Insulin Resistance and Salt Sensitivity
A Renal Hemodynamic Abnormality?

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Salt has been a staple of the human diet for millennia and has long been known to be a critical factor in blood pressure regulation. The threshold and precise relationship between dietary salt and blood pressure has not been established. Moreover, there is significant variability in blood pressure responses to changes in dietary salt between patients. This variation approximates a Gaussian distribution, is highly reproducible in individual patients, and is persistent over time. Recent clinical studies have demonstrated that blood pressure, salt sensitivity, and insulin resistance frequently coexist. It is likely that neurohormonal systems, particularly the sympathetic nervous system and the renin-angiotensin system, play a critical role in explaining the interrelationship of salt sensitivity, insulin resistance, and an impaired pressure-natriuresis response. © 1996 American Journal of Hypertension, Ltd. Am J Hypertens 1996;9:193S-199S

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Salt is an important staple of the human diet. Western diets include considerable processed food with a high salt content.1 Substantial variation in dietary salt consumption in the world relates to cultural, sociological, occupational, and geographical considerations.2

There is significant controversy concerning the advantage or disadvantage of dietary salt modification in controlling blood pressure and how this may interact with antihypertensive therapy.2,3 Moreover, there is a similar debate concerning the use of diuretics, particularly in higher doses, which can induce volume depletion4-5 and activate the renin-angiotensin system. This response could potentially be detrimental, although a number of long-term clinical trials have demonstrated a reduction in morbidity and mortality associated with blood pressure reduction with these drugs.6-9

The purpose of the subsequent discussion is to focus on understanding the physiology of the relationship between dietary salt, salt sensitivity, and how the sympathetic nervous system or renin-angiotensin system, or both, may play an important role in promoting an impaired pressure-natriuresis response in the kidney (Figure 1). Blood pressure responses to dietary salt may help predict those prehypertensives destined to become hypertensive as well as those hypertensives who are at greater risk for cardiovascular sequelae. Consequently, greater attention to each patient’s unique blood pressure response to dietary salt may serve as a useful tool to stratify risk and develop appropriate therapeutic interventions.

DIETARY SALT, SALT SENSITIVITY, AND CARDIOVASCULAR RISK CLUSTERING

A significant amount of both experimental and observational data illustrates the important relationship between dietary salt and levels of blood pressure.1-3,10-14 However, there is still significant con-
Controversy regarding the role of dietary salt in the development of hypertension. Some clinical studies have demonstrated that reducing dietary salt lowers blood pressure whereas others do not. The variability of this response in populations follows a Gaussian distribution, but an individual patient's blood pressure response to dietary salt manipulation remains reproducible. Importantly, both genetics and the environment play a role in this response. Age, race, and body habitus interact to modulate the genetic predisposition for salt sensitivity. In Westernized societies, obesity increases with increasing age and may be coupled with other abnormalities, such as insulin resistance, to propagate the development of salt sensitivity.

Many factors have been described as being important in causing salt sensitivity (Table 1). Guyton and colleagues pointed out that abnormalities of the renal function curve (pressure-natriuresis) may be critical in the genesis of salt sensitivity. Others have suggested a role of the sympathetic nervous system in causing salt sensitivity as a result of evidence showing a lack of dietary salt-induced reduction in plasma norepinephrine levels as well as increased vascular responsiveness to norepinephrine in salt sensitive patients.

Some have suggested that abnormalities of the response of the renin-angiotensin system to increased ingestion of salt may result in inadequate renal vasodilatation and impaired salt and water excretion. Others have proposed that salt sensitivity may result from a deficiency of the activity of the kallikrein-kinin system or inadequate renal dopamine production. There is also experimental evidence to suggest that a deficiency in urinary eicosanoids or nitric oxide may also explain salt sensitivity. Others have suggested that salt sensitivity results from a defect in atrial natriuretic peptide secretion.

Whatever the cause or causes, the lack of an easy clinical means of describing salt sensitivity in patients, as well as significant variability and the arbitrary nature of the definition, has hindered characterization of the delicate relationship between dietary salt and blood pressure salt sensitivity. The likelihood that the salt sensitive phenotype may be indicative of a clustering of cardiovascular risk factors in a given patient is of growing interest since there is clinical evidence demonstrating that salt sensitive patients manifest greater left ventricular mass and urinary albumin excretion, as well as elevated levels of LDL cholesterol and lower levels of HDL cholesterol. Moreover, researchers have demonstrated that increasing dietary salt in young, non-obese salt sensitive patients results in greater area under the curve of serum insulin and glucose concentrations during an oral glucose tolerance test, and impairment of insulin sensitivity, as reflected by reduced glucose disposal as measured during the hyperinsulinemic euglycemic clamp.

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**TABLE 1. PUTATIVE CAUSES OF SALT SENSITIVITY AND DIMINISHED PRESSURE-NATRIURESIS RESPONSE**

| † Sympathetic nervous system |
| † Renin-angiotensin system |
| † Renal-kallikrein activity |
| † Renal dopamine production |
| † Renal eicosanoid production |
| † Nitric oxide production |
| † Atrial natriuretic peptide production |
SALT SENSITIVITY, INSULIN RESISTANCE, AND THE KIDNEY

Clinical investigation has demonstrated that blood pressure salt sensitivity and insulin resistance often coexist. They may coexist as epiphenomena, or they may be primarily associated with each other, perhaps through one or both of their effects on the pressure-natriuresis relationship of the kidney.

The kidney may play a primary role in the development of blood pressure salt sensitivity through an inability of the kidney to excrete sodium with a consequent increase in volume and blood pressure. Guyton has theorized that a rise in blood pressure should compensate for the decreased capacity for the kidney to excrete sodium. Clinical studies have demonstrated that there are differences in renal hemodynamic responses to greater dietary salt intake, which may, in part, explain the variability of salt ingestion on blood pressure. Hollenberg et al. and van Paassen have described diminished effective renal plasma flow in response to greater dietary salt intake in those patients who are salt sensitive. Hollenberg and colleagues further noted that blood pressure salt sensitivity appeared more prevalent in what they described as their “nonmodulator population” although no direct correlation between salt sensitivity and nonmodulation was observed. The results of other clinical studies reveal a definite impairment in dietary salt-mediated increase in renal plasma flow in those subjects who were salt sensitive versus those who were salt resistant. Thus, these observations strongly suggest that impaired natriuresis in salt sensitive hypertensives is related to an incapacity of the kidney to increase renal blood flow in response to greater dietary salt intake (Figure 2).

The inability of the kidney to respond with increasing renal blood flow in response to increasing dietary salt intake could be related to functional (i.e., vasoconstriction) or anatomical (i.e., arteriolosclerosis) problems within the kidney. As will be subsequently discussed, the sympathetic nervous system may play a role in the genesis of salt sensitive hypertension and is known to induce preglomerular vasoconstriction that could reduce renal blood flow. Vascular damage to the preglomerular arteriole, which is more common with greater duration of hypertension, could also result in a fixed impairment in renal perfusion. Aging and hypertension has been demonstrated to result in a greater impairment in renal blood flow than aging alone. Thus, fixed vascular damage and functional preglomerular vasoconstriction together could result in an accentuation of impairment of renal blood flow and an impaired pressure-natriuresis response.

Investigators have also described an increase in glomerular filtration fraction in response to greater dietary salt ingestion in salt sensitive patients. This glomerular hemodynamic response could result in an accentuation of salt retention through an associated reduction in peritubular hydrostatic pressure and an increase in peritubular colloid osmotic pressure. This glomerular hemodynamic change could result from either greater effenter glomerular arteriolar vasoconstriction relative to afferent glomerular arteriolar vasodilatation or an impaired ability of the kidney to autoregulate blood flow in response to higher systemic pressure, as might be indicated by greater afferent glomerular arteriolar dilatation relative to efferent glomerular arteriolar dilatation. The latter possibility could occur if vascular damage to the afferent glomerular arteriole results in impaired vasoconstriction in response to higher systemic blood pressure.

SALT SENSITIVITY, INSULIN RESISTANCE, AND THE SYMPATHETIC NERVOUS SYSTEM

Dysfunction of the sympathetic nervous system may play a role in the interrelationship between salt sensitivity and disorders of carbohydrate metabolism. This link may be mediated, in part, by hyperinsulinemia, which occurs in the insulin resistant state, or by an abnormality in cellular sodium transport systems associated with the insulin resistant state. Insulin resistance is associated with enhanced vascular responsiveness to adrenergic stimuli. Elevated plasma insulin levels are associated with increased sympathetic nervous system activity and higher levels of blood pressure in the absence of changes in blood glucose. Enhanced adrenergic activity can also induce insulin resistance.

Campese et al. have demonstrated that salt sensitive patients with essential hypertension, when fed a high salt diet, do not suppress plasma concentrations of norepinephrine to the same extent as normotensive subjects fed a high salt diet. Experimental studies in spontaneously hypertensive rats have revealed an interesting paradox in that higher salt diet stimulates rather than suppresses the sympathetic nervous system. In these same experimental models, renal denervation enhances the ability of the kidneys to excrete salt and water and delays the development of hypertension. These data suggest that the sympathetic nervous system may play an important role in altering the pressure-natriuresis curve of the kidney to facilitate greater salt and water retention.

Dietary salt may induce greater insulin resistance. Donovan et al demonstrated that increasing dietary sodium from 20 to 200 mEq per day was associated with a 16% reduction in the glucose disposal rate in young, healthy normotensive volunteers whether they were salt sensitive or salt resistant. Moreover, Sharma et al demonstrated, by measuring the serum glucose and insulin responses to an oral glucose tolerance test, that this phe-
SALT SENSITIVITY, INSULIN RESISTANCE, AND THE RENIN-ANGIOTENSIN SYSTEM

Since the renin-angiotensin system is an important determinant of efferent glomerular arteriolar tone and its activity is modulated both by dietary salt ingestion and systemic blood pressure, it is likely that it also plays a role in the disturbed pressure-natriuresis response in salt sensitive hypertensives. It is possible that, as with the sympathetic nervous system, greater dietary salt ingestion in salt sensitive hypertensives results in diminished suppression of the renin-angiotensin system and therefore reduced vasodilatation during higher salt intake. A correlation has been observed between dietary salt-induced plasma renin activity decrease and a resulting increase in renal plasma flow in both normotensive and hypertensive subjects. However, most salt sensitive patients typically have lower plasma renin activity. Therefore, plasma renin responses to greater dietary salt ingestion would be minimized. Despite this discrepancy, even subtle changes in plasma renin activity might be magnified within the kidney, with a significant impact on renal hemodynamics.

Supporting the concept that the renin-angiotensin system plays a role in the renal abnormalities associated with salt sensitivity, Redgrave et al. and Dluhy et al. have demonstrated that angiotensin converting enzyme (ACE) inhibition can partly correct the impaired renal hemodynamic response to increased dietary salt in nonmodulating hypertensives. Moore et al. subsequently demonstrated that the antihypertensive and renal vasodilatory effects of ACE inhibition were as great in salt sensitive as in salt insensitive patients. These studies are important as they refute the hypothesis that salt sensitivity is a low renin, volume expanded state that would have minimal response to angiotensin II suppression. AE inhibitors can induce renal vasodilatation not only through blocking angiotensin II formation but also through reducing bradykinin degradation and increasing prostaglandin and nitric oxide formation.

The role of angiotensin II as being the critical factor in the impaired renal hemodynamic response to increasing dietary salt has been supported by the subsequent research of Fisher et al. and van Paassen et al. who have used renin inhibitors that have no in-
fluence on kinin or prostaglandin production and yet enhance renal vasodilatory responses in both normotensive and salt sensitive hypertensives. These clinical studies strongly suggest that an abnormality in the renin-angiotensin system, in part, explains the impaired pressure-natriuresis response in the salt sensitive patient.

The interrelationship between dietary salt, insulin resistance, and the renin-angiotensin system in the salt sensitive patient needs further clinical evaluation. Our group demonstrated that greater insulin resistance is associated with higher glomerular filtration fraction in older, obese sedentary hypertensives. Moreover, this relationship persisted despite a 3 or 10 g salt diet. Interestingly, on the lower salt diet (3 g) the slope of the line approximating this relationship was much steeper than on the higher salt diet, indicating, perhaps, that activation of the renin-angiotensin system on the lower salt diet could play a role in increasing the glomerular filtration fraction. The resultant glomerular hemodynamic change could aggravate dietary salt sensitivity through enhancing sodium and water reabsorption through alterations in peritubular capillary hydrostatic pressure and colloid osmotic pressure. In our study, since the patients had their glomerular hemodynamics measured during the fasting state when insulin levels are likely not to be elevated, as opposed to during or after the hyperinsulinemic euglycemic clamps when serum insulin is likely to be elevated in the postabsorptive state, these results suggest that this relationship is associated with insulin resistance per se and not hyperinsulinemia.

Consequently, a reduction in dietary salt from 10 to 3 g/day may modify glomerular hemodynamics in insulin resistant patients. This observation raises the interesting question as to whether more stringent dietary salt restriction or perhaps even pharmacologic desalting with diuretics may pose a risk in insulin resistant hypertensive patients by elevating the glomerular filtration fraction and possibly increasing glomerular hypertension, a pathophysiologic response known to accelerate development of glomerulosclerosis in experimental models of renal disease.

Despite the fact that salt sensitivity and insulin resistance frequently coexist in hypertensive patients, the intrarenal mechanism(s), which result in a depressed pressure-natriuresis response, remain poorly described. Abnormalities of the sympathetic nervous system, renin-angiotensin system, or both, in response to greater dietary salt ingestion remain strong candidates to explain the relationship between blood pressure salt sensitivity and insulin resistance.

CONCLUSIONS

Future clinical studies are needed to assess the role of dietary salt restriction in the management of hypertension. There is evidence to suggest that modest dietary salt restriction can be beneficial in facilitating blood pressure control. However, excessive dietary salt restriction may pose a hazard for the kidney, particularly if there is a resultant increase in the activity of either the sympathetic nervous system or renin-angiotensin system. Likewise, overzealous pharmacologic desalting may also pose a risk. Therapeutic approaches that attenuate the sympathetic nervous system or the renin-angiotensin system may correct the impaired pressure-natriuresis response of the salt-sensitive hypertensive and facilitate blood pressure control. Additionally, efforts to modify insulin resistance through weight reduction or exercise or through medication (metformin, thiazolidinediones) may also prove to be useful in facilitating blood pressure control.

REFERENCES


