*Seventh Symposium on Salt*, Vol. II 227–230 (1993)
Elsevier Science Publishers B.V., Amsterdam



# Salt and Hypertension: The Current Evidence Reviewed

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Dietary salt intake has been linked to blood pressure at least indirectly for over 5000 years. In the oldest known medical writing the Nei Ching, the "Yellow Emperor", is quoted as having stated that: "If too much salt is in the food, the pulse hardens, the complexion changes, and tears make their appearance." About the same time, Job, the suffering character from the Old Testament, raised the question: "Can that which is unsavory be eaten without salt?" Mythology and folklore abound in stories and proverbs about salt, from the metamorphosis of Lot's wife to the building of the fabled Saharan city of Taghaza out of bricks of salt. The history of salt, its role in food preservation, and in cardiovascular regulation is a rich one.

Data relating salt intake to blood pressure are derived from epidemiologic observations, animal investigations, experiments addressing mechanisms at the animal and the cellular levels, and from dietary intervention trials. The data in support of the "salt hypothesis" are imperfect (Editorial, 1989), but nevertheless compelling. Epidemiologic evidence has been presented to support the notion that by reducing dietary salt intake, blood pressure may be lowered, or the development of hypertension may be avoided. Hypertension is virtually nonexistent in unacculturated societies, and blood pressure does not increase with age (Freis, 1976). An often-cited epidemiologic study is that published in 1960 by Dahl (Dahl, 1960) which included a graph with very few data points that indicated an almost perfect, linear relationship between the prevalence of hypertension and salt intake among five separate populations around the world. Estimates of salt intake were not uniform, the methods of blood pressure measurement were not described, and the age and sex distributions differed within each population (Prineas and Blackburn, 1985). The Eskimo group was represented by only 20 individuals, and the estimates of salt intake and prevalence of hypertension in Japan were much higher than later estimates.

An international epidemiologic study termed "Intersalt" sheds definitive light on these issues (The Intersalt Cooperative Research Group, 1988). Fifty-two centers with 200 subjects each from 32 countries participated in the study. Blood pressure was measured with a Hawksley random zero sphygmomanometer and accurate 24-h urine specimens were obtained in 10,079 subjects. Sodium excretion ($U_{Na}V$) ranged from 0.2 to 242 mmol/day; however, in 48 of the centers, which represent the bulk of the subjects, the range was only 100–242 mmol/day. $U_{Na}V$ was related to blood pressure in individuals, but the relationship was not robust. When data from the four centers with the lowest intakes were deleted, no relationship could be identified. When the slope of blood pressure with age within the centers was considered, a relationship was identified between that variable and median sodium excretion. However, $U_{Na}V$ was not related to median blood pressure or to the prevalence of hypertension as had been previously claimed by Dahl. Including potassium excretion in the analysis did not serve to improve the relationships. Body mass index and alcohol consumption had strong, independent effects. Intersalt indicates that the relationship between blood pressure, the prevalence of hypertension, and dietary salt intake is not as strong as proposed by Dahl. Law et al. (1991) and Frost et al. (1991) have recently published meta-analyses of epidemiologic data viewed both 'across' and 'within' populations. They conclude that the association of blood pressure with salt intake is substantially larger than generally appreciated. However, numerous studies in which salt intake was estimated by questionable methods were included, the methodology of salt intake estimation was heterogeneous, the "intersalt" data were not included, and confounding variables may have influenced their analysis.

Studies in experimental animals have elucidated the relationship between salt intake and blood pressure (Rascher, 1985). The salt-sensitive and re-

sistant strains bred first by Dahl illustrate the effect of genetic variance on salt-sensitivity of blood pressure in animals. Cross-transplantation experiments suggest that the kidney is somehow responsible for the hypertensinogenic effects of salt in this model. The DOCA-salt rat is an acquired model of salt sensitivity in which uninephrectomy is coupled with mineralocorticoid administration in order to produce hypertension. In this model, both volume and neural mechanisms appear to contribute to the development of increased blood pressure. Other rat models of hypertension, including the Milan strain, the Sabra strain, and the New Zealand strain exhibit variable degrees of salt sensitivity. The Okamoto strain of the spontaneously hypertensive rat is largely resistant to hypertensinogenic effects of salt. In contrast, other models including uninephrectomized rats, Goldblatt hypertensive rats, and in some instances otherwise normal Sprague–Dawley rats, may exhibit *increases* in blood pressure if the dietary salt intake is reduced.

Investigations at a cellular level raise the possibility that problems with sodium transport may be related to the development of hypertension (Hilton, 1986). Increased intracellular sodium may result in increased intracellular calcium secondary to sodium calcium exchange, which in turn may promote contraction of smooth muscle cells (Oshima et al., 1988). De Wardener and MacGregor, Blaustein, and Haddy have each proposed a rather similar mechanism to account for salt-sensitive hypertension (Blaustein and Hamlyn, 1985). They reason that a renal defect in salt excretion promotes the secretion of an inhibitor of sodium-potassium dependent ATPase probably from the brain. Such a material would facilitate natriuresis, but would encourage an increased peripheral vascular resistance related to an increase in intracellular calcium by the mechanisms described above. Such an inhibitor would also influence sympathetic nerve activity by affecting the release and re-uptake of norepinephrine.

Intervention trials of reduced salt intake as a treatment for hypertension have been performed in humans. Grobbee and Hofman (1986) reviewed the results of 13 well-performed, prospective, randomized, controlled clinical trials of dietary salt restriction in patients with hypertension. Reductions in salt intake in the trials were generally in the area of 80 mmol (2 g Na, 5 g NaCl) per day. A significant decrease was observed in only three of the 13 trials. The decreases in blood pressure were modest. Grobbee and Hofman also found that the fall in blood pressure was related to the height of the initial blood pressure. In addition, they identified a relationship between age and fall in blood pressure. Older individuals were more likely to decrease their blood pressure with dietary salt restriction. Similar observations concerning initial blood pressure and response to the intervention were made by Morgan and Nowson (Morgan and Nowson, 1986), who plotted the relationship between blood pressure and the logarithm of sodium excretion in over 40 trials of dietary salt restriction. A meta-analysis of intervention trials has also been recently published by Law et al. (1991), in which they conclude that a reduced salt diet would decrease stroke incidence by 26% and ischemic heart disease by 15%. Sixty-eight heterogeneous studies were included in their analysis, not all of which were adequately controlled. Their estimates of effects on blood pressure by salt restriction are somewhat greater than those of Grobbee and Hofmann (1986).

The most impressive results of dietary salt restriction were reported by MacGregor et al. (1982) who performed a randomized, cross-over, placebo-controlled trial of dietary salt restriction in patients with hypertension. Mean blood pressure in their patients dropped by 8 mm Hg. MacGregor et al. (1989) recently completed a trial of three sodium intakes (200, 100, and 50 mmol/d) in 20 older hypertensive patients. Blood pressure was significantly reduced on the middle and lowest sodium intake compared to the highest level. In the largest placebo-controlled trial to date, the Australian National Health and Medical Research Council Study (1989), sodium chloride restriction (<80 mmol/day) produced early, modest reductions in blood pressure. However, at the end of the eight-week study, there was no difference between the group on restricted dietary sodium intake and the group receiving the same diet plus 80 mmol/day supplemental sodium chloride.

Dietary salt restriction trials have produced rather heterogeneous results. One explanation is the possibility that only a fraction of hypertensive individuals are sensitive to the blood pressure-raising effects of salt while the rest may have hypertension related to other mechanisms. Weinberger et al. (1986) formulated a definition of salt sensitivity on the basis of responses to either acute salt loading and depletion, or to a dietary intervention. They found that one-third of normal individuals were salt-sensitive according to their definition. Among hypertensive subjects, approximately half were salt-sensitive. Older individuals and African–American subjects were more likely to be salt sensitive. These investigators have identified an influence of genetic variance on salt-sensitivity of blood pressure, and have proposed a possible genetic marker for the condition. Similar heterogeneous responses were also iden-

tified in normal individuals. The heterogeneous nature of the human blood pressure response has been further extended to include the blood pressure changes observed when calcium channel blockers are combined with low sodium chloride diets (Nicholson et al., 1987). Recently, Rocchini et al. (1989) identified an important interaction between salt-sensitivity and another nonpharmacological intervention, namely weight loss. They were successful in reducing the salt-sensitivity of 36 obese adolescents by means of reduced caloric intake and increased exercise.

Since salt restriction seems to evoke responses in blood pressure that are distributed in a Gaussian fashion, the possibility has been raised that salt restriction might increase blood pressure in some patients with hypertension. This possibility warrants additional study. Several reports, in which salt intake was sharply reduced for a short time, suggest a slight but significant increase in plasma lipids (Sharma et al., 1990), plasma insulin (Weder and Egan, 1991), and potentially deleterious effects on blood viscosity and platelet function (Ruppert et al., 1991). The relevance of these reports is at this time not clear. Although it is imprudent to suggest that salt restriction is necessarily harmful, this and all other dietary interventions are best performed under the supervision of a dietitian and physician. Finally, a correlation between salt intake and left ventricular mass has been described which was independent of blood pressure (Schmieder et al., 1988), and which was associated with abnormal responses to exercise of ventricular function (Blake et al., 1990). The notion that salt intake might adversely affect vascular tissue independent of blood pressure is a disturbing one that calls for additional investigation.

In summary, salt restriction lowers blood pressure in some individuals but not in all, and is generally more effective in older and in more severely hypertensive patients. Persons of African origin in particular may benefit. Patients with decreased renal function, particularly those with volume-related problems such as edema, fall into a special category, and generally should be aware of their salt consumption, that of other electrolytes, and their protein intake. Their dietary behavior should be carefully monitored by a physician. Compliance to a low salt regimen is difficult and can limit the effectiveness of this treatment.

In conclusion, dietary salt reduction is not a panacea for essential hypertension, nor has it been shown to preclude the development of the condition. Nevertheless, decreased salt intake is a valuable adjunct in certain patients, and until reliable means of identifying salt-sensitivity are available, salt reduction is a reasonable approach to the nonpharmacologic management of hypertension. Such nonpharmacologic management must include simultaneous attention to weight reduction, alcohol consumption, physical activity, and other dietary electrolytes.

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