Review

Alteration of Cation Metabolism: a Prototype Etiological Model of Hypertension

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Essential hypertension (EH) is a progressive rise in blood pressure (BP) with age for which there is no obvious cause. Its unique clinical marker is the high BP itself. No other abnormality appears to be common to all hypertensive patients. Our understanding of the mechanisms that keep BP high has improved considerably and a number of clues to potential causes have been found. High BP arises from the interactions between an organism’s attributes and environmental factors. The former may include abnormal transmembrane ion transport systems. There are a number of hypotheses postulating how abnormal sodium or calcium metabolism causes increased systemic vascular resistance through altered vaso-active responses, structural changes in the vasculature, or both. (Hypertens Res 1994; 17: 149-155)

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Potential Causes of Essential Hypertension

By definition, essential hypertension (EH) is a progressive rise in blood pressure (BP) with age for which there is no obvious underlying cause. The only definite clinical marker of EH is the high BP itself. No other abnormality appears to be common to all hypertensive patients.

EH is now recognized as a highly heterogenous condition, not only in its clinical and laboratory picture but also in the variability of the patients’ responsiveness to available therapeutic agents. Multiple forms might therefore exist, each perhaps with its own etiology, with high BP as the common denominator.

Although the pathophysiology of EH is not completely clear, much progress has been made in our understanding of the mechanisms that help maintain a high BP. Moreover, a number of clues to the identification of potential underlying or initiating causes have been found.

High BP arises from interactions between a patient’s attributes and environmental factors. The patient’s attributes are the genetic and acquired characteristics that influence the behavioural patterns that allow environmental factors to determine the BP. Environmental influences operate via complex physiological control systems, which are themselves interrelated, and the reactivity of these systems may be genetically determined. These systems are also affected by high BP itself, which can result in a self-perpetuating cycle. Finally, the behavioural patterns that predispose a person to high BP are determined by a combination of genetic and cultural factors (I).

Attributes of the patient that are suspected of being underlying causes of EH include mineralocorticoid excess (2), primary renal defects (3, 4), increased sympathetic nervous system activity (5), cell membrane alteration (6), and abnormal transmembrane ion transport systems (7). These attributes only play a permissive role. The phenotype of a genetic susceptibility to high BP is only expressed in the presence of appropriate environmental stimuli; otherwise BP would converge toward lower levels (I).

The principal environmental factors that can increase BP with age in susceptible people include excess body weight, alcohol consumption, physical inactivity, psycho-social stress, and dietary habits regarding salt, potassium, calcium, and fibre. Drugs such as oral contraceptives and non-steroidal anti-inflammatory agents may play some role in some portions of the population. Since these factors relate to the way people eat, drink, and exercise, they suggest that hypertension is neither essential nor inevitable in modern societies (I).

The present work attempts to summarize the data supporting the hypothesis that alterations in cation metabolism (mainly sodium and calcium) can cause EH. The wide acceptance of the concept of salt sensitivity stems from large epidemiological surveys, clinical observations, experimental data in animals and humans, and results of pharmacological trials in hypertensive patients. This evidence will be briefly reviewed.

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Dietary Sodium and Blood Pressure

Associations between BP and estimated sodium intake in isolated populations have been found only rarely (8-11). Several explanations for this failure have been offered (12, 13).

In the urban Bantu of Zaire (10), such an association was found after the systolic BP data were adjusted to take anthropometric characteristics and urinary excretion of other cations (potassium, calcium, and magnesium) into account. In these data each 100 mmol of sodium excretion was associated with 6 mmHg higher systolic BP.

By contrast to studies of single communities, several surveys of people from various geographic areas and ethnic groups have shown a positive correlation between BP and estimates of sodium intake (14-16). These studies have reported a higher point prevalence of EH in populations with high levels of sodium consumption (16). In populations whose sodium intake is low, BP does not increase with age and there is virtually no hypertension (16).

As part of the Cardiac Study, the BP and salt intake of people aged 50-54 years in three Tanzanian communities, one urban and two rural, were recorded (17). The pastoral Masai had the lowest daily salt intake (34 mmol) and the lowest prevalence of hypertension (2%), whereas the urban population with the highest salt intake (92 mmol/day) had the greatest prevalence of hypertension (30%).

Variation in dietary salt intake can alter BP in both normotensive and hypertensive experimental animals.

Dahl's salt-sensitive rat strain offers an illuminating example of salt sensitivity in an animal model of hypertension. These rats have been bred so that their BP only rises when they are exposed to a high level of dietary salt (18).

Similarly, in susceptible individuals, variation in salt consumption alters BP. In this respect, Africa has witnessed a few natural experiments of community exposure to high salt consumption. For example, Samburu warriors recruited into the Kenyan army received a daily ration of 16 g of salt (19). Their BP rose significantly over the period of increased dietary sodium. Likewise, the Luo migrants moving from their tribal area to urban slums in Nairobi experienced an early increase in BP, which was attributed to acculturation (20). Among the factors associated with the increase in BP in these Luo migrants was an increment in the urinary sodium-to-potassium ratio, which reflects a change in the consumption of these two minerals.

The hypothesis that sodium has an etiological role in hypertension is strengthened by the observations that both drastic and moderate salt restriction can lower BP in hypertensive patients (21-23). Up to 60% of hypertensive patients have been said to be salt-sensitive: their BP increases with dietary salt supplementation and decreases with salt reduction (24). Finally, the fact that various natriuretic agents (drugs that promote excretion of sodium) can lower BP further supports the hypothesis that sodium contributes to hypertension (25). It is well established that the anti-hypertensive action of diuretics can be counteracted by dietary sodium loading (26).

There is some evidence that young people respond little to wide variations in sodium intake. This would be evidence against the hypothesis that dietary sodium is a major initiating factor in the age-related increase in BP (27). It must be stressed, however, that given the genetic and cultural heterogeneity of humans, it is likely that the changes in BP in response to changes in dietary salt will be a matter of degree rather than an all-or-nothing phenomenon (28).

Ion Transport Abnormalities in Hypertension

To improve our understanding of the processes involved in EH, intensive effort has been invested during the last decade in studies of cellular ion handling. The abnormalities of ion handling that have been demonstrated in animals and humans offer important insights into the pathogenesis of EH, and the way environmental and organismic factors interact to increase BP.

Most studies have used circulating blood cells because they are readily accessible, and because any abnormality would probably be shared by all body cells including those involved in the regulation of systemic vascular resistance (SVR). Several abnormalities of ion handling in these cells have been reported.

Intracellular levels of sodium (Na,) were found to be higher in hypertensive patients than in normotensive subjects and this was attributed to altered transmembrane fluxes of this cation (29-34).

Studies have shown abnormally high passive influx of sodium through ouabain-insensitive pathways (35, 36) and abnormally low activity of the ouabain-sensitive sodium pump (30, 33, 34, 37-39). There is convincing evidence for impaired sodium pumping in the leucocytes of patients with EH, but the reports concerning Na, and sodium pump activity in red cells are conflicting (40-42).

Similarly, there is much controversy in the literature about the activity of the Na,K-cotransport and Na+,Li-countertransport systems. Results of earlier studies indicated that there were clear-cut differences between normotensive subjects and patients with EH (43-45).

Subsequent studies either failed to reproduce earlier observations or found less marked disturbances (46-49), because of better handling of confounding factors such as weight, race, sex, physical fitness, and drug intake. Thus, in some cases the previously apparent associations between BP and altered sodium handling disappeared after corrections were made for the aforementioned confounding factors.

Alterations in Na, and in the activity of the sodium transport systems have also been observed in some studies of normotensive relatives of patients with EH. Their occurrence in normotensive people could argue against the hypothesis that these abnormalities are directly responsible for, or secondary to, abnormally high BP. In our studies, Na, and sys-
tolic BP were both higher in the offspring of hypertensive patients than in subjects without a family history of hypertension (29). It is therefore likely that alterations in cation metabolism in normotensive persons characterize those prone to develop hypertension later in life, but this cannot be verified without longitudinal follow-up of such individuals.

Several environmental factors influence cellular sodium metabolism. In the red cell model, a reduction in Na\textsubscript{1} has been associated with a low-salt diet and with an increase in the activity of the sodium pump (50-52). By contrast, a high-salt diet has been associated with an increase in Na\textsubscript{1} and with a decrease in the activity of the sodium pump (50, 53-55). Dietary weight reduction was associated with a fall in Na\textsuperscript{+},Li\textsuperscript{+}-countertransport as well as a fall in BP (56).

Another confounding factor is the degree of physical activity. Acute exercise was accompanied by decreases in intraerythrocyte potassium concentration and Na\textsuperscript{+},Li\textsuperscript{+}-countertransport activity (57). Physical training has been reported to significantly decrease Na\textsuperscript{+},Li\textsuperscript{+}-countertransport (58, 59), and has been associated with an increase in HDL-cholesterol (59). This is compatible with the negative correlation between these variables reported by Hunt et al. (60). Moreover, the dependence of Na\textsuperscript{+},Li\textsuperscript{+}-countertransport on HDL-cholesterol could explain why blacks, as a group, have on average lower Na\textsuperscript{+},Li\textsuperscript{+}-countertransport than other racial groups.

Reported abnormalities are not confined to monovalent cations. In patients with EH, calcium binding and the number of binding sites on the inner surface of the red cell membrane are lower than normal (61, 62). Calcium-dependent ATPase activity is low in these red cells (63, 64), whose membrane vesicles have a low level of calmodulin-stimulated calcium transport (65). Reports on abnormally high cellular calcium in EH have also been published (66-68). Calcium ATPase activity is abnormally high in platelets from patients with EH (69). This is compatible with the finding of a low pH in erythrocytes from these patients (70). Indeed, calcium ATPase exchanges internal calcium for extracellular protons. However, according to a recent study platelet calcium ATPase and magnesium ATPase are low, with the result that platelet calcium is high in black patients with EH (64).

Of particular interest is the observation that not all of these membrane transport disturbances are present in every patient with EH.

**From Cation Metabolism to High Blood Pressure**

The possibility that altered cation metabolism causes hypertension has fueled a number of hypotheses. The hallmark of established hypertension, whatever its etiology, is an abnormally high SVR. To link a given factor with the etiology of EH, one has to explain how that factor increases SVR, which is to a large extent a manifestation of abnormally high systemic vascular contractility.

The first hypothesis to explain the association between sodium and BP was probably that put forward by Tobian (71). He suggested that retention of sodium and fluid within the arterial wall reduces the luminal area and increases resistance to flow. This hypothesis provides a link between sodium at the cellular level and the pathogenesis of hypertension. However, according to Swales (72) it suffers from three major difficulties: It was not possible for Tobian to exclude the possibility that high levels of sodium and fluid in the arterial wall were secondary to an increase in wall mass that resulted from high BP; it was difficult to differentiate intracellular sodium retention from extracellular binding of sodium; and finally, there was no explanation of how waterlogging of the resistance vessels could result in maximal contraction.

Blaustein formulated a more provocative hypothesis, based on the existence of a sodium-calcium exchange system (73). According to this hypothesis, the primary abnormality in EH is an alteration in sodium metabolism.

In a susceptible individual on a high-sodium diet a reduction in the capacity of the kidney to excrete sodium would result in expansion of the extracellular fluid volume. This would lead to the release of a sodium transport inhibitor, which would inhibit the sodium pump in the renal tubule, and thus cause natriuresis and help restore the extracellular volume to normal. However, sodium pump inhibitors are not tissue-specific, so they also increase Na\textsubscript{1} in tissues other than the renal tubule, which results in inhibition of sodium-calcium exchange. Cytosolic free calcium then increases in various tissues including vascular smooth muscle. It has been calculated that an increment in Na\textsubscript{1} of 5% would increase the intracellular calcium level by 15%, which would raise muscle tension by 50% of the resting value (74). In the adrenergic nervous system, the increment in cytosolic free calcium promotes the release of neurotransmitters that would further increase SVR.

Blaustein's hypothesis has three premises: a primary renal defect, a sodium pump inhibitor, and the sodium-calcium exchanger.

One key premise used to explain the development of hypertension in salt-sensitive subjects is that there is a defect, whether inherited or acquired, in the ability of the kidney to excrete sodium and that this defect may be undetectable by standard tests of renal function. Transplant experiments have clearly demonstrated that hypertension “goes with the kidney” in an animal model (75). This concept has been extended to humans, based in part on the observations by Curtis et al. (76). The nature of the renal defect is not yet established. Sensitivity to salt seems to be linked to increased sodium reabsorption in the renal tubule, and, in turn, to an increased density of alpha-2-adrenergic receptors in the kidneys (77). More recently, Brenner et al. (78) proposed that the abnormality is an innately low number of nephrons.

The second key premise is that there is a need for a messenger between salt intake, Na\textsubscript{1}, and BP, since sodium chloride has no local constrictor effect on
vascular smooth muscle cells. In contrast, it has an indirect local vasodilatory effect, which occurs immediately via a change in osmolality (79). Sodium chloride has, however, a delayed and indirect vasoconstrictor effect, which occurs via volume expansion and overrides its local vasodilatory effect.

Artificial acute volume expansion imparts to the plasma the ability to inhibit the Na,K-ATPase pump, to cause natriuresis, and to sensitize blood vessels to vasoconstrictor agents. In a low-renin expanded-volume condition, the plasma has similar properties and can also increase BP. The plasma of some hypertensive patients contains an inhibitor of Na,K-ATPase (39, 80, 81), an enzyme that correlates with BP.

The plasma level of the inhibitor increases with increases in sodium intake, particularly in hypertensive patients (39, 82). We showed that the ability of plasma from healthy subjects to inhibit canine Na,K-ATPase decreased during dietary salt restriction (50). In hypertensive patients diuresis by reduction of the extracellular volume increases the activity of the sodium pump, probably by removing the inhibitor (83).

The source and nature of the plasma inhibitor of the Na,K-ATPase pump are not yet clearly understood. Various observations (84–86) are compatible with the hypothesis that the hypothalamus is the source of the inhibitor. However, the hypothalamus may simply influence secretion of the inhibitor from another source, such as the adrenal glands. The possibility that the inhibitor is secreted by the adrenal glands is supported by the finding that it is not a peptide but rather a steroid, similar to the cardiac glycosides that are known to bind to and to inhibit the Na, K-ATPase (87). More recently, the inhibitor was recognized as endogenous ouabain (88).

The last premise is the existence of a sodium-calcium exchanger. Although such a system exists in vascular smooth muscle cells (89, 90) its contribution to calcium metabolism in these cells appears to be uncertain (91, 92).

Some hypotheses have emphasized the role of monovalent cation fluxes in maintaining membrane polarity. Because the transport rates of sodium and potassium are not equal, inhibition of the sodium pump reduces the negative charge inside the cell and causes depolarization. The latter would increase calcium permeability in smooth muscle cells by opening voltage-dependent calcium channels (93). Cytosolic calcium would increase, which would result in vasoconstriction. The sensitivity of the smooth muscle to vasoconstrictor agents, such as norepinephrine, would increase.

Myography was used to study isolated subcutaneous resistance vessels from humans, and there was no evidence of an abnormally strong constrictor response to any agonist, either in patients with EH or in their relatives (94, 95). Instead, hypertensive patients were found to have a 29% greater wall-to-lumen ratio in the resistance vessels, which could be sufficient to account for the increase in BP. Indeed, increased SVR may also stem from narrowing of the vascular lumen because of hypertrophy, hyperplasia, or both. This process can be induced by both vasoconstrictors and growth factors (96, 97). At the cellular level, both growth and vasoactive responses are associated with an increase in calcium and activation of the sodium-proton (Na+/H+) antiport (98–101).

Thus, structural changes in the vasculature in EH should not necessarily be viewed as a consequence of high blood pressure. They could result from hyperresponsiveness of vascular smooth muscle cells to agonists and herald the development of hypertension (102).

Accordingly, a change in the regulation of intracellular calcium could be the primary abnormality. Such a change would be coupled with sodium regulation through the Na+/H+-antiport, a system that is involved in a variety of processes including vascular smooth muscle contraction, cell growth, and sodium reabsorption in the renal proximal tubule. Another advantage of this hypothesis is that it links salt-sensitive EH with salt-resistant EH. Indeed, when high levels of cytosolic calcium are associated with agonist-induced increases in the activity of the Na+/H+-antiport in vascular smooth muscle cells, only salt-resistant EH would develop secondary to an increase in SVR caused by increases in vascular tone and in the thickness of the tunica media. When the amount of cytosolic calcium is abnormally high and the Na+/H+-antiport is hyperactive not only in the vasculature but also in the renal tissues, then hypertension will manifest with low levels of plasma renin and salt-sensitivity.

The latter form of EH is associated with increased levels of parathyroid hormone and with the presence of the natriuretic Na, K-ATPase inhibitor. Both of these hormones can correct, at least in part, the increase in extracellular fluid volume, with the Na, K-ATPase inhibitor increasing SVR.

The Na+/H+-antiport is activated by a high-salt diet in normotensive subjects. Whether it is similarly activated in the two types of EH remains to be established.

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