Dietary Sodium and Blood Pressure

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The importance of dietary sodium chloride in the regulation of blood pressure has received much attention over the past few years. This area of research and knowledge has been controversial for several reasons. The major reason for controversy is that the science of the relationship is difficult to ascertain. Population science is limited by the narrow range of dietary sodium intake by most populations and individuals and the multiple confounders in those populations at the extremes of intake. Results from clinical trials have been difficult to interpret because of the difficulty in maintaining a given level of sodium intake over a period of time sufficient for study. Furthermore, basic science studies have been challenged by identifying appropriate models that mimic salt-sensitive hypertension in humans. Moreover, a lack of a well-funded proponent in industry complicates the research challenges.

Guyton’s concept that the role of the kidney in handling sodium is key to the long-term regulation of blood pressure is now generally accepted. However, the exact role that dietary sodium plays in this relationship remains controversial. The relationship between renal handling of sodium and blood pressure is apparently influenced by a complex combination of factors including nutritional, other environmental, genetic, neurohormonal, and metabolic factors.

The skepticism of many regarding the role of dietary sodium in blood pressure regulation and control has been tempered by the results of the DASH sodium study. Most acknowledge that this study reliably confirmed the benefit of dietary sodium restriction in blood pressure management. The study showed a dose-dependent impact of dietary sodium restriction on blood pressure in older hypertensive and nonhypertensive subjects. For many interested in this area of research, the questions have shifted as a result of the DASH sodium study. Rather than questioning whether dietary sodium is important, many investigators have turned their attention to other important unanswered questions related to dietary sodium and blood pressure: Are all persons salt-sensitive if exposed to changes in intake for a sufficient period of time? What are practical methods for determining salt sensitivity in humans? What are the mechanisms involved in the dietary sodium/blood pressure relationship? Are there significant blood pressure-independent effects of dietary sodium on cardiovascular disease morbidity and mortality?

This Hypertension Highlights article reviews evidence from the past 2 years that enhances our knowledge and understanding of the role of dietary sodium in the complex regulation of blood pressure.

Salt Sensitivity

Now that there is broad consensus that dietary sodium can influence blood pressure, one of the most pressing questions regarding salt sensitivity is, who benefits from manipulation of dietary sodium? On one side of the issue are those who believe that moderate dietary sodium restriction is beneficial for all, harmful for none, and that adequate methods for identifying sodium sensitivity in humans do not exist. These individuals propose a population (and sometimes regulatory) approach to restricting dietary sodium.

The opposite view is that the strongest evidence for the benefit of dietary sodium restriction exists primarily in those who are hypertensive, older than age 50, black, or who have renal disease, either primary or secondary to disorders such as diabetes. Concern is raised that dietary restriction of sodium in others is without the benefit of strong evidence, expensive, inconvenient, and potentially harmful. Many with this point of view also feel there are adequate clinical tools to identify the salt-sensitive individual from the nonsalt-sensitive.

Several recent studies in humans attempted to address this complex area. Wright et al examined ethnic differences in salt sensitivity in a study of 199 women. In this crossover protocol, normotensive and hypertensive participants were given a low-salt (20 mEq/d) and high-salt (200 mEq/d) diet. The prevalence of salt sensitivity was similar in blacks and whites (just >50%), but the magnitude of blood pressure change was greater in the black women. In black women only, salt sensitivity was positively associated with erythrocyte sodium, serum calcium, serum sodium/serum potassium, and serum calcium/serum magnesium.

The DASH–Sodium Trial investigators examined data from that study to determine if identifying individuals with salt sensitivity was practical. Their study used multiple, very carefully performed measurements of blood pressure. They determined that identifying individuals as salt responders was very difficult. Based on these findings, the authors supported sodium restriction in the general population. In an accompanying commentary, Egan notes the limitations of the blood pressure measurement methods in the study and raised
concerns about concluding that identification of individual responders to dietary sodium is not possible.\textsuperscript{5} In another study looking at methods for determining salt sensitivity in individuals, Flack et al conclude that “variability-adjusted blood pressure” was more sensitive than traditional statistical approaches.\textsuperscript{6} This variability-adjusted blood pressure was defined as the difference in blood pressure level after high- and low-sodium diet periods, divided by the intraperson standard deviation of the average blood pressure obtained at 3 consecutive screening visits. This study also showed usefulness of the urinary sodium-to-creatinine ratio in determining salt sensitivity.

He et al demonstrated in a human study that the larger decrease in blood pressure with sodium restriction in hypertensive compared with normotensive subjects was partly explained by less responsiveness in the renin-angiotensin-aldosterone system in hypertensive patients.\textsuperscript{7}

Several animal experiments examined potential mechanisms that may explain the link between dietary sodium and blood pressure. Two of these studies specifically dealt with salt sensitivity. Smith et al noted that endothelin increased the sensitivity of the mechanisms of vascular smooth muscle contraction to high dietary salt.\textsuperscript{8} Harrison-Bernard et al demonstrated that ovariectomy in salt-sensitive rats made them more sensitive to salt. An activation of the renin-angiotensin system was proposed to be involved in the change.\textsuperscript{9}

**Mechanisms Explaining the Dietary Sodium Blood Pressure Relationship**

Other animal studies explored a wide variety of mechanisms that might influence the dietary sodium blood pressure relationship. A number of studies focused on vasoreactivity and how modulation of dietary sodium influences nitric oxide or its precursors.\textsuperscript{10–13} A study by Giardina et al examined the impact of a low-sodium diet on vascular contractility during pregnancy.\textsuperscript{14} They demonstrated an increase in vascular reactivity with a low sodium diet, adding to the concern about potential adverse effects of sodium restriction during pregnancy. In nonpregnant rats on a high-sodium diet, Ying and Sanders demonstrated an increase in production of transforming growth factor-beta and nitric oxide.\textsuperscript{15} Their study demonstrated that dietary salt modulated gene expression in the arterial wall.

The sympathetic nervous system was also investigated as a potential pathway for dietary sodium modulating blood pressure. DiBona and Swain showed that arterial baroreceptor denervation leads to the development of increased blood pressure during high dietary sodium intake.\textsuperscript{16} This increase in blood pressure was associated with renal sodium retention. Kopp et al showed in rats on a high-sodium diet, interruption of the renal afferent nerves was associated with retention of sodium and an increase in blood pressure.\textsuperscript{17} In another rat model, Tanoue et al demonstrated a role of alpha receptors leading to an increase in blood pressure when challenged with a high-sodium diet.\textsuperscript{18} Other investigators made important observations in other regulatory systems including the renin-angiotensin system and others.\textsuperscript{19–23}

The DASH Study investigators also demonstrated that the DASH diet, rich in fruits, vegetables, and low-fat dairy products, was natriuretic.\textsuperscript{24} Apparently, the DASH diet enhanced the pressure–natriuresis relationship.

**Dietary Sodium and Potential Blood Pressure-Independent Cardiovascular Effects**

There has been increasing circumstantial evidence from population and basic science studies that dietary sodium may contribute to cardiovascular target organ injury through blood pressure-independent effects. Two animal and 2 human studies published recently provide evidence for blood pressure-independent effects on blood vessels, the heart, and the kidney.

Et-taouil et al reported that a high-sodium diet decreases aortic hyaluronan content and large artery compliance through blood pressure-independent mechanisms.\textsuperscript{25} An animal study and a human study showed an adverse impact on cardiac structure by dietary sodium. The animal study used a uninephrectomized deoxycorticosterone acetate/salt rat model to demonstrate sodium/hydrogen exchange isoform 1 (NHE 1) induced cardiac hypertrophy and perivascular fibrosis.\textsuperscript{26} The perivascular fibrosis was reversed by the aldosterone antagonist spironolactone and by cariporide, a specific inhibitor of NHE 1. Cardiocyte hypertrophy induced by DOCA/Salt was completely inhibited by cariporide, but not by spironolactone. The human study confirmed a positive relationship between dietary sodium and echocardiographic left ventricular mass after adjustment for several factors, including blood pressure.\textsuperscript{27}

A study in normotensive blacks and whites evaluated the response of the intrarenal renin-angiotensin system to low- and high-dietary sodium intake.\textsuperscript{28} The authors noted a more active system in blacks than whites on exposure to an increased sodium load. The authors speculate this may contribute to the increased susceptibility to renal injury in blacks.

**Salt Appetite**

An interesting area of investigation on dietary sodium and blood pressure has to do with appetite for salt. One criticism of efforts to reduce dietary sodium for the general population is that people desire food with a high salt content because the flavor is preferred. The counterargument is that this preference for high salt intake is mostly acquired. Additionally, it is thought by some that the “genetic drive” to eat salt was an advantage in years past when humans lived in a low-salt environment. The drive to eat salt may be a detriment now, when salt is easily acquired and humans live long enough for cardiovascular disease to be the leading cause of death.

In an animal experiment, Rigatto et al explored the possibility that oxytocin was more responsible for salt appetite than the renin-angiotensin system.\textsuperscript{29} This study demonstrated an angiotensin-independent role for oxytocin-induced salt appetite. In a study of human neonates, the preference for water, 0.1 or 0.3 molar sodium chloride solution, was measured.\textsuperscript{30} Those neonates favoring the taste of salt had higher blood pressures than those preferring water.

An Australian study addressed the issue of whether a reduction in the sodium content of bread would be acceptable to the general population.\textsuperscript{31} In this blinded study, sodium was
gradually reduced over a 6-week period by a total of 25% of baseline. Participants were not able to distinguish the period of time they were on the low-sodium bread. This is encouraging given the general resistance to lowering sodium in processed foods.

Population Studies: The Association of Dietary Sodium and Blood Pressure

The best available population-based data on the relationship between dietary sodium and blood pressure has been provided through the INTERSALT study, although the interpretation of that data has certainly been controversial. Clinical trials, primarily the DASH–Sodium study and the Trials of Hypertension Prevention, have confirmed conclusions of the INTERSALT investigators demonstrating changes in blood pressure in response to dietary sodium reduction of the magnitude predicted by INTERSALT.

Many of the INTERSALT investigators have collaborated in another major nutrition–blood pressure study, the INTERMAP study. Two early articles from that group shed additional light on the dietary sodium blood pressure relationship. The first article reports general nutrient intakes in the 4 countries with study sites: China, Japan, the United Kingdom, and the United States. These data confirm findings from INTERSALT that the stroke-prone countries of China and Japan, compared with the United Kingdom and the United States, have a higher intake of dietary sodium, lower dietary potassium, and, therefore, a higher sodium/potassium ratio. The second INTERMAP article of note to this discussion relates to the relationship between education level and blood pressure. The inverse relationship between education level and blood pressure is well known. However, the reasons for that association have been uncertain. In this study, the investigators demonstrate that almost all the adverse effect of a low education level can be accounted for by dietary variables, including a higher dietary sodium intake in those with a low education level.

Perspectives

In recent years, great strides have been made in understanding the dietary sodium–blood pressure relationship. Certainly, there is a wider consensus that sodium restriction is beneficial for many. In the past 2 years, much of the additional progress in our understanding has come in the area of salt sensitivity. There are no definitive answers, but we are closer to understanding what needs to be done. Clearly, practical methods to predict salt sensitivity in individuals will require rigorous attention to blood pressure measurements. It appears that excess dietary sodium may be harmful through a number of mechanisms that increase blood pressure and, perhaps, through mechanisms unrelated to the increase of blood pressure. Future studies should strive to unravel the science of the relationship between dietary sodium chloride and blood pressure. In the meantime, we will continue to debate the optimal level of sodium intake for various groups and individuals. Most in the US and in most countries around the world consume much more dietary sodium than is necessary for good health. Reduction of dietary sodium in most people would likely reduce mean arterial pressures as well as cardiovascular morbidity and mortality.

References

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