Perspectives

Racial Differences in Ion Regulation and Their Possible Links to Hypertension in Blacks

Abraham Aviv and Jeffrey Gardner

To illuminate cellular processes that cause essential hypertension, it is important to distinguish genetic factors in the predisposition to this disease from the environmental elements that facilitate its expression. Two major approaches have been undertaken to attain this goal. One approach is to study various cellular parameters in normotensive first-degree relatives of patients with essential hypertension, and the other is to examine cellular differences between blacks and whites, because both familial history of essential hypertension and racial extraction play a role in the predisposition to this disease. The focus of this communication is on the second approach, namely the cellular mechanisms that may be responsible for the greater prevalence of essential hypertension in blacks. Inasmuch as blacks in the United States manifest a higher frequency of essential hypertension than whites, particularly the salt-sensitive form of the disease, it is likely that elucidating the mechanisms responsible for the racial differences in ion transport will also unravel the specific genetic factors responsible for at least some aspects of this disease.

Because blood is easily accessible, most investigations have used blood cells to identify and gain insight into alterations of cellular regulation of ions in essential hypertension. Underlying these studies are two major assumptions: 1) alterations in blood cells represent a generalized phenomenon, and 2) if similar alterations are present in specific target cells, such as vascular smooth muscle cells (VSMCs) or the renal tubular epithelium, they can predispose or contribute to blood pressure elevation in susceptible individuals. These assumptions have not been rigorously tested. Erythrocytes and to a lesser extent leukocytes have been main targets of research.

In addition to examining blood cells, our group has investigated cultured skin fibroblasts from normotensive and hypertensive blacks and whites. This approach has been undertaken to eliminate the effects of circulating factors that may exert their lasting influence on blood cells. Thus, if observed differences in cellular parameters in cultured cells between normotensive and hypertensive persons, or blacks versus whites, would represent variations in the genetic makeup of these cells that may account for the increased propensity to develop essential hypertension. However, as in studies with blood cells, caution must be exercised in extrapolating findings in cultured skin fibroblasts to target cells that are involved in the pathophysiology of essential hypertension.

In the following narrative we will 1) review the differences between blacks and whites in the regulation of ions at the cellular level, 2) present evidence showing that a special relation exists between agonist-mediated cytosolic free Ca\(^{2+}\) response and the Na\(^+\)-H\(^+\) antiport (exchange) and the role of the parathyroid hormone (PTH) in regulating these variables, 3) propose mechanisms by which the link between the Na\(^+\)-H\(^+\) antiport and Ca\(^{2+}\) may play a pivotal role in essential hypertension, and 4) suggest that alteration in the activity of the Na\(^+\)-H\(^+\) antiport and agonist-mediated Ca\(^{2+}\) response in specific target cells underlie the predisposition of American blacks to essential hypertension.

Racial Differences in Na\(^+\) Pump and Its Enzymatic Analogue—Sodium-Potassium Adenosine Triphosphatase

In 1968 Balfe and coworkers described a black family with reduced erythrocyte sodium-potassium adenosine triphosphatase (Na\(^+\),K\(^+\)-ATPase) activity and in 1983 Beutler et al demonstrated that the
activity of the enzyme was influenced by ethnic extraction. These observations have been confirmed by our group and others. The lower Na⁺,K⁺-ATPase activity in blacks apparently relates to a lower Na⁺ pump density and is associated with a higher red blood cell Na⁺ concentration. Not all investigators agree with these findings. Wood et al did not identify increased Na⁺ concentrations in erythrocytes from blacks, and Woods et al demonstrated no racial differences in the ouabain-sensitive Rb⁺ uptake (the Na⁺ pump) of these cells. The latter study cannot be interpreted because the transport medium contained only 3 μM Rb⁺ and no K⁺. Rb⁺ concentration of 3 μM is insufficient for maximal activation of the Na⁺ pump. Others measured the ouabain-sensitive Na⁺ efflux in erythrocytes that were loaded with Na⁺ using p-chloromercuribenzenesulfonic acid. These measurements revealed no racial differences in the maximal activity of the Na⁺ pump. As noted by the authors, the use of p-chloromercuribenzenesulfonic acid could alter the measurements. The consensus emerging from most studies suggests, however, that erythrocytes from blacks have a lower Na⁺,K⁺-ATPase activity and a higher Na⁺ concentration than erythrocytes from whites.

Racial Differences in Na⁺-K⁺ Cotransport and Li⁺-Na⁺ Countertransport

Racial differences in erythrocytes have also been shown in the efflux component of the Na⁺-K⁺ (2 Cl⁻) cotransport. Studies in the United States have demonstrated a lower activity of this transport modality in blacks than in whites. Furthermore, in a study by Tuck et al hypertensive whites showed increased cotransport activity as compared with normotensive whites, whereas hypertensive blacks showed a lower activity of this transport than normotensive blacks. Similar observations were noted by others. It appears, however, that this transport system manifests geographical variability; in Europe it has been shown to be lower and in the Ivory Coast it was shown to be higher in hypertensive whites. Garay et al have reported decreased cotransport activity in both normotensive and hypertensive blacks in the Ivory Coast, but Davidson and coworkers could not substantiate these findings in South African blacks. Thus, differences in patient populations, as well as geographical and technical factors may contribute to the diversity of results obtained for erythrocyte Na⁺-K⁺ cotransport.

More consistent observations have been noted with respect to erythrocyte Li⁺-Na⁺ countertransport. Although manifesting a substantial degree of variability, the Li⁺-Na⁺ countertransport appears to be more active in the erythrocytes of white hypertensive than in white normotensive persons. In contrast, both hypertensive and normotensive blacks appear to exhibit a lower activity of the erythrocyte Li⁺-Na⁺ countertransport as compared with their white counterparts.

Taken together, results based on studies using red blood cells strongly suggest the existence of racial differences in the cellular regulation of Na⁺ and K⁺. However, it is uncertain whether these differences relate to variations that are innate to the structure of erythrocytes or the effects of circulating factors, or both. Furthermore, the role of Li⁺-Na⁺ countertransport in the cellular regulation of Na⁺ is poorly understood. If this system represents a Na⁺-Na⁺ exchange, it would not affect the overall cellular Na⁺ metabolism except that its elevation would indicate a higher cellular Na⁺ turnover. Aronson and coworkers demonstrated a lower activity of this transport system in blacks than in whites.6-20 Furthermore, in studies showing that stimulation of PK-C-dependent and PK-C-independent pathways, both of which are modulated by Ca²⁺.

The Na⁺-H⁺ antiport has been the subject of intense investigation within the last decade. This transport system participates in multiple cellular processes, which include cellular Na⁺ and volume regulation, cytosolic pH (pH) control, platelet function, mitogenic and growth responses, and Na⁺ reabsorption by the renal tubules (for reviews, see References 38 and 39). It is activated by diverse agonists including vasoactive agents and growth factors. Agonist-mediated activation of the Na⁺-H⁺ antiport occurs through protein kinase C (PK-C)-dependent and PK-C-independent pathways, both of which are modulated by Ca²⁺.

Although the role of agonist-mediated stimulation of the Na⁺-H⁺ antiport in cellular physiology is not fully delineated, it appears that activation of the Na⁺-H⁺ antiport functions as a negative feedback that attenuates the agonist-mediated rapid increases in Ca²⁺ (Ca²⁺ transients). This conclusion is derived from studies showing that stimulation of PK-C-dependent and PK-C-independent pathways results in the blunting of agonist-mediated Ca²⁺ transients, Ca²⁺ influx, amplitude of Ca²⁺-dependent vascular contractility, and the magnitude of platelet activation, whereas their inhibition results in exaggeration of these effects. The work by Siffert and Akkerman does not support this concept, inasmuch as it suggests that activation of
the Na⁺-H⁺ antiport is a prerequisite for thrombin-induced Ca²⁺ mobilization in platelets. Others have challenged this idea. In the VSMC, altered Ca²⁺ modulates agonist-mediated activation of the Na⁺-H⁺ antiport. Studies by our group (Reference 40 and unpublished data) show that a rise in Ca²⁺ can directly activate the Na⁺-H⁺ antiport in these cells. Whether activation of the Na⁺-H⁺ antiport is a prerequisite for agonist-induced rise in Ca²⁺ or is the result of such a rise, it is expected that agonist-mediated elevation of Ca²⁺ would be accompanied by increased Na⁺-H⁺ antiport activity. Moreover, increased responsiveness to agonists that exert their effect through Ca²⁺ would be expressed by a hyperactive Na⁺-H⁺ antiport.

Na⁺-H⁺ Antiport, Ca²⁺, and Essential Hypertension

We have proposed a novel hypothesis for the etiology of essential hypertension. Central to this hypothesis are the concepts that 1) both the salt-sensitive and the salt-resistant forms of essential hypertension are expressions of increased response to agonists that exert their effect through the Ca²⁺ messenger system; 2) elevated Ca²⁺, which reflects this hyperresponsiveness, is associated with increased Na⁺-H⁺ antiport activity; and 3) the difference between the salt-sensitive and salt-resistant forms of essential hypertension relates to the extent of involvement of particular target cells.

Increased responsiveness to agonists of VSMCs of resistance arteries could result in two major effects. First, these vessels would exhibit increased vasoconstriction. Second, they may demonstrate increased thickening of the tunica media resulting from hypertrophy or hyperplasia of the vascular smooth muscle, inasmuch as the mitogenic and growth responses are associated with increased Na⁺-H⁺ antiport activity. Such effects are likely to increase the peripheral vascular resistance because of narrowing of the vascular lumen.

Salt-sensitive essential hypertension is postulated to occur when agonist-mediated elevation of Ca²⁺ and activity of the Na⁺-H⁺ antiport are exaggerated not only in VSMCs but also in renal cells. At the level of the juxtaglomerular cells, because of hyperresponsiveness to agonists, increased Ca²⁺ would retard renin release (for review, see Reference 63), whereas in the renal proximal tubule it would augment Na⁺ reabsorption due to hyperactivity of the Na⁺-H⁺ antiport, which is a major element in Na⁺ reabsorption at this level of the tubule. Thus, salt-sensitive essential hypertension is expected to be associated with a low plasma renin activity not only because of expansion of the extracellular fluid volume, if it occurs, but also because of elevated Ca²⁺ at the level of the juxtaglomerular cells.

The key element in our hypothesis is the increased responsiveness of specific target tissues of hypertensive individuals to agonists exerting their cellular effect through the Ca²⁺ messenger system and the Na⁺-H⁺ antiport. Whether a rise in Ca²⁺ can directly stimulate the Na⁺-H⁺ antiport, or a higher activity of the Na⁺-H⁺ antiport can attenuate the agonist-mediated Ca²⁺ transients are issues not addressed by this thesis. The Ca²⁺ transient is an in vitro phenomenon. In vivo, cells are subjected to fluctuating levels of multiple agonists; such a condition would be expressed by oscillating levels of Ca²⁺, the mean values of which are expected to be higher in essential hypertensive individuals.

Parathyroid Hormone and Essential Hypertension

Recently, it has been shown that PTH inhibits the Na⁺-H⁺ antiport in the renal proximal tubule. The hormone also exerts vasorelaxing and hypertensive effects that are likely to be mediated via cyclic adenosine monophosphate–induced lowering of Ca²⁺ in VSMCs. Hypertension in primary and secondary forms of hyperparathyroidism is probably related to other metabolic complications associated with these conditions. Thus, elevated levels of PTH in some patients with essential hypertension may indicate a compensatory response that is particularly important in salt-sensitive hypertensive persons. In these individuals higher PTH levels would not only counteract the vasoconstrictive process, but also attenuate the augmented Na⁺ reabsorption associated with a hyperactive Na⁺-H⁺ antiport in the renal proximal tubule.

Cellular Mechanisms for Essential Hypertension in Blacks

Several characteristics of ion metabolism that distinguish blacks from whites in the United States provide clues for the underlying predisposition of the former group to essential hypertension. As compared with whites, blacks exhibit low plasma renin activity, salt sensitivity, and higher PTH levels. Moreover, hypertensive blacks exhibit a further increase in PTH levels with a high salt intake. These observations suggest that salt sensitivity in blacks may relate to different cellular regulation of Na⁺ and Ca²⁺. Recently our group demonstrated that the Na⁺ turnover (i.e., efflux and influx) is higher in serially passed skin fibroblasts from blacks than whites and that this difference is probably related to an augmented activity of the Na⁺-H⁺ antiport. Moreover, fibroblasts from blacks exhibit hyperresponsiveness to serum stimulation as compared with fibroblasts from whites. This increased responsiveness is associated with increased magnitude of Ca²⁺ transients and accelerated Ca²⁺ efflux. Because such observations were made in serially passed cells, they suggest that the racial differences are innate to the genetic makeup of the fibroblasts. Similar differences, if they occur in the renal tubular epithelium and VSMCs, can explain the predisposition of blacks to the salt-sensitive form of essential hypertension. In this regard, Livne et al by using the electronic cell sizing technique, showed that platelets of hypertensive whites manifest a greater volume change asso-
associated with Na+ propionate treatment. They suggested this reflects increased Na+-H+ antiport activity. Such a finding awaits confirmation by direct measurements of the Na+-H+ antiport.

One possible element that can provide a link between increased Na+-H+ antiport activity in fibroblasts from blacks with the lower Na+,K+-ATPase activity in their erythrocytes is the Na+ transport inhibitory factor of hypothalamic origin, which has been postulated to inhibit the Na+,K+-ATPase in a variety of cells (for review, see Reference 86). It has been suggested that the circulating levels of this factor are primarily elevated in salt-sensitive individuals. Thus, although increased Na+-H+ antiport activity and hyperresponsiveness to agonists in blacks may relate to their cellular makeup, the lower erythrocyte Na+,K+-ATPase activity in blacks could result from the lasting effect of higher levels of the circulatory inhibitor of Na+,K+-ATPase.

If racial differences in the cellular regulation of Na+ and Ca2+ are the underlying causes for increased incidence of essential hypertension in blacks, why are not all American blacks hypertensive? By categorizing individuals as hypertensive or normotensive, the systemic blood pressure is treated as a discontinuous entity, whereas in reality it is a variable with a continuous distribution. Thus, specific alterations in Na+ and Ca2+ regulation by themselves may be insufficient to produce essential hypertension in many individuals, as defined by present criteria. Rather, they are associated with a shift of the blood pressure profile toward higher levels within the so-called normotensive range, or they lower the threshold for its further elevation. Similar considerations should be applied with respect to subjects with a strong family history of essential hypertension; as a group, they manifest alterations in various electrolyte transport systems, which are similar to those of hypertensive individuals, yet their blood pressure levels may fall within the defined normotensive range. However, the profile of the distribution of blood pressure in this population is likely to be shifted in the direction of a higher blood pressure.

In conclusion, investigations using red blood cells show that differences exist between blacks and whites in several transport processes of Na+ and K+. These include the Na+,K+-ATPase, the Na+-K+ cotransport, and Li+-Na+ countertransport. Mechanisms responsible for racial differences in the latter two ion transport systems and their contribution to the predisposition of blacks to essential hypertension are poorly understood. The lower Na+,K+-ATPase activity in erythrocytes from blacks may indicate the lasting effect of a circulating factor that inhibits this enzyme. This contention is supported by findings that as a group blacks manifest several characteristics suggestive of salt sensitivity, a condition in which the levels of this factor are expected to be elevated. Cultured skin fibroblasts from blacks demonstrate increased Na+-H+ antiport activity and augmented response to factors in the serum that raise Ca2+. If similar hyperresponsiveness to agonists in the serum is also present in renal cells and VSMCs, it could provide one mechanism for the predisposition of blacks to salt-sensitive essential hypertension. However, in the final analysis, the underlying causes for essential hypertension in blacks in the United States will be delineated only by a direct examination of the behavior of specialized cells that are involved in the pathophysiology of this disease.

References


**KEY WORDS** • race • sodium-potassium cotransport • sodium-potassium ATPase • lithium-sodium countertransport • sodium-hydrogen antiporter
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