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Hypothesis

Why is salt-sensitive hypertension so common in blacks?

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Introduction

Hypertension is more prevalent among blacks and it carries a worse cardiovascular and renal prognosis than in whites. Data from the United States Renal Data System (USRDS) show that over the past decade, the incidence of ESRD has steadily increased, more in blacks than in whites. In 1982, 102 new cases per million blacks were reported to develop ESRD from hypertension, compared with less than 20 new cases per million whites. By 1987, the number of blacks with ESRD from hypertension had increased to 143 new cases per million compared with 22 new cases per million whites, and by 1991 the rates were 217 and 36 per million, respectively [1]. This phenomenon is particularly striking when one considers that definite progress has been made in the treatment of established hypertension and in the prevention of other cardiovascular complications in this and other ethnic groups.

The mechanisms responsible for the greater prevalence of hypertension and renal disease in blacks are largely unknown. The extent of our knowledge is that Na^+ homeostasis and the haemodynamic adaptation of the renal circulation to high NaCl intake are different in hypertensive blacks and whites. Blacks have greater prevalence of 'salt-sensitivity' and excrete a NaCl load more slowly and less completely than Whites [2,3]. In salt-sensitive hypertensive patients, the slope of the renal function (pressure-natriuresis) curve is lower than in salt-resistant patients [4], suggesting a disturbance in renal tubular Na^+ reabsorption. Hypertensive blacks have more severe nephrosclerosis, involving primarily the arcuate renal arteries [5], and greater reduction of renal blood flow (RBF) than whites [6]. During high NaCl intake, RBF increases and filtration fraction decreases in salt-resistant patients, whereas RBF decreases and filtration fraction and intraglomerular pressure increases in salt-sensitive patients [7]. The sodium-dependent rise in intraglomerular pressure may be in part responsible for the increased propensity of hypertensive African Americans to develop end-stage renal disease. The mechanisms responsible for these pathophysiological changes remain unexplained.

Hypothesis

The hypothesis we propose is that in their original environment black individuals may have modified their genome to adapt to an environment low in NaCl and in calories. Thus, they overexpress Na^+-retaining mechanisms (such as increased renal sympathetic activity, hyperinsulinaemia, faster renal Na^+ transport), and underexpress Na^+-excretory mechanisms (such as dopamine, kallikrein, prostaglandins, and atrial natriuretic factor). The 'rapid' change to an environment rich in NaCl and calories may have resulted in Na^+ retention, obesity and hypertension (Figure 1).

Blacks evolved in an environment low in Na^+ and in caloric intake. In this environment, genetic mechanisms may have evolved aimed at preserving sodium and calories. Since blood pressure is regulated by a multitude of mechanisms (and therefore genes), mutations (or lack of) of several of these genes may have occurred for the purpose of preserving the species in an unfavourable environment. This may have led to gene selection favouring Na^+-retaining over Na^+-excretory mechanisms. With the slave trade and colonization of Africa, blacks were 'suddenly' exposed to an environment rich in Na^+. This may have led to maladaptive changes characterized by Na^+ retention and hypertension. Caloric deprivation may also have played a role. Populations subjected to periodic caloric deprivation, such as the Pima Indians, Micronesians, Polynesians, and Asian Indians have developed mechanisms aimed at avidly storing energy to survive periods of famine. Hyperinsulinaemia may represent the deleterious expression of a trait which in the past had selective advantage, as first proposed by Neel in the 'thrifty genotype hypothesis' [8]. Exposure to an environment rich in calories, may lead to obesity, dyslipidaemia, and eventually to diabetes mellitus. Because of the frequent coexistence of these two environmental factors (high sodium and high calories) the corresponding traits also may have developed in paral-

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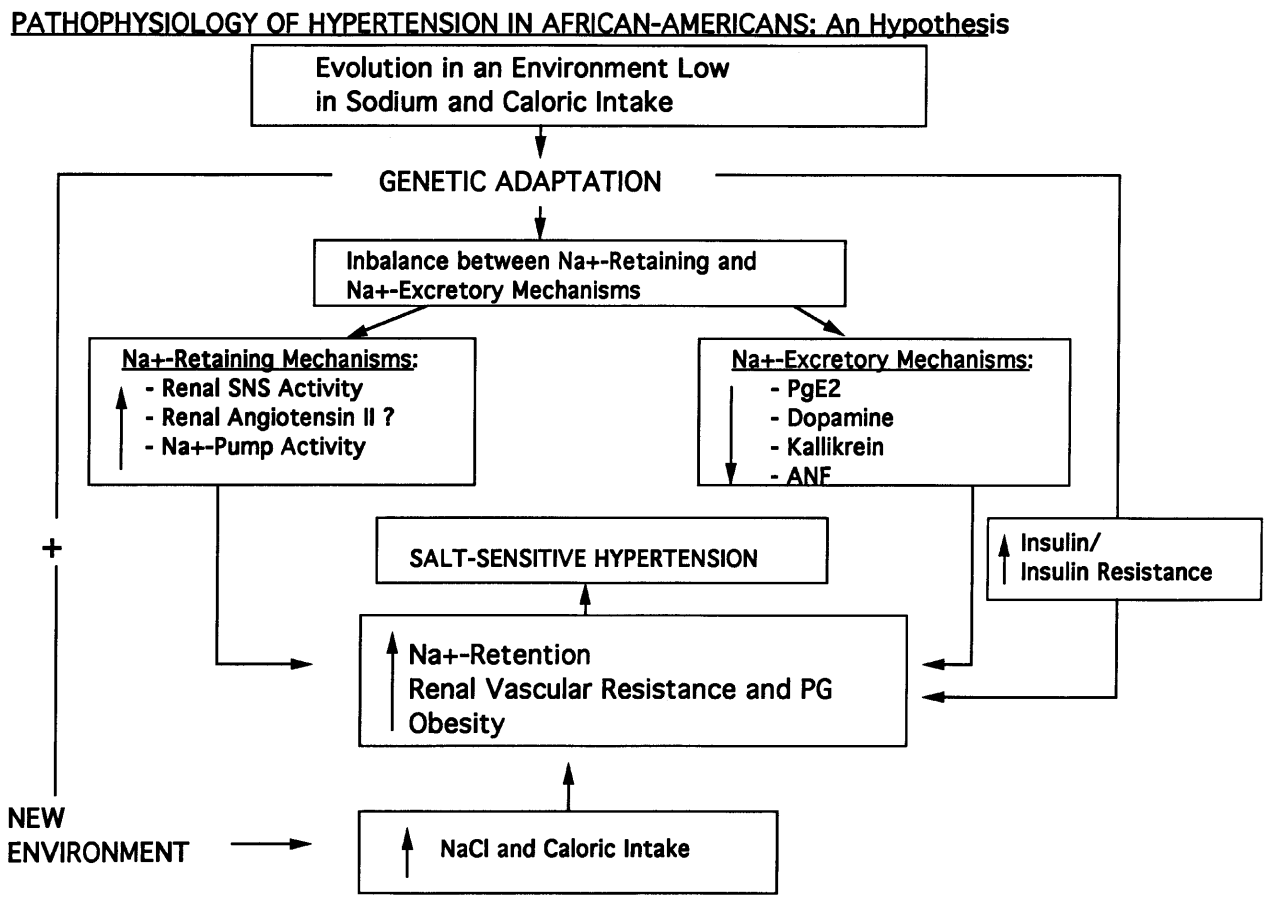

Fig. 1.

lel. This may explain the frequent association of phenotypes such as salt sensitivity and hyperinsulinaemia. These traits are less frequent in the Western civilization because of the more gradual and prolonged adaptation to the same environment.

Na^+-retaining mechanisms

Increased activity of the sympathetic nervous system

Increased activity of the sympathetic nervous system inhibits Na^+ excretion and may cause Na^+ retention. We were the first to show that salt-sensitive patients with essential hypertension display an abnormal relationship between urinary sodium excretion and plasma noradrenaline levels. A high NaCl diet was accompanied by a decrease in plasma concentrations of noradrenaline in normal subjects and in salt-resistant patients, but by a rise, no change, or a decrease in salt-sensitive patients [9]. This has been confirmed by others.

Hyperinsulinaemia and/or insulin resistance

African-Americans are more hyperinsulinaemic and insulin resistant than whites. This is in part due to greater prevalence of obesity among them, but the difference in obesity does not fully explain the excess insulin resistance and hyperinsulinaemia [10]. Hyperinsulinaemia could provide the stimulus for hypertensive mechanisms such as sodium retention, stimulation of the sympathetic nervous system, and alteration of cation transport.

The renin–angiotensin system

The renin–angiotensin system plays an important role in the regulation of the sodium/volume status and blood pressure. Thus, alterations of this system can lead to hypertension. The role of the renin–angiotensin system in blacks remains uncertain because they usually have low renin. This, however, does not rule out the possibility that local renal production of renin might shift the relationship between pressure and natriuresis and cause hypertension.

Alterations of ion transport

The greater prevalence of hypertension and salt-sensitivity in African Americans could be due to intrinsic alterations of ion transport. Several mechanisms that regulate cellular ion transport have been evaluated in hypertensive patients with conflicting results. A classic hypothesis suggests that hypertension in salt-sensitive patients may be due to a faster renal

Na^+ reabsorption and reduced ability of the kidney to excrete a Na^+ load. The subsequent volume expansion stimulates the secretion of a ouabain-like substance [11]. This substance would inhibit Na^+, K^+-ATPase in the kidney and maintain Na^+ balance, albeit at higher levels. The inhibition of Na^+, K^+-ATPase activity in vascular smooth-muscle cells and in the central nervous system would result in hypertension. This notion is supported by evidence that prolonged administration of ouabain induces hypertension in normal rats [12]. Many investigators have measured circulating levels of this ouabain-like compound with conflicting and inconclusive results. Dichtchekenian *et al.* [13] observed higher serum levels of digoxin-like factor in salt-sensitive than in salt-resistant hypertensive patients and a significant correlation between plasma digoxin-like factor and blood pressure. However, high NaCl diet failed to increase serum levels of the digoxin-like factor in both groups. Lasker *et al.* [14] showed lower Na^+, K^+-ATPase activity and density and higher intracellular Na^+ in erythrocytes of blacks compared with whites.

There is no conclusive evidence that genetic mutations of the Na^+-pump subunits are implicated in the pathogenesis of hypertension. Shull *et al.* [15] in their study of three families consisting of 18 white members, 11 of whom were hypertensive, observed a discordant segregation of Na^+, K^+-ATPase alleles with hypertension. In a study of 293 members of 74 randomly selected families, Perusse *et al.* [16] showed linkage between the b locus of Na^+, K^+-ATPase and changes of blood pressure with age.

An alternative possibility is that a mutation of the adducin a and b subunits affects the actin-based cytoskeleton and the activity of the Na^+ pump. Adducin is an a/b and c heterodimer involved in cellular signal transduction, probably through a modulation of actin cytoskeleton. Point mutations in rat adducin a (F316Y) and b (Q529R) subunits are responsible for up to 50% blood pressure difference between MHS and MNS [17]. The adducin isoforms differentially modulate the actin assembly in rat kidney epithelial cells and Na^+ pump activity at Vmax (this would be faster with the mutated isoforms) [18]. In a case-control study of patients with essential hypertension, an association was found between the alleles of four polymorphic markers located at different distances from the a-adducin locus (from 20 to 2000 Kb) and hypertension [19]. The same group has shown a significant linkage for three DNA markers mapping at different distances from the a-adducin locus (20–2500 Kb) in 137 hypertensive sib-pairs. The excess shared alleles as well as the significance level for linkage decreased with increasing distance from the a-adducin locus.

Taken together these studies suggest that a mutation of the a-adducin gene may affect the assembly of the actin-based cytoskeleton and the structure or function of the Na^+ pump. This could alter Na^+ transport, and cause hypertension.

Elevated rates of Na^+/H^+exchanger (NHE) in cell membrane of blood vessels and renal tubules may play a role in the pathophysiology of hypertension. Several cell types from hypertensive patients and rats exhibit increased Na^+/H^+ exchanger activity [20]. An increase in the activity of the Na^+/H^+ exchanger could be due to systemic hormonal or metabolic factors (such as increased insulin, or high NaCl intake), to intracellular factors (such as Ca^{2+}-calmodulin, protein kinase C) [21], or to overexpression, mutation, or postranslational modification. Immortalized lymphocytes from hypertensive patients express enhanced Na^+/H^+ exchanger activity under different experimental conditions [22]. However, this does not appear to be due to overexpression of the protein nor to a mutation in the Na^+/H^+ exchanger gene sequence [23]. Thus, one has to conclude that the enhanced Na^+/H^+ exchanger activity in primary hypertension can best be explained by alteration of the intracellular regulation. We have previously shown that a high dietary Na^+ intake increases Ca^{2+} in lymphocytes of salt-sensitive but not of salt-resistant patients with hypertension [24]. Resnick *et al.* [25] have shown that high NaCl intake increases $[Ca^{2+}]i$ and decreases pHi in salt-sensitive subjects. The increase in Ca^{2+} could alter the activity of the Na^+/H^+ exchanger.

Na^+-excretory mechanisms

Hypertension and salt sensitivity in African-Americans may be in part secondary to genetic or acquired alterations of mechanisms to facilitate Na^+ excretion. These may include the following

Prostaglandins. Several major classes of eicosanoids are synthesized and released from vascular tissue and the kidney. These include the cyclo-oxygenase products (PGE_2, prostacyclin (PGI_2) and thromboxane), products of the 12 and 15-lipoxygenase pathways, including 12 and 15 hydroxyeicosatetraenoic acid (12- and 15-HETE) and eicosanoids derived from the cytochrome P-450 epoxygenase pathway. Vasodilator PGs such as PGE_2 and PGI_2 play an important role as protective modulators of renal blood flow and sodium excretion during states of hypovolaemia or enhanced pressor activity [26]. Thus, reduced renal production of PGE_2 may result in Na^+ retention and volume expansion and be an important mediator of salt-sensitive hypertension. We have observed lower urinary PGE_2 in salt-sensitive than in salt-resistant black patients (personal observation).

Dopamine. Dopamine participates in the homeostatic regulation of Na^+ balance. Urinary dopamine excretion increases during dietary Na^+ loading, and administration of dopamine causes natriuresis [27,28]. Reduced dopamine secretion may cause Na^+ retention and hypertension. In a group of largely white salt-sensitive patients, Gill *et al.* [29] showed decreased urinary dopamine/NE ratio, and an abnormal conversion of DOPA to dopamine, a product of decarboxylation of DOPA. We have confirmed the same defect in salt-sensitive blacks [30].

Kallikrein. Urinary kallikrein excretion is lower in hypertensive individuals and is lower in black than in white patients with essential hypertension [31]. A blunted activity of the renal kallikrein–kinin system could be partially responsible for Na^+ retention and could participate to the pathophysiology of hypertension.

Atrial natriuretic factor (ANF). ANF is a vasodilator and natriuretic hormone. A reduction of ANF secretion could result in Na^+ retention and in salt-sensitive hypertension. This possibility is supported by studies showing that a disruption of the pro-ANF gene in mice causes salt-sensitive hypertension [32]. Measurements of plasma ANF levels in patients with essential hypertension have provided conflicting results. Some have shown low to normal plasma ANF levels [33], others have shown increased levels [34]. Sagnella *et al*. [35] showed increased plasma ANF levels during high Na^+ intake in patients with essential hypertension and Kohno *et al*. [36] showed that Na^+ loading increased plasma ANF more in salt-sensitive than in salt-resistant patients. On the contrary, Nimura [37] observed a blunted increase in plasma ANF in response to high dietary NaCl intake in salt-sensitive compared with salt-resistant patients. We also observed a paradoxical decrease in plasma ANF in response to high dietary NaCl in salt-sensitive black individuals, whereas no changes occurred in salt-resistant black individuals [38]. Ferrari *et al*. [39] also observed lower plasma ANF during high Na^+ intake in the offspring of hypertensive parents compared with the offspring of normotensive parents, suggesting that a relative ANF deficiency may predispose to the development of hypertension.

Salt-sensitivity as a cardiovascular risk factor?

Schmieder *et al*. [40] observed a positive correlation between NaCl ingestion and left ventricular mass (LVM) in patients with essential hypertension.

In normotensive and hypertensive rats the myocardial hypertrophy caused by high NaCl intake occurs independently of haemodynamic effects [41]. In both rats and human subjects, dietary NaCl increases left ventricular wall thickness, resembling pressure overload rather than volume overload. Heimann *et al*. [42] showed a higher LVM in a small number of salt-sensitive compared with salt-resistant hypertensive patients.

The mechanisms for the myocardial actions of NaCl are not clear, but several possibilities have to be considered: (1) this could be the result of increased activity of the sympathetic nervous system; (2) hyperinsulinaemia and/or insulin resistance; (3) abnormal serum lipoprotein levels [43].

Since an increase in LVM, hyperinsulinaemia, and hyperlipidaemia are now considered major cardiovascular risk factors, salt-sensitive patients with essential hypertension manifest a cluster of renal and metabolic derangements, that may potentially increase the risk of renal failure and of cardiovascular diseases.

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