Sodium-Lithium Countertransport and Hypertension in Rochester, Minnesota

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The objectives of the present study were to determine whether increased sodium-lithium countertransport is associated with essential hypertension in the general Caucasian population and to determine whether this association is independent of the effects of gender, age, body size, and plasma lipids. We studied 543 men and 589 women from the population of Rochester, Minnesota. Mean sodium-lithium countertransport was higher in hypertensive than in normotensive subjects in men (370±147 [mean±SD] versus 315±110 μmol/l red blood cells [RBC]/hr, p<0.001) and in women (339±114 versus 269±92 μmol/l RBC/hr, p<0.001). Interindividual differences in plasma triglycerides, body mass index (wt/[ht]^2), and plasma total cholesterol explained 13.0% of sodium-lithium countertransport variation in men (p<0.001) and 20.2% in women (p<0.001). Age did not predict additional sodium-lithium countertransport variation in either gender. Slopes of the regressions of sodium-lithium countertransport on plasma triglycerides, body mass index, and plasma total cholesterol did not differ between diagnostic groups in men (p=0.31) or in women (p=0.29). After adjustment to remove sodium-lithium countertransport variation attributable to these covariates, mean sodium-lithium countertransport remained significantly higher in hypertensive than in normotensive subjects in men (354±139 versus 319±104 μmol/l RBC/hr, p<0.01) and in women (311±103 versus 278±83 μmol/l RBC/hr, p<0.01). These findings in a large sample from Rochester, Minnesota, support the conclusions that increased sodium-lithium countertransport is associated with essential hypertension in the general Caucasian population and that this association is independent of the effects of gender, age, body size, and plasma lipids. Additional studies are necessary to establish whether sodium-lithium countertransport is an independent predictor of risk of developing essential hypertension. (Hypertension 1991;18:183–190)

Sodium-lithium countertransport has been proposed as an indicator of inherited predisposition to essential hypertension. This proposal is based on the finding of higher mean sodium-lithium countertransport in Caucasian patients with hypertension and in their young, hypertensive-prone offspring than in selected normotensive controls. However, since the samples for most previous studies were small and were ascertained through referral clinics or hospitals, their findings may not be representative of the community at large. Furthermore, many characteristics other than blood pressure differ between hypertensive and normotensive individuals, and some of these variables could account for differences in sodium-lithium countertransport. For instance, gender, age, measures of body size, and plasma lipids usually differ between hypertensive and normotensive samples, and each of these characteristics has been implicated as a source of sodium-lithium countertransport variation. Because most comparisons of sodium-lithium countertransport between hypertensive and normotensive subjects did not control for the effects of these covariates, the inference that increased sodium-lithium countertransport is associated with hypertension per se remains uncertain.

The objectives of the present study were to determine whether increased sodium-lithium countertransport is associated with essential hypertension in the general Caucasian population and to determine whether this association is independent of the effects of gender, age, body size, and plasma lipids. We studied a large sample of adults from the population of Rochester, Minnesota.

Methods

The Sample

The sample was made up of 543 men and 589 women, who were members of 283 families partici-
pating in the Rochester Family Heart Study (RFHS). Families participating in the RFHS were ascertained through households having two or more children enrolled in the public or parochial schools of Rochester, Minnesota, in January 1984. Selection of the households, recruitment of family members, and the protocol for examination of participants were described in a previous publication. All procedures involving human subjects were approved by the Institutional Review Board of the Mayo Clinic and Foundation, and subjects gave their written informed consent before participation. Between December 1984, and January 1987, a total of 2,004 family members visited our clinic to donate blood samples and undergo physical examinations. To define a sample for the present study, we excluded RFHS participants who were less than 20 years of age \( n=724 \), not Caucasian \( n=3 \), not fasting at the time of blood sampling \( n=33 \), women taking estrogen or progesterone \( n=45 \), hypertensive individuals with conditions causing secondary elevation of blood pressure \( n=24 \), or normotensive individuals with conditions causing secondary lowering of blood pressure \( n=35 \). We also excluded eight additional individuals (five men and three women) with plasma triglyceride levels above 500 mg/dl, a level more than 5 SDs above the mean for the remaining sample.

At the clinic visit, subjects had three blood pressure readings taken with a random zero sphygmomanometer (Hawksley and Sons, Ltd., West Sussex, England). Averages of the three systolic readings and the three diastolic readings for each subject were used in all analyses and are referred to hereafter simply as systolic and diastolic blood pressures. Each subject was assigned to one of three blood pressure diagnostic groups defined by the following criteria.

**Normotension** (417 men and 418 women). These subjects had never been treated with medication for hypertension, and their systolic and diastolic blood pressures were less than 140 and 90 mm Hg, respectively, at the clinic visit. None of these subjects were taking medications with blood pressure–lowering effects.

**Borderline blood pressure** (41 men and 87 women). These subjects were found at the clinic visit to have systolic blood pressure of 140 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater, but the diagnosis of hypertension had not been made previously. If the systolic or diastolic blood pressure exceeded 160 or 95 mm Hg at the clinic visit, previous readings were not recorded in the outpatient medical records in the last 5 years, or one of the two most recent readings was below 160/95 mm Hg. Six men (14.6%) and 11 women (12.6%) in this group were receiving antihypertensive drugs for problems other than hypertension (e.g., angina pectoris).

**Hypertension** (85 men and 84 women). These subjects reported a previous diagnosis of hypertension and were being treated with antihypertensive drugs or their systolic blood pressure was 160 mm Hg or greater or their diastolic blood pressure was 95 mm Hg or greater at the clinic visit and two or more office blood pressure readings were recorded in their outpatient medical records in the last 5 years, the last two of which were both 160/95 mm Hg or greater. Seventy-eight men (91.8%) and 78 women (92.9%) in this group were being treated with antihypertensive drugs.

**Laboratory Measurements**

Blood samples anticoagulated with heparin were kept at 4°C until processing for determination of erythrocyte lithium efflux. The maximum capacity for sodium gradient–dependent lithium efflux was determined using methods developed by Canessa et al. The technique uses red blood cells (RBC) loaded with lithium ions (Li+) to estimate the maximal rate of sodium-lithium countertransport as the difference between the rate of Li+ efflux into a medium containing sodium ions (Na+) minus the rate of efflux into a medium in which external Na+ has been replaced by magnesium ions. The loading procedure achieves intracellular Li+ concentrations sufficient to saturate the internal Li+ transport site and reduces the intracellular concentration of Na+ to minimize its competition with Li+ at the internal transport site. The intracellular Li+ concentration achieved in RBC after the Li+ loading procedure was measured in blood samples from 987 subjects in the present sample; the mean ± SD was 7.85 ± 0.89 μmol/l RBC. Further details of the procedures to determine RBC Li+ efflux are specified in our previous publications. A previous study of assay reproducibility indicated that 86% of variability in sodium-lithium countertransport measurements is due to interindividual differences. The coefficient of variability for assays done with fresh cells from the same individual on different days was 8.9%, and for replicate assays done on the same day, it was 7.5%. Thus, a single assay provides a reliable measure of an individual’s sodium-lithium countertransport level.

Plasma total cholesterol and triglyceride levels were measured by standard enzymatic methods using Dri-STAT reagents from Beckman Instruments, Brea, Calif. The high density lipoprotein cholesterol was determined in the plasma supernatant after precipitation with PEG-6000 of particles containing apolipoprotein B. Plasma apolipoproteins A1, AII, and E were measured by radioimmunooassay techniques previously described.

**Statistical Analyses**

A variety of standard statistical methods were used in carrying out the analyses presented in this study. The analysis of variance was used to contrast means of unadjusted raw data between men and women and among diagnostic groups within each gender, and Scheffé’s simultaneous confidence intervals were constructed for each pairwise comparison of these means. Forward, stepwise linear regression was used to identify a parsimonious set of statistically significant predictor variables that explained sodium-lithium countertransport variation in each gender. At each step of the
procedure, the maximum significance level for inclusion of a variable in the regression model was 0.05 and the minimum level for exclusion of a variable was 0.05. Analysis of covariance\textsuperscript{13} was used to evaluate whether slopes of the regressions of sodium-lithium countertransport on the identified predictor variables differed between men and women or among diagnostic groups within each gender and, when the slopes were not significantly different, to compare means of adjusted sodium-lithium countertransport between genders and among diagnostic groups within each gender. Test statistics with values of \( p < 0.05 \) were considered statistically significant; probability values appear in the text only when not given in an accompanying table.

Materials

Chemicals and biochemicals of the highest grade of purity were purchased from J.T. Baker Chemical Company, Phillipsburg, N.J., and Sigma Chemical Company, St. Louis, Mo. All solutions were prepared in deionized, double-distilled water.

Results

Descriptive Statistics

Seventy-four percent of subjects in the sample were normotensive (76.8\% of men and 70.9\% of women); 11\% had borderline blood pressure (7.6\% of men and 14.8\% of women); and 15\% were hypertensive (15.6\% of men and 14.3\% of women). The percentage of subjects who were hypertensive or had borderline blood pressure increased progressively with age in the sample (Figure 1).

Mean values of most traits differed significantly among the three diagnostic groups in each gender (Table 1). Mean age, weight, body mass index (wt/[ht]\textsuperscript{2}), plasma total cholesterol, triglycerides, and apolipoprotein E were significantly higher in hypertensive than in normotensive subjects. In subjects with borderline blood pressure, mean age, plasma total cholesterol, triglycerides, and apolipoprotein E were also significantly higher than in normotensive subjects and were not different from values in hypertensive subjects. Although most hypertensive subjects were treated with blood pressure-lowering medications (see "Methods"), their mean systolic and diastolic blood pressures were significantly higher than levels in normotensive subjects and were not significantly different from levels in subjects with borderline blood pressure, most of whom were untreated.

Mean sodium-lithium countertransport was significantly higher in hypertensive than in normotensive subjects (i.e., 55 \( \mu \)mol/1 RBC/hr higher in men and 70 \( \mu \)mol/1 RBC/hr higher in women) (Table 1). Mean sodium-lithium countertransport was slightly, but not significantly, higher in subjects with borderline blood pressure than in normotensive subjects. Within each diagnostic group, mean sodium-lithium countertransport was higher in men than in women (\( p < 0.001 \) in normotensive subjects, \( p = 0.013 \) in subjects with borderline blood pressure, \( p = 0.124 \) in hypertensive subjects); when subjects were pooled across diagnostic groups within each gender, mean sodium-lithium countertransport was 45 \( \mu \)mol/1 RBC/hr higher in all men than in all women (325±118 versus 281±99 \( \mu \)mol/1 RBC/hr, \( p < 0.001 \)).

Predictors of Sodium-Lithium Countertransport Variation

Gender accounted for 3.9\% of sodium-lithium countertransport variation in the sample (\( p < 0.001 \)). Forward stepwise linear regression identified plasma triglycerides, body mass index, and plasma total cholesterol as statistically significant predictors of sodium-lithium countertransport in men and in women (Table 2). Interindividual variation in these traits explained 13.0\% of sodium-lithium countertransport variation in men and 20.2\% in women (see \( R^2 \times 100\% \), Table 2). In both genders, plasma triglycerides entered the regression model in the first selection step and explained the largest percentage of sodium-lithium countertransport variation (9.8\% in men and 15.2\% in women). Body mass index and plasma total cholesterol entered in the second and third steps, respectively, and explained much smaller percentages of sodium-lithium countertransport variation (1.5\% and 1.7\% in men; 4.1\% and 0.9\% in women). Age, other plasma lipids, and plasma apolipoproteins did not predict additional sodium-lithium countertransport variation in either gender. Signs of the partial regression coefficients in Table 2 indicated that higher sodium-lithium countertransport was predicted in each gender by higher plasma triglycerides, higher body mass index, and lower plasma total cholesterol.

The percentage of sodium-lithium countertransport variation explained by the identified predictor traits varied among diagnostic groups within each gender (i.e., from 10.4\% to 32.0\% in men and from 13.7\% to 22.3\% in women) (Table 2). This variation among diagnostic groups reflected differences in the estimated partial regression coefficients (e.g., body mass index in men, cholesterol in women); however, these differences were not statistically significant (see analysis of covariance results be-
### TABLE 1. Characteristics of the Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diagnostic group</th>
<th></th>
<th></th>
<th></th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gender</td>
<td>Normotensive</td>
<td>Borderline</td>
<td>Hypertensive</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>Male</td>
<td>46±15</td>
<td>66±14*</td>
<td>66±11*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>46±14</td>
<td>68±11*</td>
<td>70±9*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Male</td>
<td>83±13</td>
<td>82±12</td>
<td>87±14*</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>67±13</td>
<td>70±14</td>
<td>72±15*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>Male</td>
<td>26±4</td>
<td>27±3</td>
<td>29±4*†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>25±5</td>
<td>27±5*</td>
<td>28±6*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>Male</td>
<td>190±40</td>
<td>208±37*</td>
<td>208±36*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>188±39</td>
<td>220±43*</td>
<td>225±40*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>Male</td>
<td>42±11</td>
<td>41±12</td>
<td>39±12</td>
<td>0.078</td>
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<tr>
<td></td>
<td>Female</td>
<td>52±13</td>
<td>52±11</td>
<td>50±14</td>
<td>0.372</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>Male</td>
<td>137±73</td>
<td>178±88*</td>
<td>177±70*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>109±57</td>
<td>151±68*</td>
<td>173±84*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apo AI (mg/dl)</td>
<td>Male</td>
<td>133±18</td>
<td>136±21</td>
<td>133±22</td>
<td>0.503</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>143±19</td>
<td>150±18*</td>
<td>149±22*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apo AII (mg/dl)</td>
<td>Male</td>
<td>34±5</td>
<td>34±5</td>
<td>33±5</td>
<td>0.108</td>
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<tr>
<td></td>
<td>Female</td>
<td>34±4</td>
<td>34±5</td>
<td>35±5</td>
<td>0.383</td>
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<tr>
<td>Apo E (mg/dl)</td>
<td>Male</td>
<td>5.0±2.5</td>
<td>6.3±2.7*</td>
<td>6.2±2.6*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>5.2±2.3</td>
<td>6.2±2.6*</td>
<td>6.6±2.6*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>Male</td>
<td>114±12</td>
<td>148±13*</td>
<td>143±23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>111±14</td>
<td>155±16*</td>
<td>148±28*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>Male</td>
<td>68±9</td>
<td>79±13*</td>
<td>79±11*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>66±9</td>
<td>75±12*</td>
<td>73±11*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Na⁺-Li⁺ countertransport (μmol/l RBC/hr)</td>
<td>Male</td>
<td>315±110</td>
<td>328±117</td>
<td>370±147*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>269±91</td>
<td>279±96</td>
<td>339±147†</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean±SD in 543 men (417 normotensive, 41 with borderline blood pressure, 85 hypertensive) and 589 women (418 normotensive, 87 with borderline blood pressure, 84 hypertensive). Probability value is for F tests contrasting means among diagnostic groups within each gender. HDL, high density lipoprotein; Apo, apolipoprotein; BP, blood pressure; RBC, red blood cells.

* p<0.05 pairwise contrast of mean vs. normotensive group.
† p<0.05 pairwise contrast of mean vs. borderline group.

The percentage of sodium-lithium countertransport variation explained by the predictors in each diagnostic group did not increase significantly when regression models that also included second-order effects of the predictor variables were considered (analyses not shown).

### TABLE 2. Predictors of Sodium-Lithium Countertransport

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>n</th>
<th>Partial regression coefficients</th>
<th>R²×100%</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trig</td>
<td>BMI</td>
<td>Chol</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>543</td>
<td>0.512*</td>
<td>4.22†</td>
<td>-0.424†</td>
</tr>
<tr>
<td>Normotensive</td>
<td>417</td>
<td>0.418*</td>
<td>4.42†</td>
<td>-0.414†</td>
</tr>
<tr>
<td>Borderline</td>
<td>41</td>
<td>0.536†</td>
<td>10.96‡</td>
<td>-0.074</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>85</td>
<td>0.761*</td>
<td>-0.65</td>
<td>-0.552</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>589</td>
<td>0.559*</td>
<td>4.11*</td>
<td>-0.256†</td>
</tr>
<tr>
<td>Normotensive</td>
<td>418</td>
<td>0.597*</td>
<td>3.41*</td>
<td>-0.308‡</td>
</tr>
<tr>
<td>Borderline</td>
<td>87</td>
<td>0.443†</td>
<td>3.61</td>
<td>0.099</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>84</td>
<td>0.528*</td>
<td>5.20‡</td>
<td>-0.716‡</td>
</tr>
</tbody>
</table>

R²×100% is the percentage of sodium-lithium countertransport variation explained by the predictor variables. Probability value is for regression model. Trig, plasma triglycerides; BMI, body mass index; Chol, plasma total cholesterol.

* p<0.001 for partial regression coefficient.
† p<0.01 for partial regression coefficient.
‡ p<0.05 for partial regression coefficient.
Adjusted Sodium-Lithium Countertransport

The analysis of covariance indicated that slopes of the regressions of sodium-lithium countertransport on the predictor variables (see partial regression coefficients in Table 2) did not differ significantly between men and women ($p = 0.530$) or among diagnostic groups in men ($p = 0.310$) or in women ($p = 0.29$). Consequently, we adjusted the sodium-lithium countertransport values to remove variation attributable to the predictor variables and then contrasted mean adjusted sodium-lithium countertransport between men and women and among diagnostic groups within each gender. Mean adjusted sodium-lithium countertransport remained significantly higher in men than in women ($316 \pm 101 \mu\text{mol/l RBC/hr}$ versus $289 \pm 101 \mu\text{mol/l RBC/hr}$, $p = 0.002$), and it remained significantly higher in hypertensive than in normotensive subjects in men ($354 \pm 104 \mu\text{mol/l RBC/hr}$ versus $311 \pm 103 \mu\text{mol/l RBC/hr}$, $p < 0.01$) and in women ($278 \pm 83 \mu\text{mol/l RBC/hr}$ versus $278 \pm 83 \mu\text{mol/l RBC/hr}$, $p < 0.01$). Thus, these adjustments reduced the magnitude of mean difference in sodium-lithium countertransport between men and women (from 45 to 27 $\mu\text{mol/l RBC/hr}$) and reduced the magnitude of mean difference between hypertensive and normotensive subjects in men (from 55 to 35 $\mu\text{mol/l RBC/hr}$) and in women (from 70 to 33 $\mu\text{mol/l RBC/hr}$). Mean adjusted sodium-lithium countertransport in subjects with borderline blood pressure ($317 \pm 100 \mu\text{mol/l RBC/hr}$ in men and $286 \pm 91 \mu\text{mol/l RBC/hr}$ in women) was lower than in hypertensive subjects ($p = 0.075$ in men and $p < 0.001$ in women) and was not significantly different from levels in normotensive subjects ($p = 0.908$ in men and $p = 0.238$ in women).

Figure 2 shows the frequency distribution histograms of adjusted sodium-lithium countertransport. Despite higher mean adjusted sodium-lithium countertransport in hypertensive subjects, the range of adjusted values overlapped extensively with the range in normotensive subjects and the range in subjects with borderline blood pressure.

Discussion

The present study supports the conclusions that increased sodium-lithium countertransport is associated with hypertension in the general Caucasian population and that this association is independent of the effects of gender, age, body size, and plasma lipid levels. The first conclusion is based on the finding that mean sodium-lithium countertransport was significantly higher in hypertensive than in normotensive subjects among adults sampled from Rochester, Minnesota (Table 1). The second conclusion is based on the finding both in men and in women that mean sodium-lithium countertransport in hypertensive subjects was lower than in hypertensive subjects ($p = 0.075$ in men and $p < 0.001$ in women) and not significantly different from levels in normotensive subjects ($p = 0.908$ in men and $p = 0.238$ in women).

Confidence in generalizing these results beyond the present sample is justified because of several characteristics of the sample. First, the sample was large. Second, gender- and age-specific estimates for the prevalence of hypertension and borderline blood pressure (Figure 1) were close to estimates in a sample of adults randomly selected from the population of Rochester, Minnesota, in 1986. Third, the gender- and age-specific distributions for body weight, body mass index, and plasma lipids were similar to estimates from other large samples of North American populations. Fourth, the estimates of mean sodium-lithium countertransport in normotensive and in hypertensive subjects (Table 1) were comparable with levels reported among 3,874 residents of Gubbio, Italy. Similarity between the findings in Gubbio and in Rochester especially bol-
Correlations of sodium-lithium countertransport with age, measures of body size, and plasma lipid levels have been reported in previous studies. However, because samples for these studies were small or were ascertained through referral clinics or hospitals, the role of these concomitant traits in predicting sodium-lithium countertransport in the general population has remained uncertain. Also unresolved has been the question of whether gender contributes to the prediction of sodium-lithium countertransport independent of differences in body size and plasma lipids. Of the quantitative traits measured in this study (Table 1), plasma triglycerides, body mass index, and plasma total cholesterol were identified as statistically significant predictors of sodium-lithium countertransport in both genders (Table 2); age was not an additional predictor of sodium-lithium countertransport in either gender. Variation in plasma triglycerides had the largest impact on sodium-lithium countertransport, inasmuch as it accounted for more than three times as much sodium-lithium countertransport variation as was explained by variation in body mass index or plasma total cholesterol. When effects of these traits were taken into consideration, gender remained an independent predictor of sodium-lithium countertransport since mean adjusted sodium-lithium countertransport was significantly higher in men than in women. These analyses help to sort out which concomitant traits are independent predictors of sodium-lithium countertransport in the general Caucasian population. They also emphasize the need to control for separate effects of gender and measures of body size and plasma lipids when assessing the relationship between increased sodium-lithium countertransport and hypertension, because each of these concomitants is also a correlate of blood pressure.

Because each quantitative trait identified as a predictor of sodium-lithium countertransport (Table 2) differed in its distribution among diagnostic groups (Table 1), it was logical to ask whether effects of these differences might account for significantly higher mean sodium-lithium countertransport in hypertensive than in normotensive subjects (Table 1). Adjustment to control for differences in plasma triglycerides, body mass index, and plasma total cholesterol reduced the magnitude of mean difference between hypertensive and normotensive subjects, but mean adjusted sodium-lithium countertransport remained significantly higher in hypertensive than in normotensive subjects in both genders. Because age was not a predictor of sodium-lithium countertransport, these results indicate that the association of increased sodium-lithium countertransport with hypertension is independent of gender, age, body size, and plasma lipid levels.

The small difference in mean adjusted sodium-lithium countertransport between hypertensive and normotensive subjects (i.e., less than one within-group standard deviation) and the nearly complete overlap of values between these groups (Figure 2) argue against two possibilities suggested by previous studies that did not sample from the general population and failed to control for effects of concomitant differences between hypertensive and normotensive subjects. First, the notion that a particular sodium-lithium countertransport value can serve as a "cut point" for diagnosis of hypertension or as a discrete marker of hypertensive risk is inappropriate. The distribution of sodium-lithium countertransport in the general population is continuous and without a nadir separating hypertensive for normotensive subjects (Figure 2). As is the case for other quantitative traits that are predictors of blood pressure (e.g., age, body size), any hypothesized relation between hypertensive risk and sodium-lithium countertransport is likely to be continuous and incrementally graded across the range of sodium-lithium countertransport values. Second, the notion that a pathophysiologically distinct subset of hypertensive individuals can be identified by elevated sodium-lithium countertransport levels is overly simplistic. The distribution of adjusted sodium-lithium countertransport gives no evidence of a discrete subgroup of hypertensive persons with values above the range observed in normotensive persons (Figure 2). Elevated sodium-lithium countertransport occurs more frequently, but not exclusively, among hypertensive persons. Consequently, many persons with elevated sodium-lithium countertransport do not have hypertension (Figure 2). These interpretations are consistent with the concept that most hypertension is mediated by effects of many different combinations of biochemical, physiological, and anatomic alterations, no one of which is sufficient or required for hypertension to occur.

The basis for statistical dependence of sodium-lithium countertransport on the predictor traits identified in this study is unknown. Although characteristics of the sodium-lithium countertransport phenomenon probably derive from a membrane protein, function of this transporter may be influenced by lipid composition of the RBC membrane. Because cholesterol, phospholipids, and fatty acids interchange between plasma and erythrocyte membranes and since an increase in the membrane content of cholesterol or in the ratio of saturated to unsaturated fatty acids can alter membrane fluidity, it is plausible to suggest that differences in gender, plasma triglycerides, body mass index, or plasma total cholesterol may be accompanied by variations in membrane lipid composition that, in turn, modify activity of the sodium-lithium countertransport. Identification of which membrane lipids and what protein-lipid interactions may be involved is beyond the scope of the present investigation.

Another limitation of this study is the inability to exclude antihypertensive drug therapy as a cause of increased sodium-lithium countertransport in hypertensive subjects. This possibility is a concern not only...
because most hypertensive subjects in the sample were treated but also because mean sodium-lithium countertransport was not significantly elevated in subjects with borderline blood pressure (Table 1), most of whom were untreated. Although other studies provide some reassurance in that mean unadjusted sodium-lithium countertransport was significantly elevated in untreated hypertensive persons and was not different from levels in treated hypertensive persons,16,18,29 the small number of untreated hypertensive subjects in this sample precluded our making similar comparisons. Furthermore, we cannot explain why mean unadjusted sodium-lithium countertransport was not significantly elevated in our subjects with borderline blood pressure, as has been reported by others.16,20 Given our findings, and notwithstanding results in other observational studies, longitudinal comparisons of sodium-lithium countertransport before and after treatment with antihypertensive drugs are indicated to properly exclude these agents as contributors to increased sodium-lithium countertransport.

In conclusion, the present study demonstrates that increased sodium-lithium countertransport is associated with essential hypertension in the general Caucasian population and that this association is independent of the effects of gender, age, body size, and plasma lipids. Further studies that take into account the interrelations between sodium-lithium countertransport and traits such as gender, body size, and plasma lipids that are established correlates of blood pressure will be necessary to define the independent contribution of sodium-lithium countertransport to predicting risk of developing essential hypertension.

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