Salt Sensitivity in Hypertension: Implications for the Kidney

Vito M. Campese¹ and Frederick Karubian

V.M. Campese, F. Karubian, Division of Nephrology, Department of Medicine, University of Southern California, Los Angeles, CA

(J. Am. Soc. Nephrol. 1991; 2:S53–S61)

ABSTRACT

The role of dietary sodium in the pathogenesis of essential hypertension has stimulated a great deal of interest and investigation in recent years. There are epidemiologic studies in the literature that suggest a link between dietary sodium intake and the prevalence of hypertension. However, not all patients are prone to the development of hypertension in response to dietary sodium. Therefore, a distinction between salt sensitivity and salt-resistant essential hypertension has evolved from this observation. The mechanisms which related dietary sodium to the pathogenesis of essential hypertension are not clearly defined, although it appears that inborn errors of renal sodium handling, along with certain components of the sympathetic nervous system, may be involved. Furthermore, intracellular sodium and its transport mechanisms have been implicated in the pathogenesis of hypertension associated with dietary sodium. Finally, there appears to be a correlation between dietary sodium, salt sensitivity, and the progression of renal disease. That is to say, patients with salt-sensitive essential hypertension appear to demonstrate a more relentless course to end-stage renal disease. This tendency may be related to deranged hemodynamic adaptation of the renal circulation in response to dietary sodium intake and the resulting rise in systemic blood pressure. The mechanism for this derangement of renal hemodynamic adaptation in salt-sensitive hypertensives remains to be determined.

Key Words: Sodium, hypertension, salt sensitivity, cytosolic calcium

In recent years, a great deal of interest has been focused on the role of sodium in the pathogenesis of hypertension and cardiovascular diseases. Epidemiologic, clinical, and experimental evidence indicates that excessive sodium intake may play a role in the development and maintenance of hypertension, as well as in cardiovascular complications.

EPIDEMIOLOGIC EVIDENCE

Several epidemiologic studies suggest a relationship between dietary sodium intake and the prevalence of hypertension (1–13). Some studies of individuals within populations do not support a causal relationship (6,14–16), whereas other studies have shown a direct relationship between these two factors (14,17,18).

Cross-sectional population studies throughout the world show a more consistent relationship between sodium intake and the prevalence of hypertension (1–13). In several unacculturated populations with low sodium intake, the incidence of hypertension is very low and blood pressure does not increase with age (19,20).

More recently, the Intersalt Study has evaluated 10,079 men and women ranging in age from 20 to 59 yr who were sampled from 52 centers around the world. In this study, blood pressure measurements were standardized and sodium intake was estimated by 24-h urinary sodium excretion. The study found a significant, albeit weak, correlation between 24-h urinary sodium excretion and blood pressure and between individual urinary sodium/potassium ratio and blood pressure, even when age, body-mass index, and alcohol consumption were taken into account (21).

Intervention studies further support a causal relationship between sodium intake and hypertension. A reduction of sodium intake or administration of diuretics lowers blood pressure in many hypertensive patients. The decrease in blood pressure after sodium restriction is directly related to pretreatment levels of blood pressure (22). However, it is important to note that a diuretic or sodium restriction does not reduce blood pressure in all hypertensive patients. Severe sodium restriction may, in fact, increase blood pressure in some hypertensive patients (Figure 1). These observations indicate that not all hypertensive patients are susceptible to high-sodium diets.

THE CONCEPT OF SALT SENSITIVITY

Dahl demonstrated variability in blood pressure response to salt loading in normal rats. By inbreeding

¹ Correspondence to Dr. V.M. Campese, LAC/USC Medical Center, 2025 Zonal Avenue, Los Angeles, CA 90033.

1044-6673/00/0005–0000/0
Journal of the American Society of Nephrology
Copyright © 1991 by the American Society of Nephrology

S53
rats with the highest blood pressure response with rats with the lowest blood pressure response to a high-sodium intake. Dahl was able to develop two strains of rats: a salt-sensitive (SS) strain and a salt-resistant (SR) strain. The former strain becomes hypertensive with time after receiving an 8% sodium chloride diet; the latter strain does not develop hypertension in response to a high-sodium diet (23).

Kawasaki et al. (24) also noted a great variability in blood pressure response to sodium loading in a group of patients with essential hypertension. On the basis of this response, patients with hypertension were classified as either SS or not SS.

We have also performed metabolic-balanced studies in 46 hypertensive patients and 12 normal subjects to determine their blood pressure response to a high-sodium diet (25). We have observed substantial variability in blood pressure response in normal subjects, but mean arterial pressure did not increase more than 8 mm Hg in any of them (Figure 1). The variability was greater in the hypertensive patients than in normal subjects. Blood pressure decreased by as much as 14 mm Hg in some patients, whereas increasing by 37 mm Hg in other patients, in response to a high-sodium diet (200 mEq/day). These measurements were compared with blood pressures during low-sodium intake (20 mEq/day). We have arbitrarily classified patients whose blood pressure increased at least 10 mm Hg during high-sodium diets as SS patients and the remaining as SR patients. We have observed that approximately 50% of patients with essential hypertension are SS.

Weinberger et al. (26,27) extensively studied the issue of salt sensitivity in 192 hypertensive patients and more than 300 normal subjects by using a short protocol involving rapid volume expansion and contraction. They found that 51% of patients with hypertension were SS, 16% were SR, and the remaining were classified as having an intermediate response.

The incidence of salt sensitivity appears to be greater in blacks and older patients than in whites or younger patients. It is also higher in obese patients than in lean patients (26,27).

MECHANISMS RESPONSIBLE FOR SALT SENSITIVITY

The mechanisms correlating sodium and hypertension remain to be determined. One hypothesis proposes that salt sensitivity might be related to an inborn decrease in the ability of the kidneys to excrete a sodium load. The consequent volume expansion would ultimately result in hypertension. Several lines of evidence support this contention. Renal cross-transplant studies in three different strains of genetically hypertensive rats have shown that hypertension is transferable along with the "hypertensive kidney" (28-30). Isolated kidney from Dahl's prehy-

pertensive, SS rats excretes a sodium load more slowly than does kidney from SR rats (31). SS patients with essential hypertension also excrete an acute sodium load more slowly than do SR patients (32) and blacks do so more slowly than whites (33).

Some evidence, however, suggests that the changes in renal sodium handling in hypertension may be a consequence rather than a cause of the elevated blood pressure (34,35). According to Guyton (35), to sustain any rise in blood pressure for a prolonged period of time, an adaptation of the sodium-handling renal mechanisms and a shift to the right of the pressure-natriuresis curve is required. Failure to adapt would result in volume depletion and a consequent fall in blood pressure. Renal adaptation differs depending on the pathogenetic mechanism responsible for the rise in blood pressure, and it may even regress when the primary etiologic factor is corrected (36).

The renal function (pressure-natriuresis) curve is different between SS and SR patients (Figure 2). In

Figure 1. Change in the supine mean arterial pressure (ΔMAP) in 12 normal subjects and in 46 patients with essential hypertension, when the values obtained during high-sodium (Na⁺) intake (200 mEq/day) were compared with the values obtained during low-sodium intake (20 mEq/day) (33).
SR patients, the renal function curve is shifted to the right but it remains parallel to that of normal subjects. On the other hand, the slope of the renal function curve is more flat in SS patients (37). This suggests that different renal-adaptive mechanisms are operative in SS and SR patients. These data also suggest that, at least in SR patients, renal mechanisms and sodium retention may not play a primary role in the development of hypertension.

The nature of these adaptive mechanisms is not clear. If the defect responsible for the increase in renal-tubular sodium reabsorption were congenital, it should precede the development of hypertension and be present in normotensive offspring of hypertensive patients. Indeed, normotensive siblings of hypertensive patients manifest a delayed excretion of an acute salt load (38). This does not necessarily prove that the renal defect is congenital and precedes the development of hypertension. Extrinsic mechanisms might be operative in these early stages and might affect the renal ability to excrete a sodium load. The renin-angiotensin system and the sympathetic nervous system are among the extrinsic factors that could affect the renal function curve in hypertension.

The renin-angiotensin system is less likely to play a role in sodium retention in SS patients, because plasma-renin activity is usually lower in these patients than in normal subjects. It is possible that local activation of the system, not reflected by measurements of blood plasma renin activity, might be responsible for the increase in renal-tubular sodium reabsorption and for shifting the renal function curve. Williams and Hollenberg (39) have suggested that salt sensitivity might be related to defective modulation of renin release and renal vascular tone, but they exclusively evaluated patients with normal-to-increased plasma renin activity.

Extensive evidence suggests that sodium retention and hypertension in SS subjects might be related to increased activity of the sympathetic nervous system. Hollenberg et al. (40) observed that administration of an α-blocking agent caused a significant rise in renal blood flow in young hypertensive patients. Esler et al. (41) observed an increase in renal spillover of norepinephrine in patients with essential hypertension. We (25,42) and others (43–46) have shown that during high-sodium diets, plasma norepinephrine levels usually decrease in normal subjects and in SR patients with essential hypertension, but levels tend to increase or not change in SS patients. Increased activity of the sympathetic nervous system may be partly responsible for sodium retention and for the increase in blood pressure in SS patients.

Urinary dopamine excretion increases during dietary sodium loading (47), and administration of dopamine causes natriuresis (48); it has been proposed that renal dopamine production participates in the homeostatic regulation of sodium balance (49,50). Dopamine appears to exert its natriuretic effect through an increase in renal blood flow (RBF) and a direct effect on the renal tubules (51). Some have previously reported that low-dose dopamine infusion increases RBF and urinary excretion of prostacyclin in normal subjects (52). Thus, a decrease in dopamine production could decrease both RBF and urinary sodium excretion.

Dopamine and norepinephrine exert opposite effects on renal-sodium handling, so an increase in the ratio of norepinephrine to dopamine might result in sodium retention. Gill et al. (45) showed a decrease in dopamine and an increase in norepinephrine excretion in SS patients. This suggests that the impaired sodium excretion in SS patients may be due to an increase in the norepinephrine-to-dopamine secretion ratio. Abnormalities in dopaminergic control of blood pressure in patients with essential hypertension have been suggested by other investigators (53,54). Bugli et al. (55) showed that dopamine and fenoldopam, a dopamine (DA) 1-receptor agonist, do not increase RBF or prostacyclin in patients with essential hypertension. This suggests an alteration in dopaminergic tone, characterized by a defect in DA receptor sensitivity. Falkner et al. (56) observed an abnormal sympathetic response to high-sodium intake in young, prehypertensive adolescents with strong familial tendencies for hypertension. Light et al. (57) showed that exposure to competitive mental tasks significantly reduced urinary sodium excretion in young men with a family history of hypertension and increased urinary sodium excretion in subjects without a family history of hypertension. In addition, the decrease in urinary sodium excretion was directly related to the rise in heart rate during stress, suggesting a higher degree of sympathetic activation in these patients.
Dietary sodium loading caused a greater fall in RBF and enhanced water retention in borderline hypertensive subjects than in normotensive subjects during upright posture (58). Abnormalities in the neuroadrenergic response to sodium loading have also been shown in rats with spontaneous hypertension. Lundin and Thoren (59) observed that during air stress, spontaneously hypertensive rats (SHR) manifested an exaggerated decrease in urinary sodium excretion in conjunction with a rise in activity of the renal sympathetic nervous system. Koepe and DiBona (60) showed that a high-sodium diet caused an even greater decrease in urinary sodium excretion and a more pronounced increase in activity of the renal sympathetic nervous system in conscious SHR compared with Wistar-Kyoto rats.

Renal denervation results in delayed onset of hypertension and attenuation of the severity of established hypertension in SHR (61,62). Richsten et al. (63) demonstrated that during an acute volume expansion, SHR manifest an exaggerated natriuresis. This effect is associated with a greater inhibition of renal sympathetic nerve activity in SHR than in normal rats. Wintternitz and Oparil (64) showed that high-sodium intake may alter the neuroadrenergic control of blood pressure in the central nervous system. Chen et al. (65) recently showed that high-sodium intake may reduce noradrenergic input into depressor neurons of the anterior hypothalamus and increase noradrenergic input into stimulatory neurons in the pons, ultimately resulting in an increase in sympathetic nervous system activity and hypertension.

All of this evidence supports the notion that an increase in activity of the renal sympathetic nervous system may play an important role in the maintenance of essential hypertension in both animals and humans. This occurs by the stimulation of sodium retention and the shifting of the pressure-natriuresis curve to the right of the curve of normal subjects.

**ABNORMALITY IN CELLULAR SODIUM TRANSPORT IN HYPERTENSION**

In 1952, Tobian and Binion (66) observed an increase in sodium content in the renal arteries of hypertensive patients compared with normotensive subjects. This early observation stimulated a great deal of research on sodium transport in human cells. Because of obvious problems in obtaining samples of blood vessels from living hypertensive and normotensive subjects, more of the investigations on sodium transport in human subjects have relied on studies performed on leukocytes, erythrocytes, or platelets. The validity of all of these studies is based on the assumption that the transport processes in these cells are representative of those taking place in vascular smooth muscle cells.

Several investigators have shown an elevated intracellular sodium content and a reduced rate constant for sodium efflux by the sodium pump in leukocytes from patients with essential hypertension when compared with normal subjects (67,68). No abnormalities in sodium influx or in ouabain-resistant sodium efflux have been demonstrated (69). The levels of intracellular sodium in leukocytes are positively correlated with the diastolic blood pressure and are reduced by thiazide diuretics (70). Several laboratories have shown no abnormalities in sodium content or transport in leukocytes from normotensive offspring of hypertensive parents (69). This suggests that this abnormality may be a consequence of hypertension rather than of genetic transmission. The sodium-lithium countertransport is higher in leukocytes from hypertensive patients than from normotensive subjects. It is also higher, albeit to a lesser degree, in normotensive offspring of hypertensive parents, suggesting that increased activity of this system may be genetically linked to the risk of developing hypertension (69).

The findings in erythrocytes have been less consistent. Some studies have shown an increase in sodium content in the erythrocytes of hypertensive patients when compared with normal subjects, whereas others could not confirm this finding. There is also no agreement regarding which of the transport processes responsible for the maintenance of intracellular sodium concentration is abnormal in patients with essential hypertension (70). Canessa et al. (71) described increased rates of sodium-lithium countertransport in red cells of patients with essential hypertension when compared with that in normotensive subjects, and this defect appears to be genetically linked to hypertension.

Hatori et al. (72) performed studies which demonstrate increased activity of the Na⁺-H⁺ antiport in cultured fibroblasts from normotensive blacks when compared with white normotensive patients. These investigators speculate that if increased Na⁺-H⁺ antiport activity is also expressed in renal tubular cells, this could explain the propensity of blacks to retain sodium and to develop hypertension in response to sodium loading. Activation of the Na⁺-H⁺ antiport could be secondary to agonist-mediated calcium inside of cells and not necessarily a primary abnormality in essential hypertension. It is also important to emphasize that the Na⁺-H⁺ antiport activity may not be equally expressed in all of the cells.

In recent years, it has been hypothesized that factors present in the serum may modify sodium transport. This in turn could cause abnormalities in sodium content in erythrocytes or leukocytes of hypertensive patients (73). It has been proposed that during
sodium loading, some hypertensive subjects tend to retain sodium. In order to maintain a normal sodium balance, they increase the production of a postulated natriuretic hormone (74). This hormone would inhibit the sodium pump not only in the renal tubular cells, resulting in natriuresis, but also in cells throughout the body, including circulating cells such as leukocytes and erythrocytes.

It is possible that an increase in intracellular sodium would result in an increase in intracellular calcium. Haddy and Overbeck (75) suggested that the inhibition of the sodium pump would result in slight depolarization of the cell membrane, which would then lead to a rise in cytosolic calcium. Blaustein, on the other hand, suggested that the rise in cytosolic calcium, which is associated with the rise in the sodium content of cells, would be the result of inhibition of the sodium-calcium exchange mechanism. The increase in cytosolic calcium in smooth muscle cells would result in increased vascular tone and in hypertension. An increase in cytosolic calcium in the sympathetic nerve terminals would result in increased release of norepinephrine.

Increased serum levels of an inhibitor of the sodium pump have been shown in several laboratories (76–78).

We and others (79,80) have shown that a high-sodium diet increases \( \text{[Ca}\text{]}^\text{2+} \) in SS, but not in SR, patients with essential hypertension. In addition, the changes in \( \text{[Ca}\text{]}^\text{2+} \) were significantly correlated with the changes in blood pressure.

IS THERE A LINK BETWEEN SALT SENSITIVITY AND PROGRESSIVE RENAL DISEASE IN PATIENTS WITH ESSENTIAL HYPERTENSION?

It is well established that accelerated or malignant hypertension frequently leads to chronic renal failure. However, the frequency of clinically significant renal insufficiency in patients with essential hypertension in the absence of an accelerated phase is still debated.

Black patients with essential hypertension develop renal insufficiency four to five times more often than do white (81–84). Rostand et al. (83) showed that hypertension was the cause of renal failure in 16% of patients with end-stage renal disease (ESRD) in a rural county in Alabama. However, the incidence was 30% in blacks and only 11% in whites. Nationally pooled dialysis data suggest that blacks represent 66% of all patients with ESRD due to essential hypertension, and 29% of all blacks with ESRD have hypertension as the primary cause.

Data from the United States Renal Data System indicate that, over the past decade, the incidence of ESRD due to hypertension has been increasing in blacks, despite a better control of hypertension and a decline in the incidence of strokes and heart disease (85). In 1982, 102 new cases per million of ESRD from hypertension were reported in blacks, compared with fewer than 20 new cases per million in whites, giving a black-to-white ratio of 6.6. This could be due in part to socioeconomic factors. It is also possible that, for any given level of blood-pressure elevation, the renal circulation may be more susceptible to injury in blacks than in whites. This possibility is supported by the studies of Rostand et al. (86) and Shulman et al. (87) showing that, despite good blood pressure control, a decline in renal function occurs more frequently in blacks than in whites. The reason for the greater susceptibility to injury of the renal circulation in blacks is not known.

There is substantial evidence to suggest that the hemodynamic adaptation of the renal circulation and the mechanisms responsible for sodium homeostasis may differ between black and white hypertensive patients. Black hypertensive patients have more severe nephrosclerosis, involving primarily the arcuate renal arteries (88), and reduced RBF when compared with whites (89,90). Blacks also have a greater prevalence of salt sensitivity than do whites, and they excrete a salt load more slowly and less completely than do whites (25,26,32,91).

Lowenstein et al. (93) estimated renal interstitial pressure by directly measuring wedged renal vein pressure. By this method, they calculated an increase in the glomerular capillary pressure in human subjects with essential hypertension despite an increase in renal afferent resistance. However, they did not study whether the renal hemodynamic adaptation to a high-sodium diet was different in SS as compared with SR patients and in blacks as compared with whites.

Williams and Hollenberg (39) observed that some patients with essential hypertension manifest a decrease in RBF in response to sodium loading rather than the increase seen in normal subjects. These patients were salt sensitive and displayed a fixed renal vascular and adrenal response to angiotensin II during low- or high-sodium intake. They called these patients "nonmodulators," because of their failure to modulate RBF and aldosterone response to angiotensin II with changes in sodium intake. These investigators did not evaluate racial differences in renal hemodynamic adaptation in response to different sodium intake. Their analysis was limited to patients with normal plasma renin activity, thus excluding in large part hypertensive blacks who commonly have reduced plasma renin levels (33).

We have recently evaluated the renal hemodynamic changes that occur during a low- and highsodium intake in 15 SR and 11 SS hypertensive black patients. We have shown that RBF increased and the filtration fraction decreased in SR patients. However,
RBF decreased and filtration fraction increased in SS patients during high-sodium intake, suggesting an increase in intraglomerular pressure (93). These findings support the notion that a rise in intraglomerular pressure in response to a high-sodium diet might be responsible for the greater propensity for black patients to develop ESRD.

Experimental evidence in rats with spontaneous hypertension supports this possibility. Renal function deteriorates faster in SS than in SHR rat models with hypertension. SHR and Dahl’s SS rats are two inbred strains genetically predisposed to develop hypertension. Hypertension in SHR develops independently of sodium intake, whereas in Dahl’s SS rats, hypertension develops only if these rats are exposed to high-sodium intake. In younger SHR rats, the superficial nephrons adapt to the rise in blood pressure with an increase in renal afferent arteriolar resistance, which protects them from the adverse effects of arterial hypertension (94–96). Dahl’s SS rats, on the other hand, are more susceptible to glomerulosclerosis and proteinuria; these animals adapt to a rise in blood pressure with a reduction of the afferent arteriolar resistance and a rise in glomerular capillary pressure (97). A more accelerated course of renal disease is also observed in other experimental models of SS hypertension in rats, such as DOCA-salt hypertension (98), uninephrectomized SHR (99), the Holtzman postasalt model of hypertension (100), and the Milan strain of SHR (101). All of these SS models of hypertension manifest a decrease in afferent arteriolar resistance and a rise in glomerular pressure in response to an increase in blood pressure. The mechanisms for the deranged renal hemodynamic adaptation in SS black patients, as compared with SR patients, remain to be determined.

ACKNOWLEDGMENTS

This study was supported by a National Center for Research Resources of the General Clinical Research Centers grant (M01 RR-43) from the NIH, by grant R01 HL 35629-03 from the NIH, and by a grant from Pfizer Laboratories Division.

REFERENCES


Salt Sensitivity in Hypertension


76. de Wardener HE, MacGregor GA: Dahl's hypothesis that a saluretic substance may be responsible for a sustained rise in arterial pressure; its possible role in essential hypertension. Kidney Int 1980;18:1–9.


