Sodium Sensitivity, Not Level of Salt Intake, Predicts Salt Effects

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The current salt debate is driven by two fundamentally different views on the role of sodium in the pathogenesis of essential hypertension [1]. The first suggests that the high intake of dietary sodium in industrialized societies is the principal cause of both hypertension and the rise in arterial blood pressure that occurs with age. This school of thought further suggests that the average level of blood pressure in a population is determined predominantly by the average amount of salt consumed, and that variability around the average reflects individual differences in intake. Proponents of this viewpoint maintain that the most efficient way to lower blood pressure, and in turn the incidence of cardiovascular disease, is to shift the whole distribution downward through universal dietary salt restriction. This could be best achieved by reducing the sodium content in processed food, the main source of dietary sodium. The opposing viewpoint claims that individuals vary markedly in their susceptibility to dietary sodium, with some becoming hypertensive while others remain normotensive with similar levels of sodium intake. It is postulated that the blood pressure distribution of the total population is a composite of two subpopulations, one salt-resistant and the other, salt-sensitive. In developed societies, the average blood pressure value of the larger salt-resistant population is lower than that of the much smaller salt-sensitive population. A health policy advising all individuals to restrict their salt intake would be inefficient from this viewpoint, because a favorable effect would be observed only in those who are salt-sensitive and might even be harmful to those who are salt-resistant.

Numerous studies in animals have examined the effects of altering dietary salt on blood pressure and have yielded findings that bear directly on the present debate. Folkow *et al.* observed no change in blood pressure in Wistar-Kyoto and Dahl salt-resistant rats, despite varying the dietary salt intake by as much as 240-fold [2]. They also demonstrated only a small increase in blood pressure in spontaneously hypertensive rats fed an extremely high salt diet and a slight reduction when fed a very low salt diet. The blood pressure of Dahl salt-sensitive rats, in contrast, rose dramatically in response to an increase in dietary salt intake. These findings illustrate the marked heterogeneity of the blood pressure response between strains of rats to changes in sodium balance.

The same investigators also noted that rats placed on a salt-restricted diet demonstrated marked salt hunger and reduced tolerance to blood loss [2]. When the animals were given free access to salt, their intake was 40 to 50 times greater than the minimum requirement for survival. This finding, also observed in sheep, suggests the possibility of an inherent salt appetite that regulates consumption to protect against the risks associated with extremes of intake. Evidence for such regulation in humans, however, is scarce. Nonetheless, it has been observed that sodium intake in most developed countries throughout the world ranges from 100 to 200 mmol per day [3], which is greatly in excess of the minimum requirements of 5 to 10 mmol per day.

Studies in humans have employed a variety of methodologic designs, ranging from ecologic studies to intervention trials, to examine the link between sodium and blood pressure. The largest and most scientifically rigorous ecologic study was the Intersalt study [3]. In 52 centers, from 32 countries world-wide, blood pressure and sodium intake were determined in 200 adult men and women. In their ecologic analysis, adjusted for age, sex, body mass index, and alcohol intake, the investigators found a significant and positive association between daily urinary sodium excretion and systolic blood pressure, but no link with diastolic blood pressure. This association, however, was critically dependent upon the inclusion of four primitive societies with a very low sodium intake. In a separate analysis in which these four societies were excluded, the association was no longer statistically significant, and the correlation became slightly negative. Low levels of salt intake in primitive communities have been reported by many investigators, and characteristically, these societies have a low mean blood pressure level and show little rise in blood pressure with age [4]. Most primitive societies vary significantly from acculturated societies, not only in their salt intake, but also in many other ways that might influence blood pressure level, including greater levels of physical activity, reduced body mass index, lower consumption of alcohol, higher intake of

dietary potassium and fiber, lower intake of saturated fats, and reduced levels of stress.

To examine the relative importance of dietary salt intake in determining blood pressure in primitive societies, Hollenberg *et al.* studied a group of Kuna Indians who lived on the San Blas archipelago off the Caribbean coast of Panama and a second group who migrated to Panama City [5]. The island dwellers had an average sodium intake of 210 mmol per day, a level equal to or higher than most acculturated societies. Despite the high sodium intake, the mean arterial pressure did not rise with age, and hypertension was virtually absent, even in the older population. On the other hand, the Kuna who were living in an urban environment demonstrated the well-described rise in blood pressure with age and the age-related increased prevalence of hypertension. These results do not support the idea that a high salt diet plays a critical role in the pathogenesis of hypertension in developed societies and that restricting intake would protect against its development.

Although experimental and observational studies have been instrumental in raising the awareness of a possible link between salt and blood pressure, intervention trials are the most methodologically robust way to demonstrate a cause-and-effect relationship. Unlike drug studies, trials that alter nutrient intake are harder to conduct, and the findings are more difficult to interpret because of difficulties in controlling for confounding and co-intervention. Moreover, it is often impossible to assess the independent effects of a single nutrient, as dietary manipulations concurrently change the intake of other nutrients that may also influence the outcome. Furthermore, blinding of the nutrient intervention is often difficult to achieve, setting the stage for possible investigator or patient bias. This problem can be reduced, but not eliminated, by a blinded outcome assessment.

Many intervention trials assessing the effects of altering dietary salt intake on blood pressure have been reported. The findings of well-designed randomized controlled trials were summarized in a meta-analysis conducted by Midgley *et al.* [6]. They noted that in trials of older hypertensive subjects there was a dramatic fall in blood pressure with dietary sodium restriction. The magnitude of the fall in trials of younger hypertensive subjects was less, although the mean change in systolic pressure was still statistically significant. In trials of normotensive subjects, however, there was virtually no effect of dietary sodium restriction on the blood pressure, particularly in those who lived outside an institutional setting. The overview was criticized for including trials of short duration, arguing that the full blood pressure- lowering potential of salt restriction had not been achieved. The critics, however, ignored a subgroup analysis contained in the original article, which showed that trials of short duration had a significantly greater fall in blood pressure than in the longer-term trials.

The hypothesis that long-term dietary sodium restriction can reduce the incidence of hypertension was tested in the Trials of Hypertension Prevention (TOHP) [7,8]. In TOHP-II, the longer of the two trials, overweight individuals (baseline mean, 94 kg) with high-normal blood pressure (baseline mean, 127/86) were randomly assigned to receive one of four treatments: sodium restriction alone, weight loss alone, the combined intervention, or usual care. The trial was designed to have sufficient power (>80%) to detect an average risk reduction of 25% in the incidence of hypertension consequent to restricting dietary salt intake. The investigators reported a net fall in blood pressure in the sodium-restricted group of 3.9 mm Hg systolic and 1.6 mm Hg diastolic at 6 months, but only 1.2 mm Hg systolic and 0.7 mm Hg diastolic after 36 months of follow-up [8]. The net differences in daily sodium intake at these respective points were 50 and 40 mmol per day. Through 36 months, the last time point at which all active participants were evaluated, sodium restriction reduced the likelihood of developing hypertension by 12%, but this treatment effect was not statistically significant. Because the impact of salt restriction was considerably smaller than anticipated, this trial did not have sufficient power to confidently exclude the possibility of no treatment effect. Nonetheless, the findings do have important public health implications. They highlighted the need for more effective interventions that can be widely applied to prevent the development of hypertension.

In the meta-analysis by Midgley *et al.* there was significant heterogeneity among trials, which could not be eliminated even when differences in trial design were taken into account [6]. This finding suggested that biologic differences among individuals might be an alternative explanation. Miller *et al.* addressed this issue in a study of 82 normotensive adults [9]. They found marked variation in the blood pressure response to sodium restriction, ranging from a fall in mean arterial pressure of 15 mm Hg to an increase of 17 mm Hg. These findings are similar to those observed in experimental animals.

The concept of sodium sensitivity as a valid and reproducible biologic phenomenon is now widely accepted [10]. Methods of ascertaining sodium sensitivity in humans vary considerably, but typically involve demonstrating an arbitrary change in blood pressure in response to acute or short-term changes in sodium balance. Currently, testing for sodium sensitivity is poorly standardized and likely accounts for some of the differences in prevalence estimates. Nonetheless, variability in population selection, particularly the age of the subjects studied, their ethnic origin, the presence of hypertension or obesity, and level of intake of other dietary minerals, is also responsible for the variation in prevalence. It is estimated that up to 60% of hypertensive, but only 15% to 25% of normotensive, individuals are salt-sensitive. Evidence that sodium sensitivity increases with age comes from cross-sectional data [11]. A stepped increase in the prevalence of sodium sensitivity occurs with each decade in hypertensive individuals beginning in the 20s, but an increase in

prevalence in normotensive subjects was observed only in patients over the age of 60 years. Trial data are in agreement with these observations. In a 4-week crossover trial of dietary salt restriction in elderly subjects who were either normotensive or had untreated hypertension, blood pressure fell significantly when salt intake was reduced and rose again after resuming baseline salt intake [12]. On the other hand, younger hypertensive, but not normotensive, individuals demonstrated a significant fall in blood pressure with dietary salt restriction [6].

The rise in blood pressure observed with age in developed societies does not appear to be inevitable. In a prospective study, salt-resistant individuals who were followed for 10 or more years showed no significant change in blood pressure with time, while in salt-sensitive subjects the increase in systolic and diastolic blood pressure after 10 years averaged 14.2 mm Hg and 6.6 mm Hg, respectively [11]. This suggests that the age-related rise in blood pressure occurs principally in individuals who are salt-sensitive.

Being overweight or obese is strongly associated with an increased prevalence of hypertension and sodium sensitivity [4]. Disturbingly, the prevalence of obesity in 1998 in the United States was 17.9%, up dramatically from 12.7% in 1992 [13]. The dynamic relationship between blood pressure and sodium was carefully assessed in an intervention study involving weight loss in obese and non-obese adolescents [14]. Only obese subjects had a significant fall in blood pressure when placed on a low sodium diet. Further examination revealed that only the obese adolescents who were prescribed a weight loss program but failed to lose weight continued to demonstrate a fall in blood pressure on a low-sodium diet. Those who successfully lost weight demonstrated no fall, or even a slight rise, in blood pressure when salt intake was restricted. These data indicate the importance of concurrent obesity as a determinant of sodium sensitivity.

Deficiencies of dietary minerals such as potassium, calcium, and magnesium may also be causally related to sodium sensitivity. Epidemiologic studies suggest an inverse relation between dietary potassium intake and blood pressure [15]. Studies involving dietary manipulation of potassium intake revealed that normotensive individuals placed on a low-potassium diet had a significant rise in blood pressure and a marked fall in urinary sodium excretion [16]. The rise in blood pressure was further exaggerated by saline infusion. These effects were quickly reversed when subjects were switched back to a potassium-rich diet. Further observations were made in a metabolic unit study of both black and white normotensive subjects who ate a basal diet low in sodium and marginally deficient in potassium (30 mmol per day) for 2 weeks, followed by a marked increase in salt intake [17]. On the high-salt diet, there was a significant increase in both systolic and diastolic blood pressure in blacks, but not in whites. The frequency of sodium sensitivity was 79% in blacks, but only 36% in whites, and this difference was statistically significant. When dietary potassium was then increased to 70 mmol per day (normal intake) on the high-salt diet, blood pressure fell significantly in blacks and was also lower in whites. When black subjects received 120 mmol potassium daily (high intake) on the high-salt diet, the frequency of sodium sensitivity decreased significantly and became the same as that observed in white subjects consuming 70 mmol potassium per day. Blood pressure was also significantly lower than that observed in blacks receiving 70 mmol potassium daily. These observations complement those made previously and strongly suggest that the sensitivity to sodium can change, depending on the intake of other minerals. Furthermore, black subjects appear to be more responsive to changes in dietary potassium and require a higher potassium intake than whites to produce a similar response to a high-salt diet.

Data from population-based studies also indicate an inverse association between dietary calcium consumption and mean population blood pressure [15]. This finding is most apparent in subjects whose sodium:potassium ratio is high and suggests that an adequate calcium intake appears to protect against the blood pressure-raising action of a high-sodium, low-potassium diet [18]. A high-calcium diet also lowers blood pressure, and this effect is most apparent in salt-sensitive individuals or Dahl-S rats with salt-induced hypertension [19]. Thus dietary calcium, like potassium, modulates the effects of salt on blood pressure.

The importance of nutrient interactions as determinants of blood pressure level was recently demonstrated in the Dietary Approaches to Stop Hypertension (DASH) trial, a landmark study sponsored by National Heart, Lung & Blood Institute [20]. This trial tested a typical American diet against 1) a diet high in fruit and vegetables, and 2) a diet enriched with low-fat dairy products and high in fiber, along with a high intake of fruit and vegetables (the combined diet). Sodium intake and body weight were not altered. The group consuming the combined diet had the greatest fall in blood pressure, and the magnitude of the change was greater in hypertensive than in normotensive individuals. Furthermore, both black hypertensive and normotensive subjects had a greater fall in blood pressure than their white counterparts. Most importantly, the change in blood pressure in the DASH trial on the combined diet was two- to fourfold greater than that observed in the pooled results of sodium restriction trials [6,20].

There are now several studies relating nutrient intake to mortality. It is well known that the risk of death from all causes and from cardiovascular disease is significantly increased in overweight and obese individuals and is more pronounced in whites than in blacks [21]. The risk of death associated with dietary mineral intake is not as well documented. In a population-based cohort of middle-aged and elderly men and women, the risk of stroke death was significantly higher in subjects consuming a low-potassium diet than in subjects whose potassium intake was high [22]. The risk of stroke in relation to intake of calcium or

fruit and vegetables was recently reported in middle-aged American women in the Nurses' Health Study [23,24]. Women in the highest quintile of calcium or fruit and vegetable intake, as compared with those in the lowest quintile, had a significantly lower risk of ischemic stroke. In the Scottish Heart Health Study, in which 11,629 men and women were followed for an average of 7.6 years, increased potassium excretion (likely reflecting increased intake) at entry showed a highly significant protective gradient for all deaths in both sexes, and significantly protected against all coronary heart disease in men [25].

Data from the National Health and Nutrition Examination Survey (NHANES-I) Epidemiologic Follow-up Study were used to examine the association between serum magnesium concentration and mortality from ischemic heart disease and from all causes [26]. The study was undertaken to test the hypothesis that adequate levels of magnesium in the body may be related to a lower risk of ischemic heart disease. In this study, the highest age-adjusted ischemic heart disease and all-cause mortality rates occurred among those in the lowest quartile of serum magnesium concentration. While the relationship between serum magnesium concentration and dietary magnesium intake is still unclear, intracellular magnesium ion concentration is suppressed in salt-sensitive hypertensive subjects in response to salt loading, and the change is significantly and negatively correlated with the blood pressure response to this maneuver [27]. These findings suggest that abnormalities in magnesium metabolism may be linked to salt-induced hypertension and possibly in turn to cardiovascular disease.

There is a long-standing hypothesis that the risk of death from cardiovascular disease is substantially increased in persons consuming high levels of dietary salt, although supporting evidence is weak and based principally on ecologic associations. Recently, two groups of investigators have used data from the NHANES-I Epidemiologic Follow-up study to assess the risk of cardiovascular disease associated with dietary sodium intake in a representative sample of the US civilian, noninstitutionalized, population aged 25 to 74 years [28,29]. A single 24-hour dietary recall survey that did not include an assessment of salt added during cooking or at meals was used to estimate sodium intake. Alderman *et al.* found an inverse relation between sodium intake and death from all causes or from cardiovascular disease [28]. These findings persisted, even after excluding individuals with known cardiovascular disease and hypertension at initial examination and confirmed their previous observation in an employee population [30]. However, harsh criticism was leveled at the study because of the haphazard method of assessing sodium intake [31]. In a similar analysis of basically the same dataset, He *et al.* found that sodium intake is significantly and positively related to cardiovascular and all-cause mortality, but only in overweight subjects, defined as having a body mass index of 27.8 kg/m^2 or greater for men and 27.3 kg/m^2 or greater for women [29]. These investigators claimed an independent effect of sodium, but failed to adjust for known predictors of mortality such as family income [32], other dietary electrolytes [22–25], and serum magnesium level [26].

The disparate results of sodium trials and epidemiologic studies relating salt intake to mortality clearly underscore the complexities of the relationship between salt and physiologic parameters such as blood pressure and clinical outcomes. A unifying factor that would tie together these different observations is sodium sensitivity. As a valid biologic phenomenon, it would account for differences in blood pressure response to dietary salt intake when different populations are studied. It might also explain the increased risk of death in individuals who are overweight or deficient in minerals such as potassium, calcium, and magnesium. There is mounting evidence that sodium sensitivity is an independent risk factor for cardiovascular disease [10,33], and that it is linked to the presence of left ventricular hypertrophy in patients with essential hypertension [34]. Thus, health policies recognizing that only subsets of the general population will benefit from reducing dietary sodium intake have strong evidentiary support. Potential beneficiaries include the elderly, the obese, hypertensive subjects, persons of African-American origin, and individuals with dietary electrolyte deficiency (*eg*, calcium, potassium, magnesium). Sodium sensitivity, induced by dietary means, is clearly best managed by correcting the primary dietary abnormality. The results of the DASH study are extremely encouraging in this regard.

Future nutritional management of clinical hypertension will require identifying dietary deficiencies as well as excesses, and tailoring interventions to meet specific nutritional needs. At the community level, education to provide greater awareness of the link between poor dietary habits and low income is essential [35]. Finally, effective new strategies are urgently required to improve the eating behavior of economically disadvantaged people.

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