 1 (n = 16); they received the control or usual diet for 24 days followed, after a 5-day interval, by the experimental sodium-restricted diet for 24 days.

Group 2 (n = 17) received the diets in the reverse order. Sodium intake was estimated from overnight urine specimens and from chemical analysis of duplicate meals.

The second intervention study was a randomized, controlled trial examining the efficacy of nonpharmacological control of BP in persons with mild hypertension previously treated with antihypertensive medications. Group 1 received dietary intervention for 2 months prior to discontinuing medication; Group 2 discontinued medication at 2 months but did not receive any intervention; Group 3 continued medication without any intervention throughout the study. Participants in Groups 1 and 2 were checked frequently and resumed taking medication if DBP rose above specifically defined levels. Intervention objectives were weight loss among overweight subjects of 10 lb or 5% of body weight, whichever was greater; reduction in sodium intake to no more than 70 mEq (1610 mg); and moderation of alcohol intake to two drinks or less per day (≤ 26 g alcohol).

Red Blood Cell Membrane Cation Transport Assays

All of the studies measured maximal rate (Vmax) of lithium efflux by sodium-stimulated lithium countertransport (LCT) in lithium-loaded cells according to the procedure developed by Canessa et al. using the nystatin-loading procedure described by Cooper et al. Maximal rates of sodium efflux by the ouabain-sensitive Na+-K+ pump and by the ouabain-insensitive fosfomycin-sensitive Na+-K+ cotransport system were measured in nystatin-treated sodium-loaded cells in two groups: adolescents divided according to family history of hypertension and adults with hypertension in the dietary intervention trial. Details of these assays are described in previous publications.

Statistical Analyses

Means were compared using two-sample two-sided t tests. When more than two groups were compared or when adjustment for covariates was required, analysis of variance and covariance were used. Chi-square tests were used to compare distributions of sex or race within various groups. Simple correlation and multiple regression analyses were also performed.

Results

Findings From Surveys: Relationship of Red Blood Cell Cation Transport to Demographic and Biological Variables

Children

The black and white schoolchildren were similar in weight, height, body mass index (BMI) (weight in kg/height in m²), and level of systolic BP (SBP; Table 1). Blacks had significantly lower plasma Na+ and K+ values (p < 0.05) and were significantly younger (p < 0.05) than whites. No significant differences were noted between the sexes within each racial group, although black girls were on average heavier than black boys. Red cell sodium concentration was signifi-
cantly higher among blacks of both sexes compared with whites \((p < 0.001)\), while LCT was significantly lower \((p < 0.005)\). These differences remained after controlling for sex \((p < 0.005)\) and for plasma Na\(^+\) and K\(^+\) \((p < 0.05)\).

LCT was positively and significantly associated with SBP \((r = 0.50, p < 0.005)\) and BMI \((r = 0.32, p < 0.05)\) among blacks, and with weight, height, and BMI \((r = 0.37, 0.26, 0.30\) respectively; \(p < 0.05)\), but not SBP, among whites. Family history of hypertension was not related to LCT in either race after matching for sex, but the sample sizes used in this analysis were too small to give adequate statistical power.

**Adolescents**

The two groups differed only in family history of hypertension. Differences in cation transport were observed between those with and without a family history of hypertension in those components determining net sodium efflux (Na\(^+\) pump and Na\(^+\)-K\(^+\) cotransport), but these differences were not significant after controlling for DBP. Mean LCT in both groups was identical \((0.26 \text{ mmol/L cells/hr})\). LCT was significantly correlated with DBP \((r = 0.45, p < 0.05)\) for those with a positive family history of hypertension, but not for those with a negative history. A sex difference in LCT was noted for the total sample, with girls having significantly lower LCT than boys.

**Young Adults**

LCT was significantly higher in the high BP group compared with the normal BP group \((p < 0.05\); see Table 1). The high BP group was also significantly older than the normal BP group \((p < 0.01)\), had a higher proportion of men, and a greater BMI. Control for possible confounding effects of age, sex, and BMI revealed that both sex \((p < 0.05)\) and group assignment \((p < 0.05)\) had independent effects on LCT. LCT was significantly lower among women, but there was no significant interaction between sex and group assignment. In the high BP group, LCT did not differ significantly between those taking antihypertensive medication \((n = 6)\) and those who were not \((n = 12)\). More individuals in the high BP group had a family history of hypertension than in the normal BP, but the higher LCT observed among those with the positive histories was not significant after controlling for BP group as-

### Table 1. Red Blood Cell Sodium Concentration and Lithium Countertransport, Blood Pressure, and Related Variables in Three Populations

<table>
<thead>
<tr>
<th>Variable</th>
<th>White</th>
<th>Black</th>
<th>Young adults</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Normal BP</td>
<td>All hypertensive</td>
</tr>
<tr>
<td>Number</td>
<td>18</td>
<td>23</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>12.7*</td>
<td>12.6*</td>
<td>12.1</td>
<td>11.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>51.3</td>
<td>51.4</td>
<td>50.7</td>
<td>55.7</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.6</td>
<td>1.6</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>20.8</td>
<td>21.0</td>
<td>21.1</td>
<td>23.2</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>107.2</td>
<td>110.9</td>
<td>107.1</td>
<td>105.0</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>69.3</td>
<td>82.2</td>
<td>77.8</td>
<td>93.1</td>
</tr>
<tr>
<td>Pulse (beats/min)</td>
<td>77.7</td>
<td>71.0</td>
<td>67.6</td>
<td>83.3</td>
</tr>
<tr>
<td>Men (%)</td>
<td>67.6</td>
<td>6.4</td>
<td>4.2</td>
<td>8.79</td>
</tr>
<tr>
<td>Whites (%)</td>
<td>91.9</td>
<td>88.9</td>
<td>83.3</td>
<td>87.7</td>
</tr>
<tr>
<td>Serum Na (mmol/L)</td>
<td>142.0*</td>
<td>142.7*</td>
<td>138.6</td>
<td>138.9</td>
</tr>
<tr>
<td>Serum K (mmol/L)</td>
<td>4.3*</td>
<td>4.2*</td>
<td>4.0</td>
<td>4.1</td>
</tr>
<tr>
<td>RBC [Na] (mmol/L cells)</td>
<td>6.75†</td>
<td>6.13†</td>
<td>8.71</td>
<td>8.79</td>
</tr>
<tr>
<td>LCT (mmol/L cells/hr)</td>
<td>0.29‡</td>
<td>0.26†</td>
<td>0.20</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Mean values are given. Rx = antihypertensive medication; BMI = body mass index; RBC = red blood cell; LCT = lithium countertransport.

Significant differences in white vs black children (two-tailed t test): \(*p < 0.05\); \(†p < 0.001\); \(‡p < 0.005\).

Significant differences among young adults: \(#p = 0.01\) (two-tailed t test); \(\|p = 0.001\) (two-tailed t test); \(\|p = 0.02\) (one-tailed t test); \(#p = 0.05\) (two-tailed t test).

Significant differences among adults: \(*p < 0.01\) vs normotensive subjects; \(††p < 0.01\) vs untreated hypertensive subjects; \(‡‡p < 0.001\) vs normotensive subjects; \(§§p < 0.05\) vs normotensive subjects.
signment. It was not possible to determine whether BP or family history was the primary factor associated with LCT in this study.

**Adults**

LCT was significantly higher among those with definite hypertension, both treated \((p < 0.001)\) and untreated \((p < 0.05)\) than those with normotension (see Table 1). Persons with borderline hypertension had mean LCT comparable to that of normotensive subjects. Correlation analysis with all subgroups except those with treated hypertension revealed a significant positive relationship between LCT and DBP \((p < 0.001)\), but not SBP. All subgroups of hypertensive persons were significantly different from normotensive subjects in age, weight, and BMI. Of these variables, only BMI was significantly correlated with both LCT and BP. Controlling for BMI in analysis of covariance did not change the significance of the relationship between LCT and BP-treatment status for the total sample. The BMI was a significant independent covariate in this relationship, but no interaction effect was found.

**Relationship of Dietary Intervention to Red Blood Cell Cation Transport**

**Normotensive Adolescents**

Both groups in this study received the experimental sodium-restricted diet, but in a different order. The groups were comparable at baseline in age, weight, BMI, SBP, and DBP. Group 2, receiving the experimental diet first, had a higher proportion of boys than girls \((12/5, \text{compared with } 9/7 \text{ in Group 1})\). Baseline LCT was slightly but not significantly higher in Group 2, reflecting the higher proportion of boys in this group. In both groups combined, baseline LCT was significantly correlated with SBP \((r = 0.31, p < 0.05)\), but not DBP. Urinary sodium excretion confirmed a reduction in sodium intake from 110 to 40 mEq with the experimental diet for both groups. BP and weight did not change significantly during the experimental periods for either group. Change in LCT was significantly correlated with change in DBP for Group 2 \((r = 0.43, p < 0.05)\) but not for Group 1; this relationship was of borderline significance when both groups were combined \((r = 0.24, p < 0.09)\).

**Hypertensive Adults**

Sodium pump activity, Na\(^+\)-K\(^+\) cotransport, and LCT did not differ significantly between the dietary intervention group (Group 1) and either of the groups not receiving intervention: Group 2, whose subjects also stopped taking antihypertensive medication, or Group 3, continuing medication (Table 2). Of the 83 participants with cation transport measurements in Group 1, 35 had not needed to reinstitute medication to achieve BP control by Year 4. LCT at Year 4 was significantly lower in this subgroup not taking medication compared with those taking medication in Group 1; differences in the other cation transport systems between these subgroups were not significant. Mean LCT for those who stopped medication in this group was 0.29 mmol/L cells/hr, within a range reported for normotensive persons. \(^{17}\) For those taking medication, mean LCT was 0.38 mmol/L cells/hr, comparable to values for Group 2 \((0.34)\) and Group 3 \((0.38)\), consisting almost entirely of participants on medication at Year 4 \((39/41 \text{ for Group 2 and } 43/43 \text{ for Group 3})\). Baseline characteristics among the three randomization groups and between those taking and not taking medication in Group 1 were comparable. Sex, race, and proportion with a family history of hypertension did not differ either among the three randomization groups or between the medication subgroups in Group 1. The effect of medication status on LCT in Group 1 participants remained significant after adjusting for age, weight, BMI, SBP, and DBP. Results of multiple linear regression revealed that for those overweight in Group 1, medication status, alcohol intake at Year 4, and changes in BMI and urinary sodium were all significantly and independently related to LCT at Year 4. The direction of the changes in BMI and urinary sodium indicated that the larger the change in these intervention variables, the lower the LCT. When the lean hypertensive subjects were included in the analysis, only the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Not taking medication</th>
<th>Taking medication</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>35</td>
<td>48</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>[Na(^+)] (mmol/L cells)</td>
<td>(8.48 \pm 2.58)</td>
<td>(8.66 \pm 1.64)</td>
<td>(8.76 \pm 2.07)</td>
<td>(9.13 \pm 1.67)</td>
</tr>
<tr>
<td>[K(^+)] (mmol/L cells)</td>
<td>(107.3 \pm 5.9)</td>
<td>(107.8 \pm 7.5)</td>
<td>(108.0 \pm 5.5)</td>
<td>(107.6 \pm 5.4)</td>
</tr>
<tr>
<td>Na(^+) pump (mmol/L cells/hr)</td>
<td>(5.16 \pm 1.88)</td>
<td>(4.88 \pm 1.51)</td>
<td>(4.88 \pm 1.34)</td>
<td>(4.55 \pm 0.99)</td>
</tr>
<tr>
<td>Na(^+) cotransport (mmol/L cells/hr)</td>
<td>(1.07 \pm 0.41)</td>
<td>(1.21 \pm 0.53)</td>
<td>(1.22 \pm 0.48)</td>
<td>(1.19 \pm 0.54)</td>
</tr>
<tr>
<td>K(^+) cotransport (mmol/L cells/hr)</td>
<td>(1.45 \pm 1.55)</td>
<td>(1.24 \pm 0.53)</td>
<td>(1.44 \pm 0.55)</td>
<td>(1.26 \pm 0.54)</td>
</tr>
<tr>
<td>Na(^+)-LCT (mmol/L cells/hr)</td>
<td>(0.29 \pm 0.13^*)</td>
<td>(0.38 \pm 0.15)</td>
<td>(0.34 \pm 0.15)</td>
<td>(0.38 \pm 0.24)</td>
</tr>
</tbody>
</table>

Values are means ± SD. LCT = lithium countertransport.

\(^{1*}\)p < 0.01, compared to those taking medication in Group 1.
ship between LCT and change in urinary sodium was changed to borderline significance.

Discussion

The findings from these studies describe red blood cell cation transport in free-living populations. Although several of the studies measured other cation transport systems, most of the data related to LCT, a system that has been suggested to function as a cellular sodium-hydrogen or sodium-sodium exchanger. The survey data indicated that LCT is significantly related to BP independently of sex and BMI in black children, adolescents, young adults, and middle-aged adults. This result is consistent with earlier reports from clinical studies showing elevated values of LCT among hypertensive individuals. and has been confirmed by more recent data showing an association between LCT and BP in two populations.

In our population-based groups, LCT was elevated 20% in hypertensive adult men and 27% in the young adults with high-normal and high BP. Values for hypertensive subjects in both age groups were similar and comparable to those for the hypertensive adults participating in the dietary intervention study. LCT was significantly higher in adults with hypertension surveyed compared with those with normal BP, although lower levels were found among persons with untreated borderline hypertension compared with those with definite hypertension. Treatment with antihypertensive medications was not associated with lower values of LCT among persons with definite hypertension.

Race, sex, age, BMI, and family history of hypertension were also examined in relation to LCT. Our data in children are in agreement with clinically based results indicating racial differences in LCT in adults with normal BP and hypertension. LCT was lower in both black boys and black girls compared with whites. A significant positive relationship between LCT and BP was also found among the black children, but not among the whites, an observation opposite to what has been reported for black and white adults.

This analysis did not reveal a clear relationship between family history and cation transport is weak and therefore difficult to demonstrate in the general population.

BMI had a significant independent relationship with LCT in children of both races, young adults, and adults. This relationship was not examined in either group of adolescents. The young adults classified with high BP had higher BMI than those with normal BP, but this difference did not contribute to the higher LCT observed in the high BP group. BMI was significantly correlated with both BP and LCT among the adults, but did not explain the difference in LCT observed between persons with normal BP and those with hypertension. Other studies also confirmed a relationship between LCT and weight and BMI.

The results from the intervention studies suggest that dietary factors may be related to LCT among hypertensive adults. LCT was significantly lower in the subgroup of hypertensive persons receiving nutrition intervention who were able to maintain normotension for a 4-year period by this means alone, compared with the subgroup also receiving nutrition intervention but requiring a return to medication to achieve normotension. LCT at Year 4 was significantly and inversely related to changes in the intervention variables, weight expressed as BMI, and sodium from baseline to Year 4 among those overweight in the intervention group. Alcohol intake at year 4 was also significantly related to LCT among both the overweight and lean hypertensive subjects in this group. These findings are suggestive of an influence of weight, sodium, and alcohol on LCT. Alternatively, it is possible that low LCT may have been present at baseline in the subgroup with hypertension whose BP was responsive to dietary intervention.

In contrast to the findings among adult hypertensive subjects, a sizable reduction in dietary sodium intake was without an effect on LCT in normotensive adolescents consuming this diet for a 3-week period; BP also did not change significantly in this study. This finding may be explained by the possibility that either sodium restriction did not influence BP or LCT, that is, normotensive values are not modifiable, or that the time period was too short for the effect of a change in sodium intake to be manifest at the membrane level. It is also possible that the sample size may have been too small to detect a significant effect of dietary sodium on either BP or LCT.

The results of the studies described here indicate that LCT may be an important factor associated with BP and hypertension. The nature of this relationship is unclear, but the association of LCT with factors related to BP such as BMI raises the possibility that LCT may be a mechanism for the development of hypertension. This possibility is supported by recent data indicating that LCT may reflect renal proximal tubular sodium reabsorption. The observation that changes in dietary factors influencing BP are also related to LCT among
adults with hypertension also suggests that LCT may be modified by environmental influences and that this may relate to BP. These findings warrant additional research regarding the role of LCT in the etiology of hypertension to increase understanding of the pathogenesis of this disease.

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