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, Wessels 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 vesigial transport systems or are compensated by the pump (Table 1).

Table 1 shows that the most frequent red blood cell abnormalities affect vesigial 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⁺ pump 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(-)] is compensated by an increased maximal 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 with reduced renal mass (due to the presence of circulating endogenous "digitalislike" factors, see References 13-15). This results in a decreased pump activity (under physiological conditions) and increased erythrocyte Na⁺ content. The work of Rygelski et al.⁴ suggests that a very small fraction of essential hypertensive patients may have such "decreased pump/increased cell Na⁺ content." In addition to the pump, the second transport pathway controlling red blood cell Na⁺ content is the membrane Na⁺ leak. However, 50-70% of the hypertensive patients with increased membrane Na⁺ leak have normal red blood cell Na⁺ contents due to the presence of compensatory increases in pump function.⁵ Only the remaining "Leak (+)/Pump (-)" hypertensive patients (without pump compensation) exhibit increased red blood cell Na⁺ contents.³ This is a small Na⁺ content increase that affects no more than 10% of hypertensive patients.⁶ Therefore, red blood cell Na⁺ content is a poor reflection of membrane Na⁺ transport abnormalities in primary hypertension.

One word needs to be said about the frequency of red blood cell abnormalities summarized in Table 1. These values are representative of Caucasian hypertensive patients from Mediterranean countries: France,² Spain,³ and Italy,⁵,⁶ and from Quebec.¹ However, by unknown reasons a high fraction of Caucasian hypertensive patients with increased Na⁺-Li⁺ countertransport or increased Na⁺-K⁺ pump were found in the United States (between 50-80%) (for review see Reference 12). Besides methodological problems let me suggest that this can reflect population differences. However, concerning the "increased" red cell blood Na⁺ contents in essential hypertension,¹ no remarkable population differences were found by Canessa et al.² in the United States with respect to France and other countries. Indeed, these authors were unable to detect any abnormality in the erythrocyte Na⁺ contents of American hypertensive patients.²

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 vesigial 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
Letters to the Editor


The following is in response to:
The Editor:

Despite considerable effort, it has proven difficult to establish consistent relations between cell cation metabolism and high blood pressure. Dr. Garay is perhaps correct that we overstated the case regarding the strength of the association between increased intracellular sodium (Na⁺) and blood pressure. Reviewing this question in the light of more recent work, it would appear that although a number of studies do report higher Na⁺ in blood cells of hypertensive patients, almost as many negative reports have also been published. Our previous conclusions were heavily influenced by the procedures for carrying out the meta-analysis are not provided, and we are not able to verify these findings. Unfortunately, the individual studies included in this review and the procedures for carrying out the meta-analysis are not provided, and we are not able to verify these findings. Among the individual large studies, the outcome has likewise been mixed. It is in fact curious that case-control studies have detected higher Na⁺ more often than population-based surveys. A study of 1,445 Japanese men, published to date only in abstract form, has reported a significant association between blood pressure and red blood cell Na⁺. On the other hand, the community survey in Gubbio, Italy, detected only a weak association between blood pressure and Na⁺, and this finding was restricted to older women.

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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Red blood cell Na+ content is poorly related to essential hypertension and to membrane Na+ transport abnormalities.
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Hypertension. 1990;15:234-236
doi: 10.1161/01.HYP.15.2.234

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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