Salt and Aldosterone
A Concert of Bad Effects
Maria Czarina Acelajado, Eduardo Pimenta, David A. Calhoun

A very large number of experimental and human studies independently link high dietary salt intake and aldosterone excess to the development and progression of end-organ damage. Observational and dietary interventional studies clearly establish high diet salt intake as an important contributor to the development of hypertension, cardiac hypertrophy, and proteinuria. Likewise, observational data and studies of aldosterone blockade demonstrate that hyperaldosteronism significantly relates to level of blood pressure, intracardiac volumes, left ventricular mass, and urinary protein excretion. As such, these studies establish both high dietary salt intake and excess aldosterone to be important and independent mediators of cardiovascular risk.1,2

It is interesting, however, that animal models of hyperaldosteronism have consistently demonstrated that the unfavorable target-organ effects of aldosterone are in fact dependent on the concomitant dietary sodium intake. Beginning with landmark studies by Brilla and Weber,3 it has been repeatedly demonstrated that the proinflammatory and profibrotic effects of excess aldosterone induced in end organs, including the heart, vasculature, and kidney, do not manifest unless the dietary salt intake is also excessive.4,5 That is, the deleterious tissue effects of aldosterone could be largely avoided by maintaining the rats on a low-salt diet.

Until recently, such an interaction between sodium and aldosterone in humans, while anticipated, had not been clearly observed. Now, however, a growing body of data, including the article by du Cailar et al6 in this edition of Hypertension, demonstrates that the blood pressure and target-organ effects of excess aldosterone and excess dietary sodium are in large part dependent on each other. That is, as had been predicted by animal models of excess aldosterone, endogenous aldosterone and dietary sodium consumption in hypertensive patients do not contribute in solo but instead act in concert to accelerate target-organ decline.

Aldosterone, Dietary Sodium, and Target-Organ Damage
du Cailar et al6 measured plasma aldosterone levels, 24-hour urinary sodium excretion, and left ventricular mass index in 182 never-treated patients with primary hypertension. The patients were then treated with an angiotensin-converting enzyme inhibitor or an angiotensin receptor antagonist, with other agents added as needed for blood pressure control. After 3 years of treatment, the biochemical and echocardiographic assessments were repeated. In response to treatment, the reduction in left ventricular mass index was positively correlated with changes in systolic blood pressure, urinary sodium excretion, and plasma aldosterone. At the end of the treatment period, when the cohort was compared by tertiles of urinary sodium excretion and high or low aldosterone levels (ie, above or below the median), it was found that left ventricular mass index increased progressively in relation to increasing urinary sodium excretion in the high-aldosterone subjects. No such relation, however, existed in the low-aldosterone subjects. That is, high dietary salt ingestion contributed to progressively higher increases in left ventricular mass only in the setting of high aldosterone levels. The results are important in relating the degree of target-organ damage not to effects of aldosterone excess and high dietary sodium independent of one another but to an interaction dependent on both factors.

These data are strikingly similar to results from our laboratory also relating aldosterone levels to target-organ damage, but instead of left ventricular mass, we had evaluated 24-hour urinary protein excretion.7 In our study, we found that, in patients with resistant hypertension, 24-hour urinary aldosterone levels correlated positively with increasing urinary sodium excretion in patients with high but not low or normal aldosterone levels. Exchanging proteinuria for left ventricular mass index, the figures in each article relating severity of target-organ damage to tertile of sodium excretion in high and low aldosterone levels are almost superimposable (Figure).

The similar results of the 2 studies highlight the independence of aldosterone and dietary sodium in relation to end-organ damage. In both studies, the deleterious effects of hyperaldosteronism were seemingly minimized by ingestion of a low-salt diet, and, conversely, high dietary sodium ingestion, at least in terms of the left ventricular hypertrophy and proteinuria, only worsened disease progression in the setting of high aldosterone levels. Of interest will be whether a similar interaction between aldosterone and dietary sodium can be observed with other disease processes linked independently to one or both of the 2 factors, such as vascular stiffness or obstructive sleep apnea, or, more importantly, to

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levels have been associated with obesity, a characteristic that may be more and more pertinent as higher aldosterone levels are attained. This may be more and more pertinent as higher aldosterone levels have been associated with obesity, a characteristic that is increasingly applicable to worldwide hypertensive populations.

The second implication relates to the prevention of the combined effects of aldosterone and sodium on cardiovascular risk. Animal and now human studies suggest that by obviating the effects of one component of the interaction, the combined effects of both can be minimized if not avoided. The effects of sodium can of course be avoided by ingestion of lower amounts of dietary salt. Such an intervention would be preferred to pharmacological therapy, but, like most lifestyle changes, meaningful reductions in salt ingestion are difficult to achieve and even more difficult to maintain.

The other approach to interrupting this interaction would be to block the effects of aldosterone with use of mineralocorticoid receptor antagonists. It may be that, by blocking aldosterone, which often remains inexplicably high in many hypertensive patients, and in particular patients with resistant hypertension, mineralocorticoid receptor antagonists may prove effective in offsetting some of the end-organ effects of high dietary sodium intake. Such benefit has been observed in patients with resistant hypertension in whom spironolactone was particularly effective in reversing left ventricular hypertrophy during ingestion of the patients’ normally high-salt diets. The benefit was true of patients with both high and normal aldosterone levels but especially true of the patients with demonstrable hyperaldosteronism.

If mineralocorticoid receptor antagonists do prove to be particularly effective in mitigating target-organ complications induced by high dietary salt intake, their use would be anticipated to be specifically appropriate for treatment of hypertensive patients at increased risk of enhanced sodium sensitivity or hyperaldosteronism, such as black patients or obese patients. Beyond such patients, however, it is interesting to speculate that use of mineralocorticoid receptor antagonists may be even more broadly useful in blunting the target-organ effects of high dietary sodium consumption in hypertensive patients in general. If so, even partial blockade of the adverse target-organ effects of sodium in such a large number of persons should translate into a large reduction in cardiovascular events. The benefit of blocking the effects of sodium by blocking aldosterone, of course, presupposes that most hypertensive patients habitually have themselves on a high-sodium diet, which, regrettably, in our experience with patients with resistant hypertension, is a generally reliable assumption.

Disclosures

None.

References

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