The Impact of Sodium and Potassium on Hypertension Risk

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Summary: The pathogenic role of sodium surfeit in primary hypertension is widely recognized but that of potassium deficiency usually has been ignored or at best assigned subsidiary status. Weighing the available evidence, we recently proposed that the chief environmental factor in the pathogenesis of primary hypertension and the associated cardiovascular risk is the interaction of the sodium surfeit and potassium deficiency in the body. Here, we present the major evidence highlighting the relationship between high-sodium intake and hypertension. We then examine the blood pressure–lowering effects of potassium in conjunction with the pernicious impact of potassium deficiency on hypertension and cardiovascular risk. We conclude with summarizing recent human trials that have probed the joint effects of sodium and potassium intake on hypertension and its cardiovascular sequelae. The latter studies lend considerable fresh support to the thesis that the interaction of the sodium surfeit and potassium deficiency in the body, rather than either disturbance by itself, is the critical environmental factor in the pathogenesis of hypertension.
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The plague of primary hypertension afflicting contemporary societies originates from the miscreant interplay of internal derangements (largely residing in the kidney) and environmental factors.[1] Massive evidence has long shown the pivotal role of a high-sodium intake in the pathogenesis of hypertension and associated cardiovascular risk.[2–4]

Another environmental factor long implicated in hypertension is potassium deficiency; indeed, a compelling body of evidence indicates its critical contribution to the pathogenesis of the disorder. However, in contrast to the universal acceptance of the role of sodium surfeit, it is perplexing that the contribution of potassium deficiency usually had been ignored or at best assigned subsidiary status.[1]

Weighing the available evidence, we recently proposed that the chief environmental factor in the pathogenesis of primary hypertension and the associated cardiovascular risk is the interaction of the sodium surfeit and potassium deficiency in the body.[1] This double disturbance in the body's main cations prevailing in hypertension emanates from the interplay between the modern diet—rich in sodium and poor in potassium—and nonadapted kidneys that intrinsically are poised to conserve sodium and excrete potassium. Exciting new insights have emerged on the multiple interactions of sodium surfeit and potassium deficiency in the brain and the periphery that culminate in increasing systemic vascular resistance and establishing hypertension. We recently presented a synthesis of these novel insights that documents the shared primacy of the body's dominant cations in the pathogenesis of the disorder.[5]

Here, we present leading pieces of evidence highlighting the relationship between high sodium intake and hypertension. We then examine the blood pressure–lowering effects of potassium in conjunction with the pernicious impact of potassium deficiency on hypertension and cardiovascular risk. We conclude with summarizing recent studies in human beings that have probed the joint effects of sodium and potassium intake on hypertension and its cardiovascular sequelae. The latter studies lend considerable fresh support to the thesis that the interaction of the sodium surfeit and potassium deficiency in the body, rather than either disturbance by itself, is the critical environmental factor in the pathogenesis of hypertension.

SODIUM INTAKE AND HYPERTENSION RISK

No human group studied develops primary hypertension if sodium intake is sufficiently low.[6–8] In fact, hypertension and age-related blood pressure increases are virtually absent in populations consuming fewer than 50 to 75 mmol/d of sodium, and are observed mainly in societies in which dietary sodium exceeds 100 mmol/d. Furthermore, mineralocorticoid-induced hypertension develops only in the presence of high sodium intake.[9] Current consumption of sodium in Western-acculturated societies averages 150 to 200 mmol/d (~9–12 g/d of sodium chloride). Nonetheless,

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in most world populations, sodium intake exceeds the threshold required for hypertension to appear, yet variable but large fractions of people are normotensive. Thus, a sodium intake exceeding the hypertension threshold is necessary but not sufficient for the development of primary hypertension. Although in early adulthood approximately 25% of the population is hypertensive, the lifetime risk of hypertension exceeds 90% in contemporary societies. The delayed appearance of primary hypertension in the second half of life likely reflects the additive effects of a decline in renal function, an override of compensatory blood pressure–lowering mechanisms with aging, and other factors.

Cross-population epidemiologic studies have long shown a positive correlation between sodium intake and blood pressure.[2,10,11] By contrast, this association had not been borne out in within-population studies until publication of the International Study of Salt and Blood Pressure (INTERSALT) in the late 1980s.[12] Several factors contribute to the difficulty in showing such an association within a population, including a relatively narrow range of sodium intake, the unreliability of a single 24-hour urine sodium excretion as an index of sodium intake, other environmental confounders, and dilutional regression bias. Nonetheless, INTERSALT showed a significant direct correlation between urinary sodium excretion and slope of blood pressure with age (mm Hg increase/y) both across and within populations. In an analysis across populations, the estimated increase in blood pressure from age 25 to age 55 was 9 mm Hg for systolic blood pressure (SBP) and 5 mm Hg for diastolic blood pressure (DBP) per 100 mmol/d higher sodium intake. After adjusting for age and sex, a 100-mmol lower sodium intake, for example, 70 mmol/d instead of 170 mmol/d, was associated with a lower SBP by 5 to 7 mm Hg across populations and by 3 to 6 mm Hg within a population. This effect was even more robust in older age groups (40-59 y) than in younger groups, with SBP being lower by 10 mm Hg.[7]

Although numerous epidemiologic and observational studies have documented the association of high sodium intake with hypertension, they obviously cannot establish causation.[3,13] In this regard, interventional studies in animals and human beings have pointed strongly to the conclusion that high dietary sodium leads to hypertension. Two landmark studies in chimpanzees (human beings share more than 98% of their genome with this species) have shown unequivocally that changes in sodium intake have a significant directional effect on blood pressure.[14,15] The first study involved 26 animals on a vegetable diet plus a liquid infant formula to supplement calcium.[14] The baseline sodium intake was up to 25 mmol/d (~1.5 g/d of sodium chloride) and blood pressure in animals on this diet did not increase with age. A treatment group received sodium-chloride supplements in increasing amounts of 5, 10, and 15 g/d. A progressive increase in blood pressure was observed in most, but not all, animals in response to the 5-g steps of sodium-chloride additions, highlighting the heterogeneous response to sodium loading. The mean SBP increased by 33 mm Hg and the mean DBP increased by 10 mm Hg with the highest sodium intake. By 20 weeks after cessation of the added sodium, the blood pressure decreased to baseline values and those of the control group. The study showed that addition of up to 15 g/d of sodium chloride to the diet of chimpanzees caused large increases in blood pressure, which reversed when the added salt was discontinued.

The second study evaluated the effects of changes in sodium intake within a range observed in human populations, while maintaining an unaltered intake of all other nutrients.[15] In two colonies of chimpanzees ($n = 17$ in Franceville, Gabon; and $n = 110$ in Bastrop, TX), the investigators explored the effects of dietary sodium in accordance with the baseline sodium intake of each colony. Although the Gabon colony lived on 75 mmol/d of sodium, the Texas colony had a baseline sodium intake of 250 mmol/d; the prevalence of hypertension in these colonies was 11.8% and 42.7%, respectively. Over 3 years, the sodium intake of the Gabon colony initially was decreased from 75 to 35 mmol/d, and then increased to 120 mmol/d, while maintaining a constant high-potassium and calcium intake. Estimates adjusted for age, sex, and baseline weight showed SBP of -12.7 mm Hg and DBP of -7.5 mm Hg per 100 mmol/d lower sodium intake. In the Texas colony, one group was continued on the standard sodium intake of 250 mmol/d for 2 years, whereas sodium intake was halved in the experimental group; both groups were maintained on an essentially similar high-potassium and calcium intake (355 and 440 mmol/d, respectively). Adjusted estimates showed a SBP of -5.7 mm Hg and a DBP of -4.4 mm Hg per 122 mmol/d lower sodium intake. Thus, the results of the second study showed in chimpanzees, the animal species phylogenetically closest to human beings, that the sodium-related decreases in blood pressure were as large or larger for sodium intakes at or below current dietary guidelines in human beings as those in the range of usual sodium intakes (120-250 mmol/d). Notably, that study was an essentially single-variable experiment because the effects of change in dietary sodium on blood pressure occurred in the presence of a constant high-potassium and calcium intake.

In the Dietary Approaches to Stop Hypertension (DASH)-Sodium study, 412 volunteers with or without hypertension were assigned randomly to receive, for 30 consecutive days, each of 3 sodium intakes (approximately 150 mmol/d, 100 mmol/day, or 50 mmol/day) in association with a control diet (typical American diet) or the DASH diet (rich in vegetables, fruits, and