Sodium Transport and Hypertension

Where Are We Going?

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The principal difficulty in your case, remarked Holmes, . . . lay in the fact of there being too much evidence. . . . Of all the facts which were presented to us we had to pick just those which we deemed to be essential and then piece them together in their order, so as to reconstruct this very remarkable chain of events.

SIR ARTHUR CONAN DOYLE
The Naval Treaty

The idea that high salt intake plays a key role in the development of "essential" (or "primary") hypertension was first suggested 80 years ago. Since then, numerous epidemiological and experimental observations and therapeutic maneuvers (i.e., low sodium diets and treatment with natriuretic agents) have provided ample support for the view that Na\(^+\) plays a role in the etiology of hypertension. Indeed, while the data in any one of these areas may not be conclusive, taken together, these three more-or-less independent approaches seem to provide compelling evidence that dietary Na\(^+\) is an important factor in the etiology of essential hypertension. The mechanism by which Na\(^+\) actually leads to the elevation of blood pressure is currently under intensive investigation.

Genetic factors also contribute critically to the development of hypertension both in animal models and in humans. Renal transplant studies in several rat models demonstrate that the genetic defects are expressed as defects in renal function and that the hypertension "goes with the kidneys." Recent observations in humans raise the possibility that the genetic defect in human essential hypertension may also be expressed as a malfunction of the kidneys: the blood pressure may rise (producing a pressure natriuresis) when the kidneys are otherwise unable to excrete the Na\(^+\) load with which they are presented. Thus, not surprisingly, the pathophysiology of hypertension focuses on the interrelationship between the kidneys and the cardiovascular system, and on fluid and electrolyte metabolism. The kidneys are the end-organs that normally control Na\(^+\) and water balance and thereby influence the hemodynamic status of the body.

In recent years a major effort has been made to identify possible genetic markers, such as defects in Na\(^+\) transport, that might be useful for 1) identifying salt-sensitive individuals or those predisposed to the development of essential hypertension, and 2) elucidating the underlying pathophysiological basis of the disease. This approach was fueled by the initial observations that red blood cell (RBC) and white blood cell (WBC) Na\(^+\) content was increased in many individuals with essential hypertension. These cells are conveniently studied, and intracellular electrolyte composition can be readily and reliably measured without contamination by extracellular electrolytes. Since many of the Na\(^+\) transport mechanisms that are present in kidney cell membranes (such as Na\(^+\) + K\(^+\) cotransport and Na\(^+\) pumps) are also present in RBC and WBC membranes, much attention has recently been devoted to the study of Na\(^+\) transport in RBCs and WBCs. Moreover, it seems reasonable to expect that genetic defects in electrolyte transport might be present in many tissues.

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Sodium Transport Mechanisms

Intracellular Sodium Concentrations: Red and White Blood Cells

A more direct approach to the elucidation of the role of Na\(^+\) transport defects in essential hypertension might be the study of intracellular Na\(^+\) concentrations ([Na\(^+\)]\(_m\)) in kidney cells, sympathetic neurons, or vascular smooth muscle cells. However, these cells are not normally accessible in humans, nor is it as easy to measure the intracellular electrolyte concentrations in these cells without extracellular contamination. Therefore, RBC and WBC studies have served as a convenient substitute — on the assumption that the transport defects may be generalized.

Numerous observations on the Na\(^+\) content of RBCs and WBCs from hypertensive patients and normotensive control subjects have been published in recent years. Those published before 1983 were reviewed by Parker and Berkowitz\(^{14}\) and by de Wardener and MacGregor.\(^{14}\) Several additional studies have recently been published — some of them in this journal. The WBC studies and many, but not all, of the RBC studies indicate that, on the average, [Na\(^+\)]\(_m\) is significantly higher in patients with essential hypertension than in normotensive individuals. Some hypertensive patients were found to have an unusually high RBC [Na\(^+\)]\(_m\) level, even in studies in which the mean [Na\(^+\)]\(_m\) values for hypertensive patients and normotensive subjects were not significantly different.\(^{15}\) While many hypertensive patients have RBC [Na\(^+\)]\(_m\) levels within the normal range, the RBC [Na\(^+\)]\(_m\) distribution curve for the hypertensive patients appears to be skewed toward higher [Na\(^+\)]\(_m\) values.\(^{16, 17}\)

Some normotensive first-degree relatives of hypertensive patients also have high [Na\(^+\)]\(_m\), as compared to normotensive individuals with a negative family history.\(^{16, 20}\) This raises the possibility that some changes in Na\(^+\) metabolism may be detectable in presumptively prehypertensive persons; but, it also indicates that there is no direct relationship between [Na\(^+\)]\(_m\) and blood pressure. Furthermore, high RBC [Na\(^+\)]\(_m\) has been observed in patients with other diseases, as well: for example, in patients with uremia,\(^{21}\) where it might be related to an elevation of blood pressure,\(^{22}\) in those with hypokalemic conditions, and with inherited hemolytic anemias or muscular dystrophy.\(^{14}\) Despite these complications, the fact that many individuals with essential hypertension, as well as some of their normotensive offspring, have high RBC and WBC [Na\(^+\)]\(_m\) may indicate that there is a widespread Na\(^+\) transport defect in at least a subpopulation of the patients we now class as those having essential hypertension.

The possibility that [Na\(^+\)]\(_m\) is elevated in various types of cells in hypertensive patients is particularly intriguing; such a defect in vascular smooth muscle cells could promote Ca\(^2+\) entry and thereby help to explain the increased vascular tone and reactivity that produces the elevated blood pressure.\(^{23, 24}\) Thus, it has seemed logical to try to elucidate the mechanism(s) that gives rise to the increased [Na\(^+\)]\(_m\). Moreover, many investigators have assumed that this may lead us to the genetic defect that appears to be responsible for the hypertensive process. Consequently, the study of ion (especially Na\(^+\)) transport processes in relation to hypertension has blossomed in the past few years, and recent issues of Hypertension have, appropriately, contained many reports on this subject; a number of them are mentioned below.

What Causes the Intracellular Sodium Concentration to Rise?

Numerous mechanisms are involved in the movements of Na\(^+\) across the plasma membranes of various cells, and a defect or alteration in any one of them could potentially affect [Na\(^+\)]\(_m\). Passive movements, facilitated diffusion, and active transport processes have all been implicated in the pathogenesis of hypertension, and each will be discussed in turn.

Increased Passive Entry of Sodium into Cells

1. Sodium-Selective Channels. Entry mediated by Na\(^+\)-selective channels such as those sensitive to tetrodotoxin or amiloride could raise [Na\(^+\)]\(_m\). However, human RBCs are not known to possess such channels. Moreover, no defects of Na\(^+\) channels in other cells that might lead to a secondary increase in RBC [Na\(^+\)]\(_m\), such as defects in kidney tubule cells or vascular smooth muscle cells, have been reported.

2. Nonspecific Leak Pathway. Increased Na\(^+\) entry via a nonspecific "leak" pathway could also cause [Na\(^+\)]\(_m\) to rise. Evidence of increased passive leak of Na\(^+\) (and K\(^+\)) has been obtained in RBCs from patients with essential hypertension\(^{25}\) and from...
rats with spontaneous hypertension. In the rat RBCs, the abnormal transport was observed only at low temperatures. This raises questions about its functional significance. Unfortunately, the term leak is usually used to denote an uncharacterized transport pathway, when all known specific transport pathways can be excluded. This leaves open the question of its possible relationship to the underlying genetic defect in hypertension.

**Increased Facilitated Diffusion**

Increased facilitated (or carrier-mediated) entry of Na\(^+\) may also cause [Na\(^+\)]\(_{in}\) to increase. There are a large number of known carrier-mediated Na\(^+\) transport systems, and several different ones have been implicated in the pathogenesis of hypertension.

1. Sodium-Lithium Countertransport. A specific increase in RBC Na\(^+\)-Li\(^+\) countertransport has been suggested as a genetic marker in essential hypertension. Of course, this transport system does not mediate the exchange of Li\(^+\) for Na\(^+\) under normal physiological conditions. In RBCs, this same transport system may mediate the exchange of H\(^+\) for Na\(^+\), as well as the isotopic exchange of Na\(^+\) for Na\(^+\). Under conditions of normal intracellular and extracellular pH, this carrier system probably operates as an Na\(^+\)-Na\(^+\) exchanger and does not mediate net transport of Na\(^+\) across the RBC membrane. Thus, it cannot account directly for the elevated RBC [Na\(^+\)]\(_{in}\).

The observed increase in RBC Na-Li exchange has been postulated to be a marker for increased Na\(^+\)-H\(^+\) exchange in the kidney; it may enhance Na\(^+\) reabsorption and, thus, contribute to the development of essential hypertension by promoting the secretion of a natriuretic hormone. Smith et al. have summarized the data from a number of previously published observations. The results are not all in agreement. Some workers have seen little or no increase in Na\(^+\)-Li\(^+\) countertransport in hypertensive patients, while others have observed a substantial increase in many patients with essential hypertension. Some investigators find this effect in hypertensive Caucasians, but not in hypertensive blacks. In some cases, but not others, Na\(^+\)-Li\(^+\) countertransport was also increased in the normotensive first-degree relatives of patients with essential hypertension. In one study, the increase was seen only in male hypertensive subjects. The situation is further complicated by the evidence that RBC Na\(^+\)-Li\(^+\) countertransport activity is increased during normal pregnancy and that activity may be dependent upon a dialyzable plasma factor.

With this wide spectrum of observations, the only conclusion warranted is that some Caucasians with essential hypertension and some of their normotensive offspring have increased RBC Na\(^+\)-Li\(^+\) countertransport activity. However, because of substantial overlap in activities between hypertensive and normotensive subjects with and without a positive family history, this RBC countertransport activity is not useful as a genetic marker for essential hypertension. Its relationship to hypertension remains questionable.

2. Sodium and Potassium Cotransport. The RBC Na\(^+\) + K\(^+\) cotransport is usually defined as the ouabain-insensitive, furosemide-sensitive equimolar efflux (or influx) of Na\(^+\) and K\(^+\). In many cases, these fluxes are measured after the RBCs are loaded to about the same level with Na\(^+\) and K\(^+\). Problems in interpretation stem from the fact that nystatin or parachloromercuribenzenzene sulphonate is often used to render the RBCs transiently permeable to alkali metal ions while loading them into the cells; furthermore, the loading is not always identical, nor are the methods employed in different laboratories always the same.

The initial reports that RBC Na\(^+\) + K\(^+\) cotransport activity was reduced in patients...
with essential hypertension also prompted a number of new investigations, including many published recently in Hypertension. Again, the findings are controversial. Some groups have been unable to detect changes in this transport system in most hypertensive patients. Others have found an increase in cotransport in the RBCs of patients with hypertension. Racial differences have also been observed in this transport system: blacks had low cotransport fluxes, and there was no increase in the hypertensive blacks, although in one study a decrease in cotransport was observed in both black and Caucasian hypertensive subjects. A study on twins indicated that RBC Na⁺ - K⁺ cotransport is genetically determined. Nevertheless, these conflicting results have dampened the enthusiasm for the idea that RBC Na⁺ + K⁺ cotransport activity might serve as a convenient genetic marker for essential hypertension.

The Na⁺ + K⁺ cotransport apparently does not normally influence [Na⁺]ᵢ in RBCs and, thus, cannot be expected to contribute to the observed elevation of RBC [Na⁺]ᵢ. Cotransport (of Na⁺ + K⁺ + Cl⁻) does play an important role in Na⁺ reabsorption in the kidney; furosemide and bumetanide, which block cotransport in the loop of Henle as well as in the RBC, are effective natriuretic agents. However, there is no information available about possible alterations in this renal transport system in hypertension.

3. Sodium-Calcium Countertransport. The Na⁺-Ca²⁺ exchange is a third Na⁺-coupled transport system that has been studied in relation to hypertension. This transport system cannot contribute directly to changes in [Na⁺]ᵢ in RBCs because available evidence indicates that the plasmalemma of human RBCs does not contain this exchanger. However, it is found in the plasma membranes of many other types of cells, including neurons, vascular smooth muscle cells, and renal tubule epithelial cells.

A critical feature of Na⁺ gradient-coupled ("secondary active") transport systems is that changes in one of the coupled electrochemical gradients may alter the other gradient. Thus, for the Na⁺-Ca²⁺ exchange system, not only may a change in the Na⁺ gradient alter the distribution of Ca²⁺, but a primary change in the Ca²⁺ gradient may secondarily alter the distribution of Na⁺. In other words, the Na⁺-Ca²⁺ exchange system need not be abnormal in any way to mediate an increase in [Ca²⁺]ᵢ in response to a rise in [Na⁺]ᵢ.

The suggestion has been made that the activity of the Na⁺-Ca²⁺ exchange system may be increased (perhaps because of an increased number of exchanger molecules) in the vascular smooth muscle cells of spontaneously hypertensive rats. The implication is that this may cause [Ca²⁺]ᵢ to increase and thereby promote increased contractile tension. However, an increase or reduction in the number of carrier molecules per cell (or per unit surface area), or a partial inhibition of the carriers, may not necessarily alter the final steady-state gradients that are achieved by Na⁺ gradient-coupled transport systems. Such changes may simply alter the rate of approach to a steady state when one of the coupled gradients is altered.

A direct correlation between [Ca²⁺]ᵢ in platelets, and blood pressure, has recently been reported. If [Na⁺]ᵢ is elevated in the platelets, as it is in the RBCs and WBCs of many hypertensive patients, the high [Ca²⁺]ᵢ in the platelets from these patients might then be the result of Na⁺-Ca²⁺ exchange. Similar changes have been postulated to occur in vascular smooth muscle cells and sympathetic neurons to explain the increased vascular tone in patients with essential hypertension.

Active Sodium Transport: The Sodium Pump

Another type of modified transport function that could alter [Na⁺]ᵢ is a change in the rate of active Na⁺ transport mediated by the Na⁺ pumps (cardiotonic steroid-sensitive Na⁺-K⁺ exchangers) present in virtually all animal cell membranes. The pumping rate can be modified either by modulation (e.g., partial inhibition) of pumps, or by a change in the number of pumps per cell. Several types of changes in Na⁺ pumping have been associated with hypertension: both stimulation and inhibition of active Na⁺ (or K⁺) transport, and the presence of circulating Na⁺ pump inhibitors.

Again, the varied and apparently conflicting findings must be sorted out and reconciled if we are to draw any meaningful conclusions. For example, if a circulating inhibitor of Na⁺ pumps (or Na⁺, K⁺-ATPase) plays a role in essential hypertension and experimental hypertension, observations of both increased and
decreased Na⁺ pumping rates can be explained on the basis of slightly different experimental methods. With the pumps partially inhibited, we might anticipate some compensatory increase in the number of pumps (or Na⁺, K⁺-ATPase molecules) per cell, as is observed during chronic treatment with cardiotonic steroids.59, 60 Under these circumstances, the cells and tissues from hypertensive patients (or animals) could manifest either increased, unchanged, or decreased Na⁺ pumping rates depending upon whether: 1) the inhibitor is dissociated from the pumps during tissue preparation for the transport assay; 2) there is a change in [Na⁺]₀ as a result of pump inhibition; and/or 3) there is a compensatory increase in the number of pumps (and to what extent) when the pumps are chronically inhibited. The latter could also influence the observed change in [Na⁺]₀, and we have no information about the factors that might affect the extent of the compensatory changes in different tissues and in different individuals.

The data of Walter and Distler57 may illustrate some of these problems. They found that the rate constant for the ouabain-sensitive Na⁺ efflux was lower than normal in the RBCs from patients with essential hypertension. However, because [Na⁺]₀ in these cells was slightly elevated, the absolute ouabain-sensitive Na⁺ efflux was equal to that in the RBCs from normotensive controls. These results could be explained by partial inhibition of the Na⁺ pumps in the RBCs from the hypertensive patients, compensated by a rise in [Na⁺]₀. Without information about the number of ouabain-binding sites per RBC, we cannot determine whether there was also a compensatory increase in the pump density. Also, a pump inhibitor, if present on the RBCs, could have been removed (at least partially) when the cells were washed prior to the flux studies.

Recently, there has been greatly renewed interest in the search for circulating inhibitors of the Na⁺ pumps (i.e., for endogenous digoxin-like substances).57 58, 62-65 Early evidence had indicated that such substances might have a natriuretic action and might be associated with uremia.21 65 66 However, since more recent evidence has linked Na⁺ pump inhibitors to essential hypertension,57 58 it seems tempting to consider the possibility that the same natriuretic, hypotensive substance may play a role in the hypertension of uremia as well as in essential hypertension.57

The experiments of Milner et al.65 may be particularly instructive in this regard. They studied Na⁺ efflux in WBCs from two groups of matched normotensive subjects: those with a positive family history (+FH) of essential hypertension, and those with a negative family history (-FH). Those with a +FH had WBCs with a depressed ouabain-sensitive Na⁺ efflux, relative to the -FH group. After 7 days of diuretic therapy, the cardiac glycoside-sensitive WBC Na⁺ efflux increased to normal in the +FH group, whereas there was no change in the WBCs from the normotensive group. These findings are consistent with the idea that prehypertensive individuals may require elevated levels of a circulating Na⁺ pump inhibitor (natriuretic hormone) to excrete their daily Na⁺ loads. This natriuretic hormone is also expected to promote Ca²⁺ retention by vascular smooth muscle indirectly via Na⁺⁻Ca²⁺ exchange, and thus it will tend to increase vascular tone. However, in the prehypertensive stage of essential hypertension, the cardiovascular reflexes may prevent the blood pressure from rising, and the direct action of the Na⁺ pump inhibitor on the kidneys may be adequate to keep the body in Na⁺ balance without a superimposed pressure natriuresis.52 Diuretics may be expected to cause a loss of Na⁺ and water and a consequent contraction of the extracellular fluid volume, which thereby removes the stimulus for the secretion of the natriuretic hormone (Na⁺ pump inhibitor).64 This would account for the increase in active Na⁺ efflux and fall in [Na⁺]₀ in RBCs and WBCs that have been observed in hypertensive and prehypertensive individuals following diuretic therapy.70, 71 In this context it is worth noting that the recently characterized atrial natriuretic peptides are vasodilators72 and that they do not affect renal Na⁺, K⁺-ATPase (J. M. Hamlyn, personal communication).73, 74

The idea that there may be a circulating inhibitor(s) of the Na⁺ pump has been a recurrent one in the literature over the past two decades. Nevertheless, no such substances (hormones) have been isolated to date. Part of the problem may be that the Na⁺ pump (and Na⁺, K⁺-ATPase) is a very complex system, with multiple "substrates" (Na⁺, K⁺, Mg²⁺, ATP). The assay conditions are very critical, and relatively slight alterations, such as changes in ion composition (in [Na⁺]₀ or ATP), may produce artifactual inhibition or stimulation of ion transport or ATP hydrolysis. The key to isolation of the circulating inhibitor will be the development of a valid and convenient assay system.
Conclusions

We are confronted with a bewildering (and perhaps excessive) array of observations, including many apparently contradictory ones. Like Holmes, we must sort out the evidence that is essential, so that we can piece together the "very remarkable chain of events" that leads to the development of essential hypertension. The recurring theme that a renal defect is the initiating event may indicate that a new focus is needed; perhaps elucidation of the precise renal transport or hemodynamic defect in the salt-sensitive animal models may provide a clue.

Thus far, the approach has been random: simply to try to identify some genetic defects in human RBC Na⁺ transport that correlate with essential hypertension. The results have been disappointing: changes in Na⁺ + K⁺ cotransport and/or Na⁺-Li⁺ countertransport activity are observed only in some patients with essential hypertension. We have no information about the quantitative relationship between these transport systems in the RBCs and their counterparts in kidney tubule cells; this may be most important. For example, does increased RBC Na⁺-Li⁺ countertransport really reflect an increase in kidney Na⁺-H⁺ countertransport activity? And even if it does, will this necessarily be expressed as a tendency for the body to retain Na⁺? Does there have to be a defective ion transport mechanism in the kidneys at all, or could a hemodynamic defect produce the same ultimate effect in Na⁺ reabsorption? Could different individuals have different types of genetic defects? These are but a few of the critical questions that require answers and that we may now be able to tackle as more information on the pathogenesis of the elevated blood pressure becomes available.

If, as suggested by the renal transplant studies in humans and animals, the genetic defect is expressed only in the kidneys, we are left with the view that only a humoral mechanism can translate this renal defect into the increased arterial and venous smooth muscle tone and reactivity that is characteristic of hypertension. The elaboration of a natriuretic agent that is hypertensinogenic, as first suggested by Dahl, would fulfill these requirements; it would help tie together at least some forms of renal hypertension, mineralocorticoid hypertension, and primary (essential) hypertension.

The evidence that the natriuretic hormone may be a circulating inhibitor of Na⁺ pumps seems particularly intriguing in view of the recent observation that digoxin, a known Na⁺ pump inhibitor, increases the reactivity of human vascular smooth muscle in vivo to agonists such as norepinephrine and angiotensin II. This increased vascular reactivity is comparable to that seen in hypertension; moreover, both cardiotonic steroids and plasma from patients with untreated essential hypertension sensitize isolated vascular smooth muscle to agonists.

Interestingly, Tobian has demonstrated that the isolated kidneys from young, prehypertensive Dahl salt-sensitive (DS) rats require a higher blood perfusion pressure through the kidney vascular bed to achieve the same rate of Na⁺ excretion as kidneys from salt-resistant (DR) rats. Nevertheless, the kidneys from the normotensive DS rats must have been able to keep the animals in Na⁺ balance. Thus, the reduced natriuretic capacity of the DS rat kidneys must be compensated for in vivo — perhaps by the secretion of relatively large amounts of a natriuretic hormone (possibly the circulating inhibitor of Na⁺ pumps). These functional changes apparently begin even before the blood pressure goes up. This may have its parallel in the human situation: the elevated RBC and WBC Na⁺ in and the inhibited Na⁺ pumps in the normotensive offspring of hypertensive parents may be a clue. The circulating inhibitor (modulator) of the Na⁺ pumps may be the missing link between the unknown primary (genetic) defect in the kidneys and the altered vascular smooth muscle tension (tone) that produces the elevated blood pressure.

If therefore some may be apt to think that I have sometimes too far indulged conjecture, in the inferences I have drawn from the events of some experiments; they ought to consider that it is from these kinds of conjectures that fresh discoveries first take their rise; for tho' some of them may prove false, yet they often lead to further and new discoveries.

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Acknowledgments

I thank Drs. John M. Hamlyn, Ann Hobbs, Peter Aronson, Belding H. Scribner, and James B. Wade for fruitful discussion, and Drs. Hamlyn and Hobbs for comments on the manuscript, and Arvette Wilder for preparing the typescript. The ideas discussed herein were based on research supported by Grants NS-16106 and AM-32276 from the National Institutes of Health, a grant from the Muscular Dystrophy Association, New York, New York, and a contract from the Upjohn Company, Kalamazoo, Michigan.

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(Hypertension 6: 445-453, 1984)
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_Hypertension_. 1984;6:445-453
doi: 10.1161/01.HYP.6.4.445

_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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