Red Blood Cell Na⁺ Content is Poorly Related to Essential Hypertension and to Membrane Na⁺ Transport Abnormalities

To the Editor:

Cooper et al.¹ have recently published that "An increase in the content of sodium (in red cells from essential hypertensive patients) has been the most reproducible finding and is supported by the larger set of data." This is not only wrong, but the opposite is true (i.e., red blood cell Na⁺ content has been found normal in most, if not all, essential hypertensive patients studied) (see References 2–4). Indeed, Wesels and Zumkley² needed to increase the number of (untreated) hypertensive patients studied to 295 to obtain statistically significant results (12% increase in mean Na⁺ content with a large overlap between hypertensive and normotensive subjects). The small relevance of sodium content is further illustrated by a recent study of 127 French urban men where blood pressure was not correlated with erythrocyte Na⁺ content.³

Cell Na⁺ content is the final resultant of the activity of all membrane Na⁺ transport systems. In human red blood cells, Na⁺ content simply depends on the balance between Na⁺ entry by passive permeability (Na⁺ leak) and active Na⁺ extrusion by the Na⁺-K⁺ pump. Interestingly, most red blood cell Na⁺ transport abnormalities in essential hypertensive patients are unable to modify erythrocyte Na⁺ content because they affect vestigial transport systems or are compensated by the pump (Table 1).

Table 1 shows that the most frequent red blood cell abnormalities affect vestigial transport systems (i.e., the one-to-one Na⁺-Na⁺ exchange [physiological counterpart of the Na⁺-Li⁺ countertransport], an Na⁺ carrier unable to perform net Na⁺ fluxes, and the Na⁺-K⁺-Cl⁻ cotransport system, a transport system catalyzing small Na⁺ fluxes which are near to equilibrium under physiological conditions). Regarding the Na⁺-K⁺ pump, the decreased affinity for internal sodium [R(–) abnormality] is compensated by an increased maximal pump rate [V(+) abnormality], ensuring normal Na⁺ efflux under physiological conditions. Another pump abnormality (i.e., decreased maximal pump rate [V(–)] in Table 1) was found in red blood cells from adult spontaneously hypertensive rats and rats where blood pressure was not correlated with erythrocyte Na⁺ content.⁴

In conclusion, the extensive investigation of Na⁺ transport systems in erythrocytes from essential hypertensive patients supports the idea that none of the red blood cell abnormalities (and even less the "increased red cell Na⁺ content") is a common denominator of primary hypertension. Conversely, it appears that "essential hypertension" is a common denominator of very different diseases at the molecular level. Most of the red blood cell Na⁺ transport abnormalities in essential hypertensive patients are unable to modify erythrocyte Na⁺ content because they affect vestigial transport systems or are compensated by the pump. Thus, red blood cell Na⁺ content is poorly related to essential hypertension.

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References


Table 1. Frequencies of Red Blood Cell Na⁺ Transport Abnormalities in Caucasian Hypertensive Patients

<table>
<thead>
<tr>
<th>Transport pathway</th>
<th>Abnormality</th>
<th>Frequency*</th>
<th>RBC Na⁺ content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺-Li⁺ countertransport</td>
<td>V(+)</td>
<td>20–50%</td>
<td>normal</td>
</tr>
<tr>
<td>Na⁺-K⁺-Cl⁻ cotransport</td>
<td>V(+)</td>
<td>30–50%</td>
<td>normal</td>
</tr>
<tr>
<td></td>
<td>R(–)</td>
<td>20–40%</td>
<td>normal</td>
</tr>
<tr>
<td>Na⁺-K⁺ pump</td>
<td>R(–) V(+)</td>
<td>5–15%</td>
<td>increased</td>
</tr>
<tr>
<td></td>
<td>V(–)</td>
<td>&lt;10%</td>
<td>increased</td>
</tr>
<tr>
<td>Na⁺ leak</td>
<td>increased</td>
<td>10–30%</td>
<td>normal or increased</td>
</tr>
</tbody>
</table>

*Data from References 3,4,7–12.


Acknowledging that this literature is most accurately characterized as inconsistent at the present time, interesting findings have emerged among blacks. First, there appears to be firm evidence that blacks of West African ancestry have higher mean levels of Na+ than do persons of European extraction. Second, the relation between red blood cell Na+ and blood pressure appears to be more important among blacks than whites, based on the data bases available at this time. For example, in a recent study comparing US whites, US blacks, and West African blacks living in the US, we noted a correlation of approximately 0.3 between red blood cell Na+ and blood pressure among both groups of blacks, while a weak, nonsignificant association was observed among the whites. Blacks were also found to have a borderline lower rate of sodium-hydrogen exchange (p = 0.08) in agreement with previous work on differences in sodium exchange in blacks and whites.

Finally, we agree with Garay that compensatory mechanisms will tend to return cell sodium toward normal levels in hypertension. Research into the etiology of high blood pressure has proven difficult precisely because the abnormality is a disorder of control mechanisms; many compensatory mechanisms come into play in an effort to realign the system. However, an average increase of cell sodium in the range of 10%, which has been demonstrated in many but not all reported studies, may have physiological importance. If real, these small deviations from normal, which we measure with imprecise tools, may provide clues about the nature of the underlying abnormality. Although the current body of evidence is indeed inconsistent, we remain convinced that high cell sodium may be one of the manifestations of this disease process.

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**References**


Red blood cell Na+ content is poorly related to essential hypertension and to membrane Na+ transport abnormalities.
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