The relation between dietary intake of sodium chloride and blood pressure levels remains controversial. The critical questions concern whether there is a susceptible subgroup at risk of elevated blood pressure because of sodium chloride consumption. If there is such a subgroup, what is its size and how can it be identified? Further clinical trials are needed to determine the long-term effects of sodium chloride reduction on blood pressure. The risk of disease, including stroke and coronary heart disease, is linear with blood pressure levels. A small change in blood pressure can have a relatively large impact on disease, even within the normal range of blood pressure. (Hypertension 1991;17[suppl I]:I-211-I-215)

**Research Directions**

Research directions for the relation between sodium intake and blood pressure should begin with a basic hypothesis. Salt intake raises the mean level of blood pressure in the population and results in a higher incidence of such hypertensive complications as stroke, congestive heart failure, and renal disease. Sodium chloride is a nutrient in the diet. The population's exposure to varying amounts of this nutrient results in increased risks of hypertension for individuals within the population based on dose, susceptibility (genetic factors) and other cofactors, obesity, behavioral stresses, alcohol, and other monovalent and divalent cations. This exposure to sodium chloride is an example of a continuous-exposure, common-source epidemic. The source is sodium chloride, and the outcome is elevated blood pressure and its complications.

Some individuals in a population are to a greater or lesser extent resistant to the effects of sodium chloride. Blood pressure in these individuals does not increase as much in response to the same dose of sodium chloride as in others. The reason for this relative resistance to sodium chloride is not completely understood. However, these individuals are believed to be better able to excrete a salt load by moderating such physiological effects as renal blood flow and secretion of aldosterone or other salt-retaining hormones, or through various neurogenic mechanisms.

Sociodemographic characteristics, phenotype, and environmental factors may facilitate identification of the more sensitive or less sensitive individuals. The demographic variables may include older age; blacks compared with whites; and the clinical factors of obesity, diabetes, or hyperinsulinemia associated with greater salt sensitivity.

The variation in sensitivity is also almost certainly due to specific genetic characteristics. Presently, the genotype has unfortunately not been identified. We can only demonstrate that there is a strong familial aggregation of blood pressure and that this aggregation is present early in life and can be identified in a variety of different ways, including measurement of blood pressure and the blood pressure response to exercise or psychological stressors.

At present, the markers of cellular sodium transport are the most likely candidates for unique genetic markers. There are probably more specific factors as yet unidentified, such as hormones or enzymes that actively control sodium homeostasis. The identification of the genotype would be a major advance in the study of the relation between salt and blood pressure. It would also provide a better approach for identification of those individuals more likely to benefit from specific interventions.

One reason for this inability to identify a specific genotype may be related to many polymorphic variations in the physiological responses that determine blood pressure level. Identification of a specific major gene effect that accounts for a substantial percentage of the heritability of hypertension or blood pressure levels may not be possible.

Obviously, it would be of great value to develop a specific test that would become a reliable predictor of elevated blood pressure resulting from sodium chloride in the diet. We could then identify individuals who are and are not "salt-sensitive." If we concluded that the prevalence of salt sensitivity was approximately 50% and that this estimation re-
required substantial testing to identify such a group, then a more rational approach to prevention of elevated blood pressure would be to modify salt intake in the diet for the population rather than searching out the 50% at risk.

Experience in many common-source epidemics suggests that the identification of a small, susceptible population from the remaining group, that is, by a major gene effect, is improbable. There are major gene effects that cause atherosclerosis, such as familial hypercholesterolemia resulting from low density lipoprotein (LDL) receptor defect, but the vast majority of individuals with atherosclerosis and hyperlipidemia do not have a known LDL receptor defect. They instead have a disease in which the common source is the dietary intake of fat and cholesterol, and there are multiple polymorphic genetic effects that determine the response to the diet. We are probably dealing with a linear or curvilinear relation between the dose of sodium and blood pressure levels. This may be extremely important, since the relation between blood pressure and risk of cardiovascular disease is linear across the usual range of blood pressure. Prevention of any rise in blood pressure may have an important effect on risk of cardiovascular and cerebrovascular disease.

We pose a problematic question: Are there other approaches that might affect the dose–response relation between salt and blood pressure level, therefore making it possible to either continue salt exposure in the diet without risk of elevated blood pressure or substantially moderate the dose–response relation?

Other dietary factors, such as intake of potassium, calcium, calories, or type of fat (e.g., \( \Omega_3 \) fatty acids), might be effective in moderating the dose–response relation between salt and blood pressure.\(^{19} \) For example, one viewpoint suggests that a high calcium intake may reduce the risk of hypertension in individuals who have a fairly high salt intake.\(^{6} \) Prostaglandin synthesis and metabolism as well as salt excretion\(^{20,21} \) might be affected by \( \Omega_3 \) fatty acids.

Indeed, if there is a linear or curvilinear relation between exposure to sodium chloride and the risk of elevated blood pressure or hypertension, we still might be able to distinguish those individuals who are “more susceptible” from those who are “less susceptible,” that is, those who are at the tail end of the distribution curve. We would then propose a more aggressive sodium chloride–restricted intervention in this subgroup of the population and perhaps other preventive interventions of high blood pressure as well.

Identification of individuals more likely to become marked responders to sodium chloride depends on the ability to measure both the exposure (i.e., sodium chloride) and the outcome (change in blood pressure). The variability of sodium chloride intake over time within the same individual makes it extremely unlikely that simple dietary questionnaires or measurement of urinary excretion could possibly identify individuals at higher risk of elevated blood pressure, given a specific exposure to sodium chloride.\(^{22} \) Instead, it requires a specific test, such as administration of an oral or intravenous sodium chloride load and measurement of sodium excretion in the urine and the change in blood pressure.\(^{2} \) Obviously, such approaches have been done repeatedly. One major question requiring an answer is the repeatability of such measurements. In other words, within a population sample, individuals who are “hyper-responders” to an oral or intravenous sodium chloride load with regard to blood pressure changes should remain in that category for subsequent analyses over time.

Which research approaches may enhance our understanding of the relation between sodium chloride and blood pressure? First, in the investigation of a nutrient and a common-source epidemic, the only approaches most likely to be successful are experimental. These approaches include natural experiments such as the INTERSALT study,\(^{23} \) in which one can observe the relation between blood pressure and sodium chloride intake in populations where exposure to the common source is quite variable and the differences in blood pressure level among populations are evaluated.

A second type of experiment is the investigation of populations in evolution. The rising prevalence of hypertension in Africa, especially in urban areas, may provide a good resource for studies of salt and blood pressure.\(^{24} \) A third type is the study of unique populations that exist within larger population groups. For example, both the American Indians and Mexican-Americans have a high prevalence of obesity, hyperinsulinemia, diabetes, and possibly elevated sodium–lithium countertransport; yet they may have less hypertensive disease.\(^{25} \) Is this apparent contradiction because they are less salt-sensitive, are there other dietary factors that protect them from hypertensive disease, or is there much less salt in their diet?

Fourth, migrant studies are a particularly interesting natural experiment. For example, the Japanese have had a high incidence of and mortality from stroke and, historically, a high salt intake.\(^{26} \) Japanese migrants to Hawaii and California show blood pressure levels that are not substantially different from the Japanese in Japan, yet the risk of stroke is substantially lower than that of Japanese living in Japan.\(^{27} \) In these instances, we are probably dealing with different types of hypertensive disease. The hypertension among the Japanese in Hawaii and California may depend more on obesity; in contrast, hypertensive disease among the Japanese in Japan primarily results from high salt intake. Further studies of these populations may provide important insights into both changes in blood pressure and types of blood pressure in relation to exposure to the various environmental factors related to hypertension, especially sodium chloride.
Clinical trials remain the major cornerstone of our research effort, relating sodium chloride to blood pressure levels or hypertension. Few long-term studies have been undertaken that successfully reduced sodium intake in the study population and measured the effects on blood pressure. Furthermore, these investigations need to couple effective genetic and physiological studies with reduction of salt intake. Such approaches will increase the likelihood of identifying the potential salt-sensitive population (if it exists) but will also provide a better understanding of the possible mechanisms of the relations between sodium chloride and elevated blood pressure. For example, such studies can test the hypothesis of the influence of insulin on salt and blood pressure, the effects of changes in sodium chloride intake on the transport system, and how these relate to the changes in blood pressure.

Another important objective in these trials is to identify methods of evaluating both the phenotype and genotype of salt sensitivity. Such studies need to be done in various populations, including those in which it is suggested that salt sensitivity is prevalent, such as in blacks and older age groups who may be more sensitive because of the loss of nephrons with aging.

Yet another approach is to evaluate short-term clinical experiments. The primary role of these studies is to experimentally test whether very resistant or susceptible individuals can be identified and relate this to the specific genetic markers. These short-term experiments will not provide us with a solution to the problem of whether long-term reduction of salt intake in a population will result in a decrease in blood pressure levels. They do provide a better approach to carefully measure an individual’s blood pressure response to sodium chloride. The investigator might identify the relation between specific genetic factors and change in blood pressure after the sodium chloride load.

Clearly, experimental studies with animals remain important in understanding the relation between sodium chloride and blood pressure. The pathophysiology of blood pressure regulation is extraordinarily complex. The controlled investigation of each unit or system may be futile. Instead, it seems more logical to focus on specific genetic markers across species, for example, the identification of specific polymorphisms that affect the regulation of hormone levels, enzymes, and salt transport.

Policy Implications

The implications of this research could translate to practical application in public health, preventive medicine, or clinical medicine. A good example is in the case of automobile accidents. The public health approach would be to build safer cars, lower the speed limit, build better roads, install air bags, and impose and enforce seat belt restrictions. All of these restrictions require minimum action by individuals. Likewise, the public health approach to salt reduction and hypertension would be to decrease the salt in processed food, the major source of salt in the diet. Such an approach would probably benefit only a percentage of people in the population. A cost increase may be associated with lower-sodium food, and it may not be palatable to many individuals. The majority of people might not benefit from the reduction of sodium chloride in the food.

In terms of automobile accidents, the preventive-medicine approach would suggest education of individuals about the hazards of driving under the influence of alcohol, the importance of using seat belts, vigorous law enforcement to reduce alcohol and drug consumption while driving, and major efforts to identify bad drivers and get them off the road. The preventive-medicine salt-hypertension method would identify as clearly as possible individuals who are at a high risk of hypertension because of family history, demographic characteristics such as age or race, or their current blood pressure levels (i.e., high-normal blood pressure or mild hypertension) and educate them to reduce the amount of salt in their diet and monitor their behavior to determine whether their blood pressure has been reduced. The intervention is limited to a smaller population at higher risk, but the approach remains prevention of high blood pressure and its complications.

The clinical approach to accidents would concentrate on improved emergency transport systems and trauma units in hospitals. The clinical approach to salt reduction would identify hypertensive individuals, test them with a salt load to determine blood pressure changes, and then treat with vigorous sodium chloride reduction the salt-sensitive individuals who are at risk from elevated blood pressure.

All three approaches have some merit and hold some promise for reducing the prevalence of hypertensive disease and its complications in the population. Each one presumes our acceptance of the fact that a cause/effect relation exists between the amount of salt intake, blood pressure levels, and risk of hypertensive disease and that decreasing the amount of sodium chloride will, at least in some individuals, reduce blood pressure levels. Most evidence would support this conclusion.

Changes in food processing (i.e., reduction of salt in foods) will probably have the greatest impact on reduction of blood pressure levels if the amount of hypertensive disease, that is, the attributable risk due to salt intake in the population, is fairly substantial. It is improbable that we can focus only on salt-reduced interventions with susceptible persons unless the number of such persons in the population is very small and a cost-effective method of finding them is used. As previously noted, the relation between sodium chloride and blood pressure is probably linear and continuous, not bimodal or trimodal. A small subpopulation of (genetically) very susceptible individuals at extremely high risk may exist, but until a specific genetic marker can be identified, we will probably be unable to expend the resources to find such individuals. Presume that 20% of the salt-
susceptible population were identified, and 10% of the nonsusceptible individuals were really susceptible but not found so by the test. Further assume that there were 100 million people in the United States at risk and that it cost $100 to test each one for susceptibility. If we tested 20 million people per year it would cost $2 billion/yr and take 5 years to test the whole population at risk. Four million of these 20 million people each year would be identified as susceptible, but 1.6 million of the remaining 16 million would actually be misclassified as not susceptible. Thus, we would have both an extraordinary cost of identifying the susceptible persons and a high probability that many of them would be missed, even if we had a test that was very specific and relatively sensitive.

From the public health perspective, a decrease in sodium chloride intake from about 9 g to about 6 g might result in only about a 1 mm change in diastolic blood pressure. If 20% of the population were susceptible, their blood pressure would drop 5 mm with no change in the other 80%, for an average 1 mm change for the total population. Therefore, a small change in blood pressure in relation to a substantial decrease in a population's sodium intake can be due either to a modest overall effect across the population (i.e., a 1 mm change for most individuals) or a substantial decline in blood pressure for the susceptible persons and little if any change for the nonsusceptible segment of the population. The variation in both the percentage of the susceptible segment of the population to the effects of sodium chloride and the ability of individuals to adhere to a lower sodium chloride diet will reduce the apparent effect of a lower sodium chloride intake on blood pressure level.

Blood pressure is normally distributed and risk of hypertensive disease is linearly associated with level of blood pressure. A relatively small change in blood pressure distribution can reduce both the number of hypertensive individuals and the occurrence of disease associated with elevated blood pressure. A better understanding of the relation between sodium, other risk factors, host susceptibility genetic factors, and blood pressure levels will almost certainly evolve from the clinical trials of nonpharmacological interventions in humans. These newer trials should link nutrition, genetics, and clinical pathophysiology.

References


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