Review

Salt Sensitivity, a Determinant of Blood Pressure, Cardiovascular Disease and Survival

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High dietary sodium has been adduced as a cause of hypertension and its target organ damage for millennia; yet careful observations using sophisticated techniques have revealed only a weak relationship between sodium intake/excretion and blood pressure in the general population. Further, studies of the effects of dietary sodium reduction on blood pressure have revealed minimal achieved reductions in blood pressure, no relationship between the magnitude of reduction in sodium intake/excretion and the blood pressure effect, and no evidence of an effect of sodium reduction on death or cardiovascular events. While blood pressure in the population as a whole is only modestly responsive to alterations in sodium intake, some individuals manifest large blood pressure changes in response to acute or chronic salt depletion or repletion, and are termed "salt sensitive". Salt sensitivity and resistance have a large variety of determinants, including genetic factors, race/ethnicity, age, body mass and diet (overall diet quality, macro- and micronutrient content), as well as associated disease states, e.g. hypertension, diabetes and renal dysfunction. Salt sensitivity can be modulated by improving the quality of the diet, e.g. the DASH diet reduced salt sensitivity by increasing the slope of the pressure-natriuresis curve. Mechanisms that appear to contribute to salt sensitivity include blunted activity of the renin-angiotensin-aldosterone system, deficiency in atrial natriuretic peptide expression, and blunted arterial baroreflex sensitivity. Salt sensitivity in both normotensive and hypertensive persons has been associated with increased cardiovascular disease events and reduced survival. Increased attention to strategies that reduce salt sensitivity, i.e. improvement in diet quality and weight loss, particularly in high risk persons, is urgently needed.

INTRODUCTION

Sodium, normally found in foods as sodium chloride, is an essential nutrient because sodium and chloride are required to maintain extracellular fluid volume and serum osmolality. Variations in plasma sodium concentration may have direct and important effects on the osmotic pressure of the plasma, plasma and interstitial fluid volumes, acid-base balance, the maintenance of the electrical activity of cells, and the responsiveness of the cardiovascular system to circulating endogenous pressor agents [1]. Thus, close physiologic regulation of the concentration and content of sodium within the body is a crucial activity for health and efficiency of function in humans and all animals.

Human populations are capable of living at extremes of sodium intake, e.g. from approximately 0.46 g/day (20 mmol/day) of sodium in the Yanomamo Indians of Brazil to over 13.8 g/day (600 mmol/day) in Northern Japan [2]. The ability to survive at extremely low levels of sodium intake reflects the capacity of normal humans to conserve sodium by markedly reducing losses of sodium in the urine and sweat. Under conditions of maximal adaptation and without sweating, the minimal amount of sodium required to replace losses is estimated to be no more than 0.18 g/day (8 mmol/day). Under specific circumstances, e.g. heat stress or vigorous physical activity, the requirement for sodium may be substantially higher. Conversely, normal human kidneys can rapidly excrete very large salt loads, allowing adaptation to acute or chronic salt challenges without major alterations in blood pressure or volume homeostasis.

Sodium intake in most industrialized societies averages 3.5 g/day (150 mmol/day, range 120–200 mmol/day), a figure far

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in excess of the minimal daily requirement. Salt is a major food additive, and is important for food preservation as well as taste enhancement. The role of dietary sodium in health and disease has been a topic of great interest and debate for many years. While high dietary sodium has been adduced as a cause of hypertension and its target organ damage for over 4000 years [3,4], careful observations using sophisticated techniques have revealed only a weak relationship between sodium intake/excretion and blood pressure in the general population [5–10].

The INTERSALT study employed state-of-the-art techniques to measure blood pressure and assess salt intake (24-hour urinary sodium excretion) in a very large sample (almost 11,000) of men and women aged 20–59 years from 52 centers in 39 countries [5]. INTERSALT showed that there was no significant relationship between 24-hour urinary sodium excretion and blood pressure in an analysis of data from 48 acculturated populations. In contrast, body mass index and alcohol intake did correlate positively with blood pressure in this analysis. A weak but significant positive relationship between sodium excretion and blood pressure emerged only when 4 centers with nonacculturated populations (Yanomamo and Xingu tribes in Brazil and tribes in Kenya and Papua, New Guinea) that had extremely low intakes of salt and alcohol, as well as low body weight and low blood pressure, were included in the analysis. A reanalysis of the data by the INTERSALT investigators with the stated purpose of correcting regression dilution bias yielded a stronger relationship between salt intake and blood pressure [11] but has been severely criticized on the grounds of assumptions unsupported by data and questionable statistical methods [12,13]. Thus, the most contemporary, extensive, and rigorous observational study of the relationship between salt intake and blood pressure has yielded results that have been the subject of controversy and variable interpretation.

Similarly, meta-analyses of studies of the effects of dietary sodium reduction on blood pressure have revealed minimal achieved reductions in blood pressure and no relationship between the magnitude of reduction in sodium intake/excretion and the blood pressure effect. Blood pressure effects of the intervention are particularly small in normotensive persons [6–10]. Further, these studies gave no evidence of an effect of sodium reduction on death or cardiovascular events.

While blood pressure in the population as a whole is only modestly responsive to alterations in sodium intake, some individuals manifest large blood pressure changes in response to acute or chronic salt depletion or repletion, and are termed "salt sensitive". Salt sensitivity is defined as the tendency for blood pressure to fall during salt reduction and rise during salt repletion/supplementation [14]. Salt sensitivity and resistance have a large variety of determinants, including genetic factors, race/ethnicity, age, body mass and diet (overall diet quality, macro- and micronutrient content), as well as associated disease states, e.g. hypertension, diabetes and renal dysfunction. This review will focus on the determinants of salt sensitivity of blood pressure in humans and animal models.

ACUTE SALT CHALLENGE STUDIES IN HUMANS

Acute intravenous saline challenges coupled with salt reduction plus diuretic treatment to achieve volume depletion have classically been used to define salt sensitivity and resistance. Weinberger et al. [14] utilized these techniques to characterize the salt sensitivity of blood pressure in 378 normotensive and 198 hypertensive volunteers. Antihypertensive medications were discontinued 2 weeks before the study in the latter group. Blood pressure was measured after an intravenous infusion of 2 L of normal (0.9%) saline at a rate of 500mL/hr and after sodium and volume depletion induced by a 10 mEq sodium diet and 3 doses of oral furosemide (40mg). Persons with a decline in mean arterial pressure (MAP) $\geq$10 mmHg after sodium and volume depletion were categorized as "salt-sensitive", and those with a decrease $\leq$5 mmHg (including an increase in pressure) as "salt-resistant". Both normotensive and hypertensive groups responded to sodium and volume depletion with decreases in MAP, but the decrease was significantly greater in the hypertensives (Fig. 1A). Thus, hypertensive persons as a group were more salt sensitive than normotensive persons, a finding that has been verified in numerous subsequent studies. In contrast, both groups had similar pressor responses to acute saline infusion.

Salt sensitive individuals were significantly older than salt resistant persons (Fig. 1B), and when the salt-sensitive and -resistant subgroups were separated into those $\leq$40 years of age and those $>$40, the salt-sensitive individuals in the older group had significantly lower plasma renin activity. Hypertensive persons, both blacks and whites, had greater decreases in blood pressure after sodium and volume depletion than normotensive individuals (Fig. 1C). Seventy-two percent of black hypertensives, but only 43% of black normotensives were salt sensitive. Among whites, 56% of hypertensives but only 29% of normotensives were salt sensitive.

DIETARY SODIUM REDUCTION IN HUMANS - BLOOD PRESSURE EFFECTS

Results of the Dietary Approaches to Stop Hypertension (DASH)-Sodium trial provide further evidence of inhomogeneity of salt sensitivity in the population [15–18]. When dietary sodium intake was lowered by ~100 mmol/d (from high to low salt intake) in persons consuming the control diet, systolic blood pressure was reduced by a mean of 6.7 mm Hg overall; by 8.3 mm Hg in hypertensives vs. 5.6 mm Hg in normotensives ($p < 0.05$); by 7.5 mm Hg in participants over age 45 vs. 5.3 mm Hg in younger persons ($p < 0.05$); and by 8.0 mm Hg in African Americans vs. 5.1 mm Hg in other racial/ethnic groups ($p < 0.01$) [16]. These responses to sodium reduction were greatly attenuated by feeding the DASH eating plan,

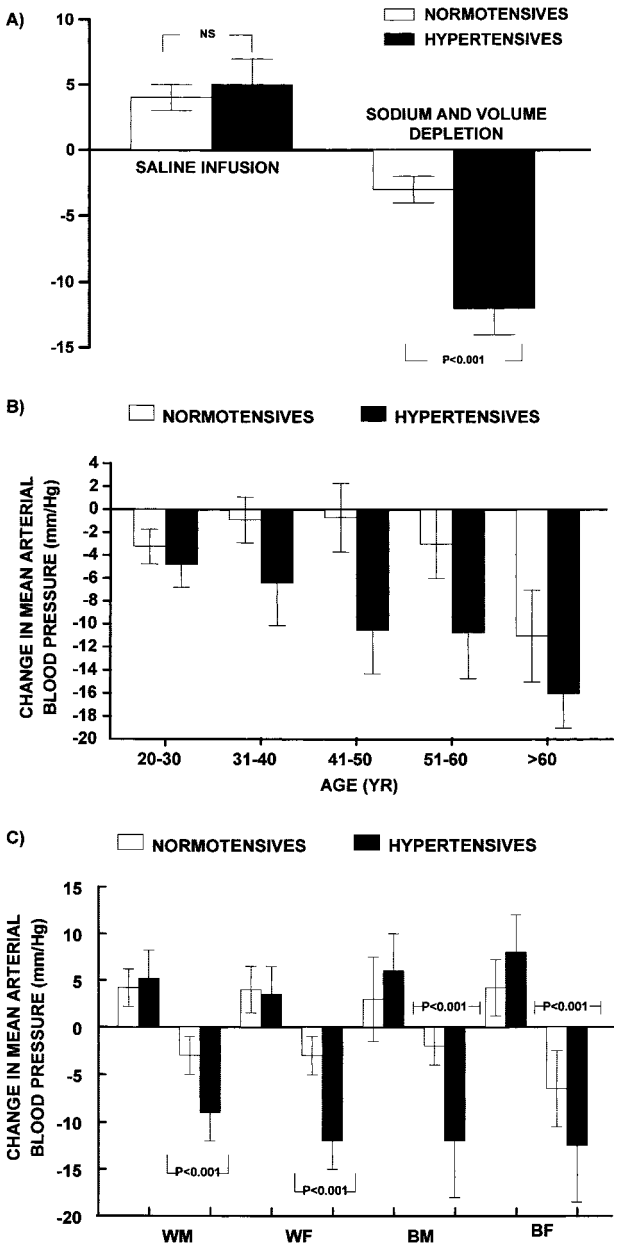

Fig. 1. A) Changes in mean arterial blood pressure in response to saline infusion and sodium and volume depletion in normotensive (white bars) and hypertensive individuals (black bars). B) Changes in mean arterial blood pressure as a function of age in normotensive (white bars) and hypertensive individuals (black bars). C) Changes in mean arterial blood pressure in white male (WM), white female (WF), black male (BM), and black female (BF) individuals in the normotensive and hypertensive groups. Reprinted with permission from Weinberger et al. [14].

which includes several portions of fruits, vegetables and low fat dairy products each day. The latter observation emphasizes the importance of diet quality as a modulator of salt sensitivity of blood pressure.

The DASH-Sodium trial collaborative research group went on to examine the variability and consistency of individual systolic blood pressure responses to changes in salt intake [17]. They found inconsistent and nonreproducible systolic blood pressure responses to changes in sodium intake over time. Overall, 29% of participants were classified as salt sensitive on 2 occasions; 28% were non salt-sensitive on both occasions, while the remaining 43% were inconsistent responders. The authors concluded from these data that identifying individuals as sodium responders is difficult and not worthwhile from the clinical or public health point of view.

SALT SENSITIVITY - LONG TERM CONSEQUENCES

Long term effects of salt sensitivity on cardiovascular disease morbidity and total mortality were determined in a remarkable 27-year follow-up study of 430 normotensives and 278 hypertensives by the Weinberger group [19]. As would be predicted, hypertensive persons, whether salt sensitive or resistant, had reduced survival compared to normotensives (Fig. 2). However, and less predictably, normotensive salt-sensitive individuals were found to have a cumulative mortality similar to that of hypertensives, whereas salt-resistant normotensives had significantly increased survival. These observations provide evidence of a relationship between salt sensitivity and mortality that is independent of elevated blood pressure. Another study [20] evaluated 350 Japanese persons with essential hypertension to determine if sodium sensitivity was an independent predictor of cardiovascular events. The rate of total cardiovascular events, both fatal and non-fatal, was significantly higher

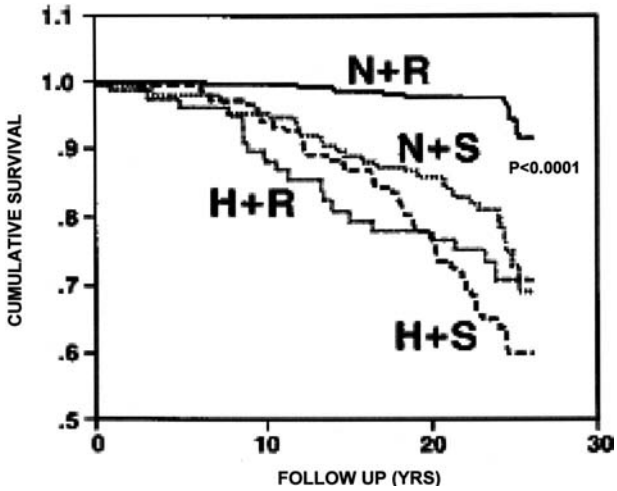

Fig. 2. Kaplan-Meier survival curves for normotensive salt-resistant individuals (N+R), normotensive salt-sensitive individuals (N+S), hypertensive salt-resistant individuals (H+R), and hypertensive salt-sensitive individuals (H+S) over the follow-up period. As noted, only the N+R group had an increased survival. Reprinted with permission from Weinberger et al. [19].

in the sodium-sensitive group (Fig. 3). Left ventricular hypertrophy was also found more frequently in the sodium-sensitive than in the resistant group (38 vs. 16%). These findings corroborate the conclusion that sodium sensitivity is a prognostic factor independent of classic cardiovascular risk factors.

MECHANISMS OF SODIUM SENSITIVITY AND RESISTANCE

Diet Quality

In a study ancillary to the DASH-Sodium trial, the investigators tested the effect of the DASH eating plan on the pressure-natriuresis relationship in an effort to elucidate the mechanisms of its blood pressure-lowering action [18]. They observed that the effect of the DASH diet on blood pressure was significantly altered by the level of sodium intake, and that blood pressure reductions in response to the combination of the DASH diet and reduced sodium intake were less than additive, although greater than the effect of either intervention alone. Conversely, the blood pressure of participants consuming the DASH diet was much less sodium-sensitive than that of the same participants while consuming the control diet. The DASH diet increased the slope of the pressure-natriuresis curve without shifting the curve along the arterial pressure axis (x) (Fig. 4). This relationship held true for all of the subgroups examined, including normotensives and hypertensives, African Americans and non-African Americans, younger and older and obese and nonobese persons, and men and women. The authors interpreted the increased slope of the pressure-natriuresis curve as evidence for a natriuretic action of the DASH diet, likely related to its high potassium and calcium content. Further, they suggested that the effect of the DASH diet on blood pressure would vanish at a very low sodium excretion, eg. 20–30 mmol/d. The slope of the pressure-natriuresis curve was shallower in hypertensives than in normotensives, in African Americans than in other races, as well as in older (>45 years) than

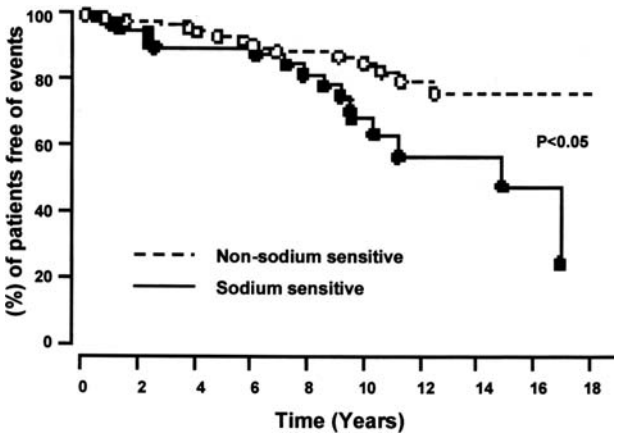

Fig. 3. Kaplan-Meier plots of total cardiovascular events by sodium sensitivity. Reprinted with permission from Morimoto et al. [20].

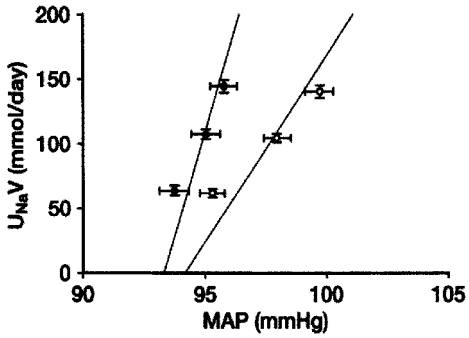

Fig. 4. Pressure-natriuresis curves in the Dietary Approaches to Stop Hypertension (DASH) Diet-Sodium trial. Urinary sodium excretion rate ($U_{Na}V$: mmol/d) and systemic mean arterial pressure (MAP: mm Hg) were plotted on the ordinate and abscissa for control and DASH diets. Open and closed circles represent data for the control and DASH diets, respectively. Error bars indicate ±1 standard errors of the means. Regression lines for 3 different amounts of sodium were $U_{Na}V=30x(MAP-94)$ in control diet, and $U_{Na}V=65x(MAP-93)$ in DASH diet. DASH diet augmented the slope of the pressure-natriuresis curve from 30 to 65 ([mmol/d]/mm Hg, $P=0.0002$) without affecting the extrapolated intercept of BP axis (94 vs 93 mm Hg, $P=0.22$), resulting in a decrease in sodium sensitivity of BP from 0.034 to 0.015 mm Hg/(mmol/d). Please note that the discrepancy between data plot and estimated pressure-natriuresis curve (line) is ascribed to the fact that a regression line was obtained from a whole cluster of data instead of averaging the extrapolated x-intercepts and slopes of the line in each participant. Reprinted with permission from Akita et al. [18].

in younger (≤45 years) participants, indicating that blood pressure was more sodium-sensitive in the former groups (Fig. 5). The authors speculated that the DASH diet effectively lowered blood pressure in persons with high sodium sensitivity mainly by making them sodium-insensitive through its diuretic action.

Neurohormonal Interactions

As suggested by the pioneering studies of Weinberger et al., the renin status of an individual may predict his/her sodium sensitivity, individuals having low plasma renin activity tending to be sodium sensitive [14]. Reducing sodium intake activates neurohormonal systems that may adversely influence cardiovascular outcomes. The renin-angiotensin-aldosterone system plays a pivotal role in the regulation of sodium excretion and balance is sensitive to alterations in sodium intake [8,21–23]. The Graudal meta-analysis [8] evaluated the effects of reduced sodium intake on blood pressure, renin, aldosterone, catecholamines and cholesterol. It included 114 randomized trials where participants were allocated to low-sodium vs. high-sodium diets and sodium intake was estimated by 24-hour urinary sodium excretion. In 58 trials of hypertensive persons, a low-sodium diet (mean urinary sodium excretion 118 mmol/day) produced a mean reduction of 4 mm Hg in systolic blood pressure. In 58 trials of normotensive individuals, the effect of a low-sodium diet (mean urinary sodium excretion 160 mmol/day) was a mere 1 mmHg decrease in systolic blood pressure.

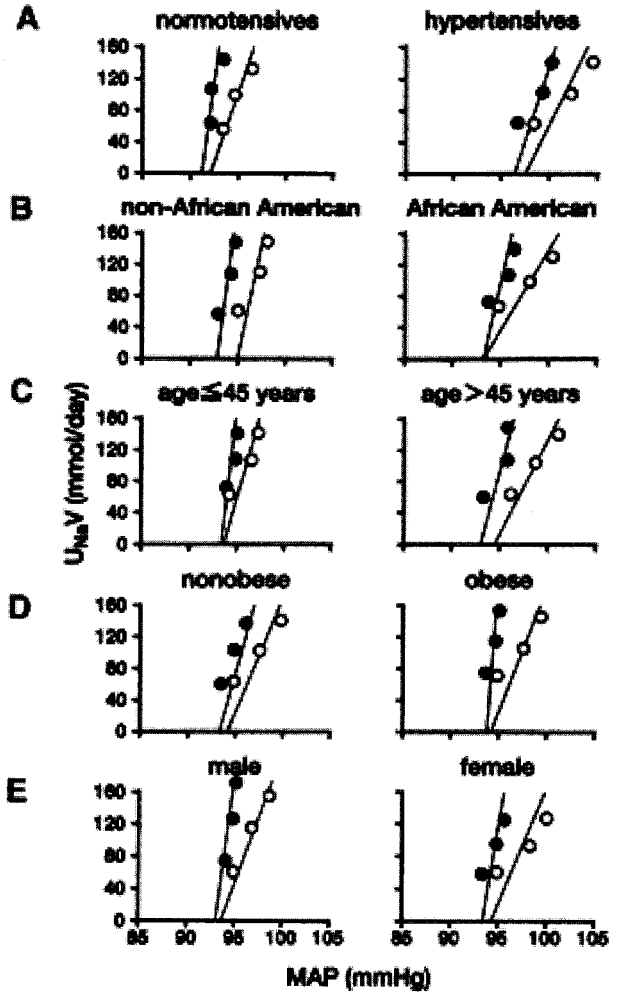

Fig. 5. Pressure-natriuresis curves in subgroups in the DASH-Sodium trial: A, normotensives versus hypertensives; B, non-African American versus African American; C, age ≤45 years versus age >45 years; D, nonobese versus obese; and E, male versus female. Open and closed circles represent data for the control and DASH diets, respectively. See legend to Figure 4 for additional explanation. Reprinted with permission from Akita et al. [18].

Renin was measured in 53 studies and aldosterone in 38. All individual studies showed significant increases in plasma renin and aldosterone levels in the low-sodium group (Fig. 6). The increase in renin and aldosterone was 5–6 fold higher in those whose sodium excretion was reduced to <20 mmol/day; in studies with a reduction in sodium excretion between 40–100 mmol/day, renin and aldosterone were increased about 2 fold. Hypertensive and normotensive persons did not differ in their renin and aldosterone responses to reduced sodium intake. This effect was sustained over time if the reduced sodium intake was maintained. Thus, this meta-analysis provided a possible explanation for the relatively small effect of reduced sodium intake on blood pressure: compensatory activation of the renin-angiotensin-aldosterone system is proportional to the degree of sodium reduction.

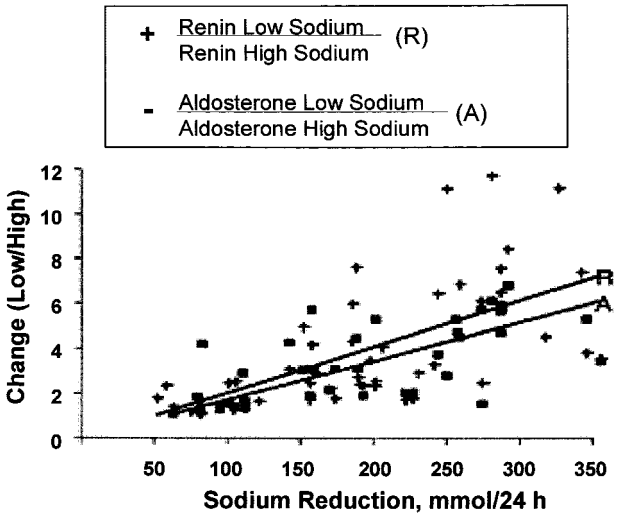

Fig. 6. Regression analysis of the relation between sodium reduction and change in plasma renin (R) and change in plasma aldosterone (A) where R=0.020 × [sodium reduction] (95% CI, 0.018–0.022), r^2=0.43, and P<0.001; A=0.017 × [sodium reduction] (95% CI, 0.015–0.019), r^2=0.41, and P<0.001. Reprinted with permission from Graudal et al. [8].

Elevations in plasma renin activity in the setting of hypertension have been associated to increased target organ damage and coronary events [24,25], and sodium intake has been shown to be inversely related to coronary and all-cause mortality based on data from the National Health and Nutrition Examination Survey (NHANES I) [26]. Activation of the renin-angiotensin-aldosterone system in response to sodium restriction might account for these adverse effects.

Studies of neurohormonal responses to short term dietary salt loading followed by salt deprivation in normotensive and hypertensive individuals have confirmed previous findings of greater salt sensitivity among hypertensive (mean decrease in MAP −9.4 mmHg vs. −1.4 mmHg) than normotensive persons despite similar decreases in urinary sodium excretion (Fig. 7) [27]. The reductions in MAP correlated inversely with the increases in plasma renin activity and aldosterone concentration that occurred in changing from the high-salt to low-salt diet, and the renin and aldosterone responses to the low salt diet were blunted in the hypertensives. These findings suggest that the larger fall in blood pressure with an acute reduction in salt intake in hypertensives compared with normotensives was, at least in part, due to a less-responsive renin-angiotensin-aldosterone system in the hypertensive patients. Thus, blunted activity of the renin-angiotensin-aldosterone system may contribute to salt sensitive hypertension in humans.

Atrial natriuretic peptide (ANP) also plays a critical role in the regulation of sodium balance and the pathogenesis of salt-sensitive hypertension [28–31]. Mice with homozygous deletion of the ANP gene (*Nppa−/−*) develop hypertension when fed a high salt diet but maintain normal (identical to nontransgenic control mice) blood pressure when fed a low salt diet

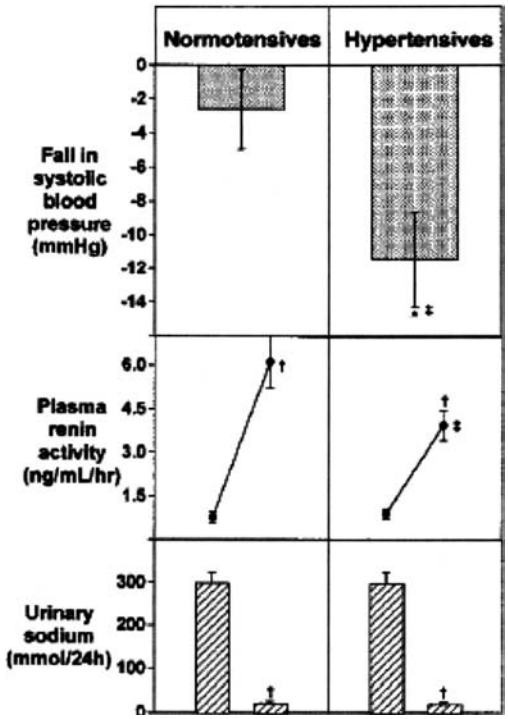

Fig. 7. Changes in systolic BP, plasma renin activity, and urinary sodium excretion from the high-salt to low-salt diet in 34 age- and sex-matched normotensive and hypertensive individuals. * *P*,0.01, † *P*,0.001 low-salt vs high-salt diet; ‡ *P*,0.05 hypertensives vs normotensives in change in systolic BP and plasma renin activity. Reprinted with permission from He et al. [27].

beginning at weaning (Fig. 8) [28]. Thus, the *Nppa*−/− mouse provides a convenient model of salt sensitive hypertension. Further, deletion of ANP results in biventricular hypertrophy and cardiomyocyte enlargement that is independent of MAP in these animals. Studies in humans indicate that secretion of ANP may be blunted in black salt-sensitive hypertensives in response to high salt diets [32]. Further, a loss of function polymorphism of the ANP gene has been observed more frequently in black salt-sensitive hypertensives, compared to normotensives or white hypertensives [33,34]. Obese individuals

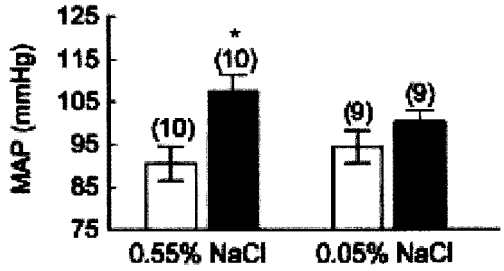

Fig. 8. Effect of 5 week low (0.05%) and normal (0.55%) salt diets on mean arterial pressure (MAP) of male *Nppa*+/+ (□) and *Nppa*−/− (■) mice. Results are the mean±SEM. Numbers in parentheses represent the numbers of mice per group. * $p<0.05$ compared with the respective *Nppa*+/+ group; † $p<0.05$ compared with the respective normal-salt diet groups. Reprinted with permission from Feng et al. [28].

demonstrate decreased levels of both ANP and brain natriuretic peptide (BNP), possibly related to more rapid clearance by adipocyte NPR-C receptors [35]. These findings suggest that deficiency in ANP expression may contribute to the salt sensitive hypertension characteristic of black and obese persons.

Oxytocin appears to regulate salt appetite in response to volume depletion in animal models. Oxytocin knockout mice [36] have been shown to consume more salt than wild type controls in response to volume depletion. Angiotensin II injection into the lateral ventricle produced a dose-related increase in salt and water intake, with no differences observed between the oxytocin knockout and control nontransgenic mice. The authors concluded that oxytocin effects on salt intake are not mediated by the brain renin-angiotensin-aldosterone system and that oxytocin plays a role in the regulation of basal blood pressure but not in angiotensin II-induced pressor responses. Studies in humans have produced inconsistent findings. Changes in plasma oxytocin levels were not observed by Rasmussen et al. [23] after isotonic saline infusion or by Anderson et al. [37] after acute 5% saline infusion. Further study is needed to define the role of oxytocin in regulating salt appetite in humans.

Sodium - Nervous System Interactions

One mechanism that has been postulated to account for variability in salt sensitivity of blood pressure is arterial baroreceptor function [38]. Arterial baroreceptors, stretch-sensitive fibers located in the arch of the aorta and carotid sinuses, provide the afferent signal to a negative-feedback circuit in the medulla that maintains MAP. An increase in MAP stimulates baroreceptors, reducing sympathetic outflow to resistance vessels and the heart and restoring MAP to normal levels. Increased renal sympathetic nerve activity increases renal tubular sodium reabsorption, whereas decreases in sympathetic stimulation of the kidney reduce renal tubular sodium reabsorption and result in natriuresis [39]. Evidence from baroreceptor-intact Sprague-Dawley rats and rats with sinoaortic denervation (SAD) during changes in dietary salt intake suggests that baroreceptor reflex activity and regulation of arterial pressure are related to extracellular volume (sodium and water) homeostasis via pressure natriuresis [40]. In this study, MAP increases associated with salt loading were minimal in baroreceptor-intact rats but were significant (~15 mmHg) in rats with SAD. Thus, the baroreceptors appear to have been chronically buffering the effects of increases in dietary sodium intake on MAP. These results support the hypothesis that primary baroreceptor dysfunction may play a role in salt-sensitive hypertension.

The relationship between baroreceptor function and control of MAP was explored in a dog model in which baroreceptors in the aortic arch and one carotid sinus were denervated [41]. The contralateral carotid artery was ligated proximal to the innervated sinus to induce baroreceptor unloading, followed by removal of the ligature to restore normal flow through the carotid. Ligation below the denervated sinus served as a control. Baroreceptor

unloading resulted in a significant and sustained increase in MAP, suggesting that arterial baroreceptors are involved in the long-term control of blood pressure. Although sodium and potassium intake remained constant throughout the experiment, baroreceptor unloading decreased sodium excretion acutely, on day 1–2 after ligation, after which it returned to baseline. Plasma renin activity increased significantly during the first 2 days after baroreceptor unloading compared to the control period and subsequently declined toward baseline but never fell below control. The paradoxical increase in renin level in the presence of a sustained increase in renal perfusion pressure may have been due to increased renal nerve activity. In addition, the fact that increased renal perfusion pressure did not result in a pressure natriuresis suggests that arterial baroreceptors alter the excretory ability of the kidneys.

Further insight into the effect of renal sympathetic tone on sodium excretion was provided by a study of excretory responses to salt loading in dogs using a split-bladder preparation and unilateral renal denervation [42]. There was a 15% to 20% greater increase in sodium excretion from innervated versus denervated kidney during high salt intake. During the recovery period, total urinary sodium excretion returned to control levels within 2 days. These effects occurred in the absence of dietary salt induced changes in MAP or heart rate. These results add further evidence that the renal nerves chronically promote sodium excretion during increased sodium intakes [40,41] and contribute to an emerging body of evidence from long-term studies that neurally induced sodium excretion plays a compensatory role in regulation of extracellular fluid volume and arterial pressure during volume excess and salt-sensitive hypertension [43,44].

A subsequent study [45] examined the effect of arterial baroreceptor denervation on sodium balance in Sprague-Dawley rats during low, normal and high dietary sodium intake. Compared with measurements made before SAD, arterial baroreceptor denervated rats had similar sodium balance during normal sodium intake but significantly more negative sodium balance during low sodium intake and significantly more positive sodium balance during high sodium intake. At the end of the high sodium intake period, MAP (under anesthesia) was 115 ± 1 mmHg before baroreceptor denervation and 159 ± 5 mmHg after denervation. Sham SAD in control rats had no effect on sodium balance or arterial pressure during the different dietary sodium intakes. These studies indicate that SAD impairs the ability to establish sodium balance during both low and high dietary sodium intake, and that SAD leads to the development of increased arterial pressure in association with increased renal sodium retention during high sodium intake. Thus, SAD results in salt-sensitive hypertension.

CONCLUSIONS

Sodium is necessary for life processes and, depending on the body's need (e.g. hot environment or physical activity), the range of sodium intake required for life varies. Our bodies can adjust to a wide range of sodium intake with hemodynamic, neural and hormonal responses. Variation in dietary sodium intake over the usual range plays a minor role in blood pressure regulation in the general population, and appears not to be a determinant of cardiovascular disease outcomes. However, a variety of genetic and environmental factors have been identified that modulate the effects of dietary sodium on cardiovascular disease events and survival, as well as blood pressure. These include diet quality, age, body mass and race/ethnicity. Emphasis on improving diet quality, as in the DASH eating plan, and on weight control with a combination of increased physical activity and reduced caloric intake, as recommended by recent guidelines for the prevention and management of hypertension [46–48], will likely reduce the salt sensitivity of blood pressure and the risk of cardiovascular disease in many important population groups. Rigorous outcome trials of this nonpharmacologic approach to cardiovascular disease preventing in high risk population groups are urgently needed.

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