The relationship between sodium (salt) intake and blood pressure has been convincingly established by epidemiological, observational, interventional, physiological, and some genetic evidence for some time. Yet the interaction remains the subject of passionate and heated debate. Even among those who are convinced of the salt–blood pressure interaction, some advocate a population-wide attempt to reduce dietary salt intake, arguing on the basis of epidemiological and interventional evidence, and others who suggest that such interventions should be targeted toward those most likely to benefit: the “salt-sensitive” subpopulation. Studies that such interventions should be targeted toward those most likely to benefit: the “salt-sensitive” subpopulation. Studies have characterized such subgroups on the basis of higher blood pressure, increased age or African-American ethnicity.1 The issue is rendered even more compelling by the findings that salt sensitivity can be identified among “normotensive” subjects (ie, those with blood pressure <140/90) as well as those with hypertension1 and the designation of those with blood pressure levels between 120 and 139 mm Hg systolic and 80 and 89 diastolic as prehypertensive2 and at increased risk for development of fixed hypertension and for cardiovascular events compared with those with lower blood pressure.3

Observational data have provided a starting point for the quantitative considerations of dietary salt intake. The most recent (1999–2000) NHANES survey provides an estimated dietary sodium intake based on food records, excluding discretionary sodium, of 135 to 204 mmol per day for men and 100 to 155 mmol per day for women in the United States.4 Questionnaires are acknowledged to underestimate actual intake, and urinary sodium excretion has been shown to provide a more accurate index of total sodium intake because it represents ~93% of intake at steady-state conditions.5 A recent British survey reported that urinary sodium excretion averaged 187 mmol per day for men and 139 mmol per day for women.5 This was very similar to the urinary excretion averages of 183 mmol per day for men and 142 mmol per day for women in the NHANES survey.4 Potassium intake estimated from questionnaires averaged 61 mmol per day for men and women.4 Recent observations of 2 Northern Chinese sites and 1 in Southern China participating in the INTERMAP study showed an average urinary sodium excretion of 271 mmol per day from the northern sites and 139 mmol per day from the southern site, with little difference in potassium excretion (37 and 41 mmol/d, respectively).6 Mean blood pressure was 7.4 mm Hg systolic and 6.9 diastolic higher in the northern subjects who also had a sodium–potassium ratio that was twice that of the southern subjects.

The results of the recent multiple-intervention DASH-Sodium Study were used to evaluate the concept of salt sensitivity of blood pressure.7 Subjects had “prehypertensive” stage I hypertension and stage I hypertensive blood pressures, were an average age of 49.4 years, 57.5% were black, and 41% were hypertensive.8 Blood pressure was measured twice during the run-in period and 1 24-hour urine collection for sodium measurement. Mean baseline urinary sodium excretion was 153 mmol per day. No assessment of collection completeness was made. The assessment of individual blood pressure responses to the mixed intervention that also increased potassium and calcium intake in addition to reducing sodium intake (the initial DASH diet was reduced in sodium with an estimated content of 124 mmol per day) was based on individual blood pressure measurements made on 2 separate occasions compared with group urinary sodium excretion measured once during each dietary period. Although such an analysis based on intent-to-treat is of interest, it says nothing about individual salt sensitivity because confirmation of sodium intake is not provided to evaluate whether the individual subject achieved the desired reduction in sodium intake. Many of the studies examining the effect of sodium intake on blood pressure have conducted more frequent measurements of both blood pressure and urinary electrolyte excretion than were used in the DASH studies. Moreover, the group analyses exclude the possibility that salt-sensitivity thresholds may differ among individuals within the range of modest levels of such reduction, an issue recently raised by He and MacGregor, who noted nonlinearity of blood pressure response in the DASH-Sodium Study at the differing nominal sodium intakes.5 The authors of the DASH study conclude that identification of salt sensitivity in their study was difficult “. . . because blood pressure varies so much from day to day in individuals. . . ” and thus that “. . . targeting sodium-lowering interventions to individuals identified as salt sensitive would not be worthwhile.”7 Increasing potassium intake has been shown to reduce salt sensitivity of blood pressure even in normotensive subjects.9 The DASH diet essentially doubled potassium intake as evaluated by reported excretion.10 Thus, the effects of the DASH diet are attributable to modification of multiple
dietary constituents, including potassium and calcium. Finally, after interpreting their analyses as failing to show any evidence of differences in salt sensitivity in the blood pressure responses to the DASH-Sodium Study, some of the same authors and other investigators have recently published yet another “extensive” analysis, presumably of the same database, interpreted as identifying subgroups of their population (hypertensives, older subjects, and those of African-American ethnicity) in whom significantly greater reductions in blood pressure were observed compared with the less hypertensive, younger, and non-African-American subjects in their cohort. They concluded, “... that adherence to a combination of the DASH diet and reduced sodium intake might blunt the well-documented increase in blood pressure occurs with age...,” as we suggested in 1986 and that has been shown to be associated with salt sensitivity. Thus, it would appear that the recent reanalysis of the DASH-Sodium data has confirmed the subgroup differences in blood pressure responses to reduction in salt intake (salt sensitivity) reported by many groups using different methods.

Another recent report from the DASH-Sodium trial provides new information about the effects of a modest reduction in sodium intake on blood lipid levels. The DASH-Sodium diet at the lowest level of sodium intake lowered total cholesterol, low-density lipoprotein, and high-density lipoprotein (HDL), and raised the total cholesterol–HDL ratio significantly. These findings suggest that earlier reports of a significant rise in lipid levels with dietary sodium restriction may apply only to reduction of sodium intake <50 mmol per day that was used in those studies.

The search for explanations for the differences in salt sensitivity of blood pressure has focused primarily on the kidney and possible genetic differences in renal tubular sodium and potassium handling and cellular electrolyte transport. A recent study demonstrated that the eicosanoid 20-HETE modulates the natriuretic response to furosemide and that this response differs between salt-sensitive and salt-resistant hypertensives. A study in 199 older normal and hypertensive white and black women using dietary sodium loading and restriction demonstrated a similar prevalence of salt sensitivity in both races among the normotensives and that hypertensive black women had greater changes in blood pressure with the change in dietary sodium intake than did white women. These findings confirmed our earlier observations using a rapid volume expansion–contraction protocol. In addition, this study demonstrated higher intracellular sodium and calcium content in red blood cells of salt-sensitive and black women. These findings confirmed and extended earlier studies. It is notable that the recent study included hormone replacement therapy in almost half of the subjects. However, no mention was made of the effect of this therapy on blood pressure or salt sensitivity, a very relevant issue. Moreover, the effect of hormone replacement therapy on electrolyte transport was not discussed, which would seem to be appropriate because earlier studies have demonstrated an increase in intracellular sodium content among women taking estrogens.

The inconsistent reports of associations between salt sensitivity and blood pressure or its probable surrogate blood pressure responsiveness to diuretic administration, and α-adducin gene polymorphisms in some subpopulations but not in others, have led to an interesting recent essay suggesting that a combination of such renal tubular abnormalities may be responsible. This short review was recently elegantly amplified by a more extensive essay focusing on a specific subgroup of salt-sensitive hypertensives: blacks.

By evaluating urinary potassium excretion, this essay attempted to identify potential sites in the kidney that may be responsible for enhanced sodium conservation. The finding by one of the essayists of presumed “insuppressibility of intrarenal renin with salt” among a small group of normotenive blacks permitted incorporation of an abnormality of renal plasma flow into the model. The relationship between these observations and the typical finding of suppression of plasma renin activity in hypertensive blacks or those with salt-sensitive hypertension eludes explanation because the normotensive blacks had levels of peripheral renin activity that were indistinguishable from their white cohorts. The model described in the essay also includes consideration of abnormalities of water reabsorption suggested by 2 recent studies.

Studies in American low-renin, presumably salt-sensitive hypertensives suggest a relationship with the 460Trp allele; however, only 10% of the low-renin subjects demonstrated this polymorphism in this study. This group reported findings from presumably the same population demonstrating a familial association of low-renin hypertension related to the G460W polymorphism of the adducin gene. However, the authors did not present information on aldosterone because hyperaldosteronism is associated with renin suppression and hypertension and may be genetically mediated.

Another area of interest has been the epithelial sodium channel, enhanced activity of which has been reported to be responsive to amiloride in Liddle’s syndrome, a monogenic form of hypertension. Among hypertensives of African ethnicity with the T594 mol/L polymorphism of this channel, representing ≈5% of those of African descent, the blood pressure response to amiloride, 20 mg per day for 2 months, was evaluated. Blood pressure control was obtained in these subjects during the study supporting a role for the increased activity of this sodium transport channel in black hypertensives. However, in a study of normotensive white and black subjects, opposite responses were observed to administration of 5 mg per day amiloride for 1 week. The white subjects demonstrated a decrease in blood pressure, whereas blood pressure increased in blacks. The racial difference was significant. Measurements of epithelial sodium channel polymorphisms were not reported in the latter study.

Sodium intake has been associated with left ventricular hypertrophy in many studies. A recent study conducted in young normotensive black and white subjects suggest that an impairment of stress-induced natriuresis is related to a relative increase in left ventricular thickness. In addition, a greater blood pressure response to laboratory stress maneuvers was also observed. These findings may provide important insight into the greater risk for development of left ventricular hypertrophy in blacks and subsequent cardiovascular events. At the other end of the blood pressure spectrum,
in older subjects with systolic hypertension, dietary salt restriction has been shown to rapidly improve elastic artery compliance. This adds to the accumulating evidence supporting the reversibility of the “stiff” blood vessels commonly found in older subjects and indicates, for the first time, that pharmacological therapy is not the only factor that can improve vascular compliance in such individuals.

In view of these compelling findings supporting reduction in sodium intake is there any benefit in an increased sodium intake? In a few patients with obvious salt-losing syndromes or orthostatic hypotension, high salt intake (100 mmol per day of supplemental slow sodium for 1 month) may ameliorate some of the symptoms of hypotension and postural tachycardia.

A panel of the food and nutrition board of the Institute of Medicine recently issued the Dietary Reference Intakes on Water, Potassium, Sodium, Chloride, and Sulfate. This report recommends 65 mmol per day of sodium and 120 mmol per day of potassium as an adequate intake for most adults. We are far from those levels currently. Perhaps future studies and reports will demonstrate new approaches and new benefits from achieving these daunting goals. Finally, reducing the prevalence of cardiovascular disease requires a comprehensive change in lifestyle for many individuals in reducing caloric and alcohol intake, ceasing smoking, and increasing exercise.

References


More on the Sodium Saga
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*Hypertension.* 2004;44:609-611; originally published online October 4, 2004;
doi: 10.1161/01.HYP.0000145404.06354.9c

*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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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