The Ochsner Journal 9:197–203, 2009

Salt, Arterial Pressure, and Cardiovascular and Renal Damage

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ABSTRACT

This brief review deals with some novel developments regarding the possible role of salt in the pathogenesis of cardiovascular and renal disorders. Studies in both humans and experimental animals are discussed. Increased salt intake is usually associated with an increase in arterial pressure although some controversies still exist. Salt sensitivity of arterial pressure (defined as an increase in arterial pressure on dietary salt overload) was demonstrated in many animal species as well as in humans. However, findings in rats, the most often used animal model, also demonstrated that this salt sensitivity was not uniform; some strains are salt sensitive, while other strains are salt resistant. Salt sensitivity of arterial pressure in humans is also not uniform; less than one-third of normotensive individuals and less than one-half of hypertensive individuals are salt sensitive. Of great importance are findings that excessive salt intake may damage target organs (cardiovascular system and kidneys) irrespective of arterial pressure. Together with an ever-growing consensus that sodium intake in acculturated societies is high, these findings also emphasize the need for reduction in salt intake. Therefore, the adverse cardiovascular and renal effects of salt continue to be a subject of intense study. Current data indicate that a reduction in salt intake should ameliorate, if not prevent, cardiovascular and renal morbidity and mortality, particularly among individuals with hypertension.

The association of salt, hypertension, and cardiovascular and renal disease has been known for a long time, but there are still many unanswered questions and controversies regarding the role of salt in the pathogenesis of hypertension and cardiovascular and renal injury.[1,2] For instance, extreme dietary salt restriction was once considered a valid therapeutic approach in the treatment of hypertension,[3] yet more recent findings demonstrate that dietary salt reduction has small, inconsistent, and controversial effects on arterial pressure and that there is little relationship between the magnitude of reduction in sodium intake and the blood pressure effect.[4] Furthermore, the results of the Intersalt study,[5] a large-population study involving more than 50 centers around the world, demonstrated that sodium intake (or urinary sodium output) correlates with the rise in arterial pressure with age but not with the prevalence of hypertension. In the same study, a better correlation of arterial pressure with obesity and alcohol consumption than with dietary sodium was also found. A recent meta-analysis[6] that evaluated 11 long-term randomized trials demonstrated only a meager, albeit significant, effect of reduced dietary salt on arterial pressure (a decrease in systolic pressure of 1.1 mm Hg was obtained with 25% salt reduction). Whereas arterial pressure in a population as a whole is only modestly affected by alterations in salt intake, some individuals experience large changes in arterial pressure and are characterized as salt sensitive. Perhaps the best experimental model of salt sensitivity is represented by the salt-sensitive and salt-resistant rats in a study by Dahl et al.[7] When exposed to dietary salt overload, salt-sensitive rats experience large and rapid increase in arterial pressure, whereas salt-resistant rats remain normotensive under the same circumstances. Thus, the arterial pressure response to variations in dietary sodium load is not uniform and depends on numerous factors, including genetic, hormonal, humoral, neuronal, and other variables.

Some experimental and clinical studies[8–10] indicate that salt excess may induce cardiovascular and renal injury in a manner independent of arterial pressure. The results of early and recent studies,[8–11] both experimental and clinical, demonstrate a good correlation between salt intake and cardiovascular and renal injury as assessed by left ventricular (LV) hypertrophy, microalbuminuria, arterial compliance, and other findings. Therefore, the available evidence demonstrates that salt may have a significant role in the pathogenesis of hypertensive disease and its target organ damage, but the exact long-term effect

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Key Words: Cardiovascular injury, heart, hypertension, kidney, salt

of salt on cardiovascular and renal morbidity and mortality still remains to be defined. The debate about the role of salt in the pathogenesis of cardiovascular and renal disease extends from scientific to political grounds. An editorial[12] in *Kidney International* suggests that the Salt Institute, a powerful group of salt manufacturers supported (among others) by the prepared food industry, managed to introduce a piece of legislation into the national budget that will help them to avoid regulatory rulings. This in turn provoked more pro and con discussion.[13–15] The objectives of this brief review are to avoid controversies and to discuss some recent research developments, with emphasis on experimental studies from our laboratory.

DIETARY SALT INTAKE AND ARTERIAL PRESSURE

Animal Studies

The effect of salt on arterial pressure has been studied in a number of animal species, including chimpanzees.[16] However, most studies were conducted in rats. The results of early studies[17,18] demonstrated that normotensive rats are not salt sensitive (ie, arterial pressure remained unchanged in rats exposed to short-term or long-term salt excess). These studies also demonstrated that renal mass is critical in determining salt sensitivity; arterial pressure increased in response to salt overload in normotensive rats in which partial nephrectomy had been performed. Later findings established the existence of rat strains with different salt sensitivity and indicated the role of genetic factors in determining arterial pressure response to salt loading.[7] Still more recent studies[8,9,19–23] from our laboratory and others' confirmed previous results on the salt resistance of normotensive rats and extended the observations on the role of salt excess in the pathogenesis of hypertension and cardiovascular and renal structural and functional injury. Our studies[8,9,20] demonstrated salt sensitivity of arterial pressure in spontaneously hypertensive rats (SHRs) and indicated that advancing age is also a factor that influences salt sensitivity. Young rats (8 weeks old), either normotensive Wistar-Kyoto rats (WKYs) or SHRs, also had increased arterial pressure in response to salt load.[20] In contrast, young adult rats (17 weeks old) are far less sensitive; WKYs remain normotensive in response to salt load, and arterial pressure rises only slightly in SHRs.[20] Of great significance is the finding that regardless of arterial pressure response both normotensive and hypertensive rats developed structural and functional cardiovascular and renal damage.[8,9,19–23]

Physiologically, the relationship between salt intake and arterial pressure is defined by the ability of kidneys to excrete sodium.[24] Normally, variable daily sodium intake is excreted by the kidney with minimal changes in arterial pressure. The relationship between arterial pressure and urinary sodium output is best described by renal function curves that may be obtained by plotting arterial pressure (x-axis) against urinary sodium excretion (y-axis).[24] Investigations in various mammals, including humans, demonstrated that arterial pressure changes little over a wide range of salt intake (and consequently sodium excretion).[25] Therefore, salt-induced hypertension can develop only when the ability of the kidney to excrete sodium is impaired, resulting in the shift of the renal function curve to higher arterial pressure values.[25]

Numerous factors may influence salt sensitivity of arterial pressure, and all of them may affect the ability of the kidneys to excrete sodium. There are 3 major groups of factors. First are alterations in the activity of various humoral systems such as the renin-angiotensin-aldosterone system, kallikrein-kinin system, prostaglandins, atrial natriuretic peptides, catecholamines, and others.[11,26,27] The latest addition to this group is renalase, an amine oxidase that metabolizes circulating catecholamines and may regulate sympathetic tone.[28] It is secreted by the kidneys, and its deficiency may increase the plasma catecholamine concentration, with consequent increase in arterial pressure.[28] Second is the sympathetic nervous system, particularly changes in the sympathetic nerve activity to the kidneys and changes in baroreceptor activity.[27] Third are genetic factors[7,27] and obviously alterations in renal structure and function.

Human Studies

There is an overwhelming number of epidemiologic, observational, interventional, prospective, and other studies in human subjects on the relationship between salt intake and arterial pressure. For this review, we selected only a few that represent various types of studies and simultaneously give an insight into the complexity of the problem.

Intersalt Study. The Intersalt study[5] was a multicenter observational study involving more than 10,000 men and women, aged 20 to 59 years from 52 centers in 39 countries, that used state-of-the-art techniques to measure arterial pressure and urinary sodium excretion. The results obtained from 48 centers around the world demonstrated no significant correlation between salt intake and arterial pressure.[5] The remaining 4 centers included tribal populations in remote areas of Brazil, Kenya, and Papua, New Guinea. Salt and alcohol intake in subjects from these centers was extremely low, the subjects were lean, and they had low arterial pressure. The prevalence of hypertension among these 4 centers ranged from 0%

to 3%. When the results from these centers were analyzed together with those from the other 48 centers, a weak but significant correlation between salt intake and arterial pressure was found.[5] Thus, the results of this comprehensive and large observational study did not resolve the existing controversy. A reanalysis of the entire data from the Intersalt study was performed several years after the original study. The results demonstrated a positive association of urinary sodium with systolic pressure of individuals within the total population.[29] However, this reanalysis was criticized for its statistical methods and for the use of unsubstantiated claims.[30,31]

A few more findings of the Intersalt study deserve comment. Individuals from the 4 centers who had extremely low salt intake also had low arterial pressure, practically no hypertension, and no increase in systolic pressure by age 55 years, suggesting that aortic stiffness is not increased with aging.[5] A possible interpretation of these findings is that salt has a ''permissive'' role in the development of essential hypertension and progressive stiffening of the large arteries. Similarly, salt is necessary for the development of mineralocorticoid-induced hypertension and myocardial fibrosis.[32]

Vanguard Study. The Vanguard Study[33] was designed to evaluate factors affecting the blood pressure response to nonpharmacologic maneuvers in otherwise untreated hypertensive and normotensive individuals with or without hyperlipidemia. The results demonstrated that urinary sodium excretion was not correlated with basal arterial pressure or diet-induced changes in arterial pressure.[32,33] However, arterial pressure was inversely related to urinary potassium excretion and directly related to urinary calcium and magnesium excretion.[33,34] Although the Vanguard Study did not confirm the role of dietary sodium in arterial pressure regulation, the results suggested the importance of other minerals in the pathogenesis of hypertension. An earlier study[35] also indicated the role of various ions in the pathogenesis of essential hypertension.

Trials of Hypertension Prevention (TOHP). The Trials of Hypertension Prevention (TOHP) were designed to identify effective nonpharmacologic means of preventing or significantly delaying the onset of hypertension in subjects with prehypertension. In the first phase of the TOHP (at 18 months), adults with high-normal diastolic blood pressure were randomly assigned to 1 of 7 nonpharmacologic interventions; only weight loss and reduction of dietary sodium (sodium excretion decreased by 44 mmol/d) proved to be effective strategies for reducing blood pressure.[36] In TOPH phase II (at 36 months), reductions in sodium excretion and arterial pressure were maintained, together with an 18% reduction in the incidence of hypertension.[37]

Dietary Approaches to Stop Hypertension (DASH) Trials. Originally, the Dietary Approaches to Stop Hypertension (DASH) trial[38] was designed to compare the effects of a standard diet low in fruit and vegetables and with fat content that is typical of the average diet, a diet rich in fruit and vegetables, and a ''combined'' diet rich in fruit and vegetables and with reduced saturated and total fat. The results demonstrated that the combined diet substantially lowered arterial pressure (11.4 and 5.5 mm Hg for systolic and diastolic pressures, respectively) in subjects with hypertension.[38] A subsequent study[39] examined the effect of different dietary sodium levels in conjunction with the DASH diet. The results demonstrated that a reduction of sodium intake below 100 mmol/d and the DASH diet both lower arterial pressure, with greatest effect in combination.[39] A further study[40] analyzed the effect of changes in sodium intake on arterial pressure in a wide variety of subgroups; subgroups defined by combinations of age, race/ethnicity, and sex were analyzed. The findings demonstrated that within each subgroup lower sodium intake resulted in lower arterial pressure.

Analysis of Data on the Relationship Between Sodium Intake and Arterial Pressure

Evidence in experimental animals demonstrated salt sensitivity of arterial pressure (defined as an increase in arterial pressure on dietary salt overload) in many animal species, including primates.[16] However, findings in rats, the most often used model, also demonstrated that this salt sensitivity was not uniform; some strains are salt sensitive, while other strains are salt resistant.[7] In contrast, the arterial pressure response to salt loading within a certain strain of rats is fairly uniform, probably reflecting genetic similarities because most strains are highly inbred.

On the other hand, the results of the studies on the relationship between arterial pressure and sodium intake in humans are not so clear-cut as the findings in animals. As already discussed, no correlation between salt consumption and arterial pressure was found in some studies.[32,33] Furthermore, even in the studies[6,34,36–40] in which a correlation was found, it was weak, and arterial pressure change was modest compared with change in sodium intake (a meta-analysis[6] of 11 trials found a mean reduction in arterial pressure of 1.1 mm Hg for a 25% reduction in salt intake). There are a number of reasons for this inconsistency. Salt sensitivity of arterial pressure in humans is not uniform; less than one-third of normotensive individuals and less than one-half of

hypertensive individuals are salt sensitive.[9,41–43] Therefore, in any given study and for any given change in salt intake, the results obtained in salt-resistant individuals will attenuate the magnitude of arterial pressure response obtained in salt-sensitive persons. There are also age differences in response to salt; older individuals are more salt sensitive than younger individuals,[43] and inclusion of younger people will also include more salt-resistant ones. Intake of other ions such as potassium, calcium, and magnesium may affect arterial pressure or salt sensitivity, and the ratio of salt to other ions should be used instead of salt intake alone for evaluation.[34] In general, the investigations of sodium intake and arterial pressure are also complicated by the use of different methods for estimating salt intake, by simultaneous hypertension treatment, by effects of sodium that are independent of arterial pressure, and by the duration of interventions.[44] Despite these inconsistencies, there is an ever-growing consensus that sodium intake in acculturated societies is high and should be reduced (gradually, in collaboration with the food industry) from the present mean of 150 mmol/d (3.5 g of sodium or 8.7 g of sodium chloride) to below 100 mmol/d.[2,11,26,45,46] This recommendation is further strengthened by the findings that excessive salt intake may damage target organs irrespective of arterial pressure (discussed herein).

DIETARY SALT INTAKE AND CARDIOVASCULAR AND RENAL INJURY

In addition to increased arterial pressure, excessive salt intake is linked to cardiovascular and renal injury.[2,9,11,26,44] Increased arterial pressure causes target organ injury; consequently, salt-induced cardiovascular and renal injury may be related to concomitant increase in arterial pressure. However, there is a plethora of evidence from animal and clinical studies demonstrating that in addition to this arterial pressure–mediated effect there are direct adverse effects on cardiovascular and renal function and structure. Herein, a brief summary of studies indicates the deleterious effects of excessive salt intake on the cardiovascular system and kidneys.

Animal Studies

As already mentioned, a number of rat strains do not develop increased arterial pressure in response to dietary salt excess; nevertheless, they developed adverse cardiovascular and renal effects.[8,9,19–23] Thus, arterial pressure did not increase in normotensive Wistar rats or normotensive WKYs exposed to salt overload, but they developed an increase in LV mass, LV remodeling, and cardiac and renal fibrosis.[8,9,19–23] Furthermore, our early studies[8,19] demonstrated that dietary salt excess increases LV mass in normotensive and hypertensive rats and alters cardiac β-adrenergic responsiveness in SHRs. More recently, we studied salt-induced cardiovascular and renal injury in greater detail.[20,47–50]

We first examined cardiac responses to salt loading, including myocardial collagen content, in young adult and old adult SHRs.[47] To this end, SHRs (ages 8 and 20 weeks) were given regular rat chow (0.6% salt) or an increased (8%) salt diet. Echocardiographic examination and determinations of arterial pressure and LV hydroxyproline concentration (as an index of ventricular collagen content) were performed at 16 and 52 weeks in the young adult and old adult SHRs, respectively. Salt excess increased arterial pressure, LV mass, and myocardial collagen. In addition, diastolic function demonstrated impaired LV relaxation as manifest by prolonged isovolumic relaxation time, decreased early and atrial filling velocity ratio, and slower propagation of E wave in all SHRs.[47] Furthermore, 25% of the young adult salt-loaded SHRs developed heart failure with systolic and diastolic dysfunction, with still greater LV mass and ventricular fibrosis. These findings demonstrated that sodium sensitivity in SHRs was manifest by increased arterial pressure and by significant LV functional impairment that was most likely related to enhanced myocardial fibrosis. Moreover, the young adult SHRs were more sensitive to salt-induced cardiac damage than the old adult ones.[47]

Next, we examined the effects of salt excess on the function of both ventricles (right ventricular [RV] and LV) and on coronary hemodynamics.[20] In young adult normotensive WKYs and SHRs (age 16 weeks at the end of the study), we determined the effects of salt excess (8% in food for 8 weeks) on arterial pressure, RV and LV function (maximal rates of ventricular pressure rise and fall, as well as diastolic time constant), coronary hemodynamics (microspheres), and ventricular collagen content (hydroxyproline assay and collagen volume fraction).[20] The salt excess only modestly elevated arterial pressure in both strains, but it markedly increased LV mass, especially in the SHRs.[20] Furthermore, the salt overload impaired RV and LV diastolic function in the SHRs but only LV diastolic function in the normotensive WKYs. Furthermore, the collagen content was increased interstitially and perivascularly, and the coronary flow reserve was diminished, as demonstrated by an impaired vasodilatory response to dipyridamole infusion. The latter adverse diminished coronary hemodynamic response was observed in both ventricles of the SHRs but not in the normotensive WKYs.[20] These severe effects of salt loading on both ventricles in the SHRs, but not the

normotensive WKYs, strongly suggested that nonhemodynamic mechanisms participated pathophysiologically in mediation of salt-induced cardiovascular injury.[20]

Finally, we examined whether the renin-angiotensin system may be mediating the adverse cardiovascular effects of salt overload.[48] To this end, 8-week-old SHRs were given an 8% salt diet, whereas control rats received standard chow. One-half of the rats on either the high-salt or regular diet were given the angiotensin II receptor blocker (ARB) candesartan cilexetil (10 mg/kg/d by gavage). The ARB failed to prevent the salt-induced rise in arterial pressure, but it attenuated LV remodeling (mass and wall thickness), myocardial fibrosis, and the development of diastolic dysfunction. Moreover, the ARB also prevented the salt-induced deterioration of coronary and renal hemodynamics but not large-arterial stiffening (as determined by pulse wave velocity).[48] These data clearly demonstrated that angiotensin II, at least in part, participated in the arterial pressure-independent effects of dietary salt overload on cardiovascular damage in hypertension.[48]

We also examined the role of salt overload on renal function.[49] The effects of salt loading were evaluated on renal function, systemic and renal hemodynamics, and glomerular dynamics (as determined by renal micropuncture). Beginning at age 8 weeks, the SHRs were given a regular diet, or their chow contained 4%, 6%, or 8% salt for the ensuing 8 weeks.[49] Proteinuria and albuminuria were quantified weekly in all rats. The mean arterial pressure increased only minimally, and the glomerular filtration rate increased in all salt-loaded rats.[49] Proteinuria and albuminuria increased significantly in proportion to the magnitude of salt loading from the second week of feeding. Most important, the renal plasma flow decreased, the renal vascular resistance increased, and the serum creatinine concentration increased in the rats receiving 6% and 8% salt diets.[49] Moreover, their micropuncture results revealed decreased single-nephron plasma flow and increased afferent and efferent arteriolar resistance.[49] These findings further supported the notion of a strong causal relationship between salt excess and renal and cardiovascular injury. Our subsequent results clearly demonstrated that angiotensin II may be involved in the mediation of salt-related renal injury, as 2 structurally different ARBs (losartan potassium and candesartan) prevented salt-induced renal injury, again without affecting arterial pressure.[50] Findings from these studies in experimental animals strongly suggest a causal relationship between salt excess and target organ injury that is independent of a sometimes coincidental increase in arterial pressure. Although it is well known that salt loading suppresses the release of renin and the systemic renin-angiotensin system, local renin-angiotensin systems in the heart and kidney seem to be stimulated, which may mediate the adverse effects of salt overload (D. S. et al., unpublished data, April 2009).

Human Studies

Few studies have directly examined urinary sodium excretion and cardiovascular and renal disease end points. The results of the Scottish Heart Health Study[51] indicated a correlation between a single determination of elevated sodium excretion at the beginning of the study and coronary heart disease after 7.6 years of follow-up, although statistical significance was shown only in women. A prospective study[52] in Finland involving 2435 men and women demonstrated that higher urinary sodium excretion was associated with increased coronary heart disease and all-cause mortality but not with risk of stroke. These results also seem to point to the local effects of salt loading rather than effects on arterial pressure.

The results of a long-term follow-up study[53] of the 2 TOHP trials have been recently published. Participants of the TOHP I trial were observed for up to 15 years after the end of the original trial, whereas the TOHP II subjects were observed for up to 10 years. The results demonstrated that those participants with prehypertension who were originally assigned to the reduced salt group demonstrated a 25% reduction in cardiovascular end points.[53] There was no difference in this effect when confounding factors such as age, sex, race/ethnicity, and body mass index were taken into account. Urinary sodium excretion was not measured during the follow-up period. However, questionnaire data suggested that subjects from the original reduced salt group continued to consume less salt.[53]

Finally, the results of another population study[54] in Finland strongly argue for the adverse cardiovascular effects of dietary salt excess. Finland instituted a policy of reduction in salt intake, and salt intake was reduced by one-third over the past 30 years. This national program reduced arterial pressure and mortality from stroke and coronary heart disease and increased life expectancy by 5 to 6 years. Because both body mass index and alcohol consumption increased during the same 30 years, this reduction in salt intake was obviously a major contributory factor to the improved morbidity and mortality.[54]

CONCLUSIONS

The results of most studies, either in the experimental laboratory or in human subjects, have dem-

onstrated that increased salt intake is a contributory factor to arterial pressure elevation and to hypertensive disease. However, the relationship between excess salt intake and the magnitude of arterial pressure response is unclear, and much controversy still exists. Furthermore, the results of numerous studies so far demonstrated that excessive salt intake is related to cardiovascular and renal injury. The extent of the relationship between salt intake and arterial pressure strongly suggests that the structural and functional effects of salt overload seem to be direct; the coincidental increase in arterial pressure may be contributive. The adverse cardiovascular and renal effects of salt continue to be a subject of intense study. Current data indicate that a reduction in salt intake should ameliorate, if not prevent, cardiovascular and renal morbidity and mortality, particularly among individuals with hypertension.

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