Three Red Cell Sodium Transport Systems in Hypertensive and Normotensive Utah Adults

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SUMMARY Sodium-lithium countertransport (SLC), sodium-potassium cotransport (CoT), and ouabain binding to sodium-potassium adenosine triphosphatase (Na, K-ATPase) sites were measured on fresh erythrocytes from hypertensive and normotensive Utah subjects with and without a first-degree relative with hypertension. SLC was measured as Li\(^+\) efflux into NaCl and MgCl\(_2\) media from Li\(^+\)-loaded cells (5–7 mM). CoT was measured by monitoring Na\(^+\) and K\(^+\) efflux from cells loaded to 20–30 mM Na\(^+\) and 20–30 mM K\(^+\). Ouabain binding was determined for fresh cells using \(^3\)H-ouabain.

Subjects were selected from pedigrees that showed a prevalence of hypertension. SLC was significantly elevated in 26.5% of the hypertensive subjects (p < 0.001) as well as in 12.8% of the normotensives with a hypertensive first-degree relative (p < 0.05). Although elevated SLC and decreased CoT have previously been associated with hypertension, no hypertensive subject in this study exhibited both abnormalities. All subjects with elevated SLC had normal CoT. A positive correlation between SLC and CoT was observed. Few hypertensive subjects (11.8%) had decreased CoT. In the majority of subjects studied, both SLC and CoT were normal: hypertensives 61.8%, normotensives with a hypertensive first-degree relative 61.7%, and other normotensives 58.7%. The number of ouabain-binding sites was not significantly altered among hypertensives, or their relatives, even though there was a positive correlation between SLC and the number of ouabain-binding sites.

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KEY WORDS • sodium-lithium countertransport • sodium-potassium cotransport • ouabain binding

THE development of hypertension appears to be multifactorial. Three probable factors are a genetic predisposition, obesity, and an inability to handle excessive sodium intake. Studies of sodium transport in erythrocytes of hypertensive subjects and their relatives suggest that these factors may be interrelated. Three of the sodium transport systems of red cells have been implicated.

1. Sodium-Potassium Adenosine Triphosphatase Pump (Na, K-ATPase). To date, studies have not clearly established whether there are abnormalities in this ion transport mechanism among hypertensive subjects. Wambach et al.\(^1\) found Na pump activity in erythrocytes from hypertensive subjects significantly higher than in erythrocytes from normotensive subjects; however, there was much overlap between the groups. Garay et al.\(^2\) also observed elevated Na pump activity in a few hypertensives and some of their relatives. On the other hand, no difference between hypertensive and normotensive subjects was found by two groups of investigators. Erdman et al.\(^3\) used \(^88\)Rb to mimic K\(^+\) transport and \(^3\)H ouabain binding to assess the number of Na pump sites. Cusi et al.\(^4\) measured ouabain-sensitive Na\(^+\) efflux. Studies using ouabain binding have suggested possible effects from diet and/or obesity.\(^5\)

2. Sodium-Lithium Countertransport (SLC). Erythrocytes loaded with lithium can exchange the intracellular Li\(^+\) for extracellular Na\(^+\) through the phloretin-sensitive sodium-sodium exchange system. Canessa et al.\(^6\) and Adragna et al.\(^7\) have repeatedly found significant differences between SLC in hypertensive and normotensive subjects with little overlap between the groups. They also have observed elevated SLC among some first-degree relatives of hypertensive subjects. Both Cusi et al.\(^4\) and Woods et al.\(^8\) have reported...
elevated SLC among hypertensive subjects and their children while Canali et al.⁶ found that elevated SLC was associated more with a family prevalence of hypertension than with high blood pressure per se. Williams et al.⁷ have also found significantly elevated SLC among hypertensive subjects; however, there was considerable overlap between the values for hypertensive and normotensive subjects.

3. Sodium-Potassium Cotransport (CoT). In this sodium transport system, which can be inhibited by ouabain, Na⁺ and K⁺ are simultaneously moved across the erythrocyte membrane in the same direction. Garay et al.¹¹,¹² found lower values for both the ratio of Na efflux to K⁺ influx and the magnitude of CoT in erythrocytes of hypertensive subjects and their relatives. Decreased CoT among some hypertensives has been confirmed by Cusi et al.⁴ using Dagher and Garay's method.¹³

Methods and Materials

Subjects

To investigate these three transport systems, we measured SLC, CoT, and [³H] ouabain binding to erythrocytes from hypertensive subjects, normotensive subjects with a hypertensive first-degree relative (positive family history: noted as +FH), and normotensive subjects having no first-degree relative with hypertension (−FH). All normotensive subjects reported in this study were over 30 years old. This age group was chosen because all the hypertensive subjects were over 30 and because the family history is more useful for these subjects since the parents are old enough of those prone toward hypertension to have developed the disorder.

Subjects were members of 37 Utah pedigrees, 21 prone to hypertension, seven prone to stroke, and five prone to early coronary heart disease. Spouses and four normal families provided other subjects of average risk for these health problems. The detailed methods for selecting and screening these families have been reported elsewhere.¹⁰

The 34 hypertensive subjects (17 men and 17 women) had an average age of 56 years. All had a history of essential hypertension treated with prescription medications. All but three were on medication when studied, and of those not on current medication, all had diastolic blood pressures greater than 90 mm Hg when taken six times in the sitting position during a 4-hour clinic evaluation. All hypertensive subjects had first-degree relatives with reported hypertension.

Of the 110 normotensive subjects, 47 had parents or siblings with reported hypertension. The remaining 63 normotensive subjects knew of no diagnosis or treatment for hypertension among their first-degree relatives. The + FH group of normotensives included 25 men and 22 women, with a mean age of 40 years. The −FH group included 34 men and 29 women, with a mean age of 45 years.

Blood pressure and anthropometric subject data are shown in Table 1. Sitting blood pressures were measured twice using a mercury manometer with a random zero muddler (Gelman Instrument Company, Ann Arbor, Michigan).

Laboratory Procedures

Blood (45 ml) was drawn in heparinized tubes and centrifuged at 1000 g for 7 minutes. The plasma and buffy coat were removed, and the red cells were then used for the three different sodium transport measurements.

Ouabain Binding

A 2 ml aliquot of red cells was washed three times in 4 ml of 140 mM choline chloride and resuspended in 4 ml of a buffer [140 mM NaCl, 30 mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethane sulfonic acid), 10 mM dextrose, at pH 7.4], to a final measured hematocrit of 15% to 20%. The mean corpuscular volume of the red cells after washing was within normal limits (90 ± 6 μm³, n = 49). An 800 μl aliquot of the cell suspension was incubated with 100 μl of labeled ouabain (0.25 pmol, 18 Ci/mmol) and a 100 μl aliquot of an unlabeled ouabain solution. Three concentrations

<table>
<thead>
<tr>
<th>Subject</th>
<th>Weight (kg)</th>
<th>DBP (mm Hg)</th>
<th>SBP (mm Hg)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>17</td>
<td>86.4 ± 19.5</td>
<td>81 ± 11</td>
<td>129 ± 18</td>
</tr>
<tr>
<td>F</td>
<td>17</td>
<td>80.9 ± 21.8</td>
<td>77 ± 11</td>
<td>132 ± 23</td>
</tr>
<tr>
<td>+ FH Normotensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>25</td>
<td>83.6 ± 12.7</td>
<td>74 ± 10</td>
<td>120 ± 16</td>
</tr>
<tr>
<td>F</td>
<td>22</td>
<td>68.2 ± 17.7</td>
<td>67 ± 10</td>
<td>110 ± 17</td>
</tr>
<tr>
<td>− FH Normotensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>34</td>
<td>78.6 ± 12.7</td>
<td>71 ± 7</td>
<td>116 ± 9</td>
</tr>
<tr>
<td>F</td>
<td>29</td>
<td>66.4 ± 16.4</td>
<td>70 ± 8</td>
<td>113 ± 19</td>
</tr>
</tbody>
</table>

DBP = diastolic blood pressure; SBP = systolic blood pressure; BMI = body mass index.
of unlabeled ouabain were used. The final volume of each assay suspension was 1 ml, with labeled ouabain at 0.25 nM and unlabeled ouabain concentrations of 0.5, 5.0, or 10.0 nM. Samples were incubated in a shaking water bath at 37°C ± 0.1°C for 3 hours. The cells were then washed three times in 140 mM choline chloride (4 ml) to remove unbound ouabain. A 5% solution of trichloroacetic acid (1 ml) was added to release the bound ouabain from the cells, and the sample was centrifuged at 800 g for 5 minutes. The radioactivity previously bound to the cell membrane was then assessed by mixing the 1 ml supernatant solutions with 10 ml of scintillation fluid (Beckman Ready-Solv HP, Fullerton, California) and counting the sample for 10 minutes (Beckman LC 7500 Scintillation counter, Palo Alto, California). The number of ouabain-binding sites was determined for each cell suspension from Scatchard plots. The number of binding sites per red blood cell was calculated using the following formula:

\[
\text{Sites per red blood cell} = \frac{\text{sites per volume of suspension} \times \text{Avogadro's number}}{\text{number of red blood cells per volume of suspension} \times \text{dilution factor of 0.8}}
\]

The number of cells per unit volume was determined from the hematocrit (hct) of the suspension multiplied by a factor relating the hct to the number of cells. The factor determined from Coulter Counter measurements on 54 samples was 11.3 ± 0.7 × 10⁶ rbc/mm³.

### Sodium-Lithium Countertransport and Sodium-Potassium Cotransport

The red cells not used in the ouabain-binding measurement were washed three times in 25 ml of a buffer containing 75 mM MgCl₂, 85 mM sucrose, 10 mM morpholinosulfonic acid-trisma base (Tris-MOPS, Sigma Chemical Company, St. Louis, Missouri) at pH 7.4. Then 5 ml of the red cells was incubated 3 hours at 37°C in 20 ml of 150 mM LiCl, yielding intracellular Li⁺ concentration of 5–7 mM. SLC was measured on these cells according to Smith et al.’s modification of Canessa’s method. Another 5 ml of the washed red cells was incubated for 20 hours at 4°C in a loading solution containing 150 mM choline chloride, 50 mM NaCl, 20 mM KCl, 2.5 M sodium phosphate buffer, 1.0 mM MgCl₂, 0.1 mM EGTA, and 0.02 mM paramylchomucuribenzenesulphonate (PCMBS) at pH 7.4. CoT was measured on these cells according to the method of Dagher and Garay. The intracellular Na⁺ and K⁺ concentrations after loading were Na⁺ = 25.2 ± 4.3 mM and K⁺ = 21.2 ± 7.5 mM for our laboratory. The hct of the efflux suspensions was approximately 5%. Duplicate samples were taken at 0, 1, and 2 hours. Mean corpuscular volume after PCMBS treatment was within normal limits (89 ± 4 μm³, n = 8). The mean of the Na⁺ and K⁺ efflux values was used in making the comparisons.

Student’s t test and Pearson’s correlation coefficients were calculated for statistical evaluations.

### Results

Mean values for hypertensive, + FH normotensive, and − FH normotensive subjects (Table 2) confirmed that SLC was significantly higher among hypertensive subjects (330 μmol/liter rbc·hr, p < 0.001) and + FH normotensives (283, p < 0.05) than among − FH normotensives (243). CoT was also significantly higher among hypertensives (508 μmol/liter rbc·hr, p < 0.001) and + FH normotensives (435, p < 0.05) than among − FH normotensives (357). However, the mean values of the number of ouabain-binding sites were nearly identical among the three categories of subjects.

The subjects were subdivided using the cut-off values suggested by other investigators (Figures 1, hypertensive; Figure 2, + FH normotensive; Figure 3, − FH normotensive). According to Adragna et al. and Canessa et al., SLC values greater than 400 μmol/liter rbc·hr are associated with hypertension. Garay et al. suggest that SLC values below 300 μmol/liter rbc·hr are below the lower limit of normal and indicative of hypertension. Group I included those with SLC >400, Group II included the remaining subjects with CoT <300, and Group III included individuals with both SLC and CoT within the normal range. No hypertensive person had both abnormally high SLC and low CoT. Among the 34 hypertensive subjects included in our sample, only 38.2% had values for either SLC or CoT in the range reported to be characteristic of hypertension (Figure 1). Thus, over half (61.8%) of the hypertensive subjects were “normal” for both SLC and CoT. One normotensive subject had both elevated

### Table 2. Sodium Transport Systems in Erythrocytes (mean ± sem)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sodium-lithium countertransport (μmol/liter rbc·hr)</th>
<th>Sodium-potassium cotransport (μmol/liter rbc·hr)</th>
<th>Sodium-potassium ATPase sites (sites/rbc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive</td>
<td>330 ± 23 (n = 34)†</td>
<td>508 ± 43 (n = 34)†</td>
<td>394 ± 18 (n = 30)</td>
</tr>
<tr>
<td>+ FH Normotensive</td>
<td>283 ± 15 (n = 45)*</td>
<td>435 ± 25 (n = 47)*</td>
<td>388 ± 16 (n = 45)</td>
</tr>
<tr>
<td>− FH Normotensive</td>
<td>243 ± 11 (n = 63)</td>
<td>357 ± 20 (n = 63)</td>
<td>390 ± 11 (n = 59)</td>
</tr>
</tbody>
</table>

*p < 0.05, compared to − FH normotensive subjects.
†p < 0.001, compared to − FH normotensive subjects.
**FIGURE 1.** Sodium-lithium countertransport (SLC), sodium-potassium cotransport (CoT), and ouabain binding (OB) to red cells from hypertensive subjects. Group I has an SLC >400, Group II has a CoT <300; Group III includes the remainder.

**FIGURE 2.** Sodium-lithium countertransport (SLC) sodium-potassium cotransport (CoT) and ouabain binding (OB) to red cells from normotensive subjects with a positive family history of hypertension. Group I has an SLC >400; Group II has a CoT <300; Group III includes the remainder.
SLC and low CoT (Figure 3). The frequency of elevated SLC correlated with hypertension, 26.5% among hypertensives, 12.8% among +FH normotensives, and 4.8% among − FH normotensives. An opposite trend was observed with CoT; 11.8% of the hypertensives, 25.5% of the + FH normotensives, and 36.5% of the − FH normotensives had CoT values below 300 μmol/liter rbc-hr. When all Group I subjects (Figures 1, 2, 3) were separated from the others, their mean number of ouabain-binding sites per rbc (467) was significantly higher \( p < 0.005 \) than for Group II (372) or Group III (382).

To examine relationships between the three different transport mechanisms, Pearson correlation coefficients were determined using all results from our population sample. Weak but significant correlations existed between SLC and CoT \( r = 0.269, p < 0.001 \) and between SLC and ouabain binding \( r = 0.246, p < 0.004 \). The correlation \( r = 0.506, p < 0.001, n = 140 \) between CoT and the \( \text{Li}^+ \) efflux into \( \text{MgCl}_2 \), the 'leak component' of SLC,\(^6\) is in agreement with an earlier report.\(^7\) Significant correlations were not found between CoT and ouabain binding or between the blood pressure of normotensive subjects and any of the sodium transport tests.

**Discussion**

Hypertension affects 10% of the human population; its propensity for genetic transmission has long been observed,\(^17, 18\) but no means of predicting its onset is known. Several sodium transport systems have been proposed as possible genetic markers; Na influx,\(^19\) SLC,\(^6\) and CoT" were found in the earlier study. Sodium-lithium countertransport and sodium-potassium cotransport have been measured in hypertensive and normotensive subjects from several countries, with widely discordant results (Table 3). Differences in experimental procedures can account for only part of the discordance. Both measurements have been performed on samples from subjects in Boston, Massachusetts,\(^7\) and in Milan, Italy.\(^4\) In Boston subjects,\(^6, 7\) a clear distinction was found between hypertensives and normotensives. The hypertensive subjects in Milan also had increased SLC, but the overlap with the normotensive subjects was much greater.\(^4\) Elevated SLC has also been reported in Parma, Italy,\(^9\) Copenhagen, Denmark,\(^20\) Leeds, England,\(^21\) Chapel Hill, North Carolina,\(^8\) and Chicago, Illinois;\(^22\) but only the English study found results quantitatively similar to those of Boston.

Sodium-potassium cotransport measurements by Garay et al.\(^12, 13\) in France have shown a clear distinction between hypertensive and normotensive subjects. Differences have also been reported in Italy in studies using Garay et al.'s method and in \(^8\)Rb influx studies,\(^23\) but there has been more overlap between the normotensive and hypertensive subject groups. In con-
Comparison of Sodium-Lithium Countertransport and Sodium-Potassium Cotransport

<table>
<thead>
<tr>
<th>Authors, ref (location)</th>
<th>Sodium-lithium countertransport (μmol/liter rbc·hr)</th>
<th>Na-K cotransport (μmol/liter rbc·hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypertensive</td>
<td>Normotensive</td>
</tr>
<tr>
<td>This study</td>
<td>330 ± 23 (n = 34)</td>
<td>243 ± 11 (n = 63)</td>
</tr>
<tr>
<td>Canessa et al.</td>
<td>550 ± 20 (n = 36)</td>
<td>240 ± 20 (n = 26)</td>
</tr>
<tr>
<td>Cusii et al.</td>
<td>310 ± 18 (n = 43)</td>
<td>248 ± 14 (n = 46)</td>
</tr>
<tr>
<td>Garay et al.</td>
<td>280 ± 24 (n = 18)</td>
<td>350 ± 23 (n = 38)</td>
</tr>
<tr>
<td>Duhm et al.</td>
<td>243 ± 11 (n = 63)</td>
<td>240 ± 20 (n = 26)</td>
</tr>
<tr>
<td>Clegg et al.</td>
<td>400 ± 14 (n = 14)</td>
<td>300 ± 10 (n = 10)</td>
</tr>
<tr>
<td>Cusii et al.</td>
<td>301 ± 18 (n = 45)</td>
<td>225 ± 18 (n = 24)</td>
</tr>
<tr>
<td>Clegg et al.</td>
<td>530 ± 28 (n = 75)</td>
<td>280 ± 15 (n = 38)</td>
</tr>
<tr>
<td>Woods et al.</td>
<td>350 ± 20 (n = 16)</td>
<td>170 ± 20 (n = 9)</td>
</tr>
<tr>
<td>Trevisan et al.</td>
<td>354 ± 15 (n = 70)</td>
<td>294 ± 10 (n = 64)</td>
</tr>
</tbody>
</table>

Values are means ± s.d.

*To have comparable results, the mean values were converted to μmol/liter rbc·hr using the correlations between the methods shown in their manuscript (see ref. 31).

Contrast, hypertensive subjects in Boston had a higher CoT than normotensive subjects, while Duhm et al. in Germany found no difference between the groups when measured by an equivalent of CoT. In our study, a large number of – FH normotensive subjects had low CoT. Since our experimental procedure was similar to that of Dagher and Garay’s, we can only assume that these differences are due to the populations studied.

Canessa et al. questioned whether SLC and CoT might be “two modes of operation of the same carrier protein.” Using a modification of Garay et al.’s method with intracellular Na+ and K+ of 50 mM each, Adragna et al. found a positive correlation (r = 0.53, p < 0.0005) between SLC and CoT. Cusii et al. also found a positive correlation (r = 0.48, p < 0.001) between the two tests in both hypertensive and normotensive groups even though SLC was elevated and CoT was decreased among the hypertensives. They followed the methods as proposed by Canessa et al. and Dagher and Garay. In our study of the interrelationships among these transport systems, we measured SLC, CoT, and the number of ouabain-binding sites on aliquots of red blood cells from hypertensive subjects, as well as normotensive subjects with and without a first-degree relative with hypertension. Following Dagher and Garay’s procedure, we too found a positive correlation (r = 0.269, p < 0.001) between SLC and CoT; however, this correlation does not necessarily indicate a causal relationship between the two transport systems. In fact, Canessa et al. have evidence that the two transport systems are independent since they have different affinities and respond differently to inhibitors. Our observation that only one subject (– FH normotensive) had both elevated SLC and low CoT (Figures 1, 2, 3) is in agreement with that of Cusii et al. They also observed that abnormal SLC and CoT were not present in the same subjects. Subjects with high SLC had a high number of ouabain-binding sites, perhaps indicating that in these subjects there is total elevation of Na transport. We have reported a similar elevation of both SLC and Na,K-ATPase sites among pregnant women.

The cut-off limits of >400 for SLC and <300 for CoT were suggested by others. Reference intervals or normal values for ouabain binding are not well established. A commonly used approach to setting reference intervals for laboratory tests is to determine the range that includes 95% of the reference sample. If the adult – FH normotensive subjects (Table 2) are used as the reference sample, the 95% confidence limits are 71 to 415 μmol/liter rbc·hr for SLC, 37 to 677 μmol/
liter rbc·hr for CoT, and 218 to 562 μmol/liter rbc·hr for ouabain binding; the outlying value of 1482 μmol/liter rbc·hr for CoT was excluded. Among the + FH normotensive subjects (Figure 2), six (12.8%) had SLC values greater than the upper limit of the reference interval, and only one had a CoT below the lower limit of the reference interval. Six (12.8%) of these subjects had a CoT greater than the 677 upper limit of the reference interval. Seven of the hypertensive subjects (20.6%) had SLC values greater than the reference interval, but no one had an abnormally low CoT. As might be expected, the reference interval for SLC derived from − FH normotensives (71-415) was somewhat narrower than the 95% confidence limits determined from all of the 511 normotensive adults (both + FH and − FH) analyzed to date in our laboratory:16 mean ± sd, 265 ± 105, which would give a reference interval of 55-475. Very few subjects had ouabain-binding values outside the reference interval; three − FH normotensive, four + FH normotensive, and two hypertensive subjects had more than 562 ouabain-binding sites. Only two subjects, both + FH normotensive, had fewer than 218 sites.

Canessa et al.27 recently reported the existence of a Li-K cotransport in which Li⁺ has replaced Na⁺ in the Na-K cotransport system. The correlation (r = 0.506) that we found between CoT and the efflux of Li⁺ into MgCl₂ suggests that part of this efflux that has previously been considered a leak16 may be due to Li-K cotransport.

Among our study group, SLC appears to be a better indicator of hypertension than either CoT or the number of ouabain-binding sites. However, the overlap between hypertensives and normotensive subje is with and without a first-degree relative with hypertension prevents the use of SLC as a marker for a propensity toward the development of hypertension. Pedigree analysis ruled out a simple major-gene explanation for the SLC values observed in 434 individuals in 10 hypertension-prone Utah pedigrees.28 Although SLC is clearly heritable, a multifactorial mode of inheritance is likely involved. The lack of a significant spouse-spouse correlation implies that common adult environment probably does not modify SLC. Pregnant women and adults on antihypertensive medication were not considered in the genetic analysis since pregnancy causes elevated SLC and ouabain binding26, 29 and because the effect of medication on SLC is not known.

The differences in results from various laboratories (Table 3) are disturbing. One might be inclined to attribute these differences to diverse experimental procedures at the laboratories. However, there has been sufficient exchange between our laboratory and the ones in Boston and Paris to eliminate procedural differences as the source of the discrepancies. Aliquots of the same samples measured both in our laboratory and in Canessa’s yielded similar results.14 We believe the differences in SLC and CoT may reflect differences in the study populations and, possibly, the heterogeneity of cell Na transport alterations in essential hypertension. Accumulating evidence30-38 suggests that elevated SLC and decreased CoT may identify different types of hypertension. Perhaps, as a better understanding of the interrelationships between membrane transport systems and hypertension develops, some of these tests will be of value in predicting certain types of hypertension.

Acknowledgments

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