The Salt Conundrum

A Hypothesis

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For millennia, salt has had an intimate history with human social, economic, and political relationships. In earlier times man’s work value was paid in salt as gauged by body weight, social stature was dictated by assigned position at the table nearest to the salt, and its etymological root still remains in common parlance.1 Early last century, however, the relationship between salt intake and health was recognized.2 Initially, this relationship was made with the association between magnitude of salt intake and hypertension; but more recently two achievements make a major impact on this subject, the quantitative measurement of dietary sodium intake and repeated recognition that the greater the daily sodium intake, the higher the prevalence of hypertension in populations.

The Problem: A Conundrum

The vital importance of the salt-hypertension relationship remains today even though several concerns exist (albeit with some controversy). Thus, despite the direct relationship between salt consumption and prevalence of hypertension in populations, when increased sodium intake of one specific patient exists, arterial pressure may not necessarily increase; and, therefore, establishment of a direct cause–effect clinical relationship has been difficult to fully appreciate. Therefore, to my way of thinking, the term “salt-dependent” hypertension has been inadequate to explain the clinical relationship between salt-loading and response of arterial pressure. Indeed, sodium-dependent hypertension so-defined exists only in about one-third patients with essential hypertension.3 So why is there such close correlation between salt and hypertension?4,5 Conversely, why has it been so difficult to demonstrate that an individual hypertensive patient is sodium-dependent? What can explain this conundrum? Some astute clinicians have suggested that the sodium sensitivity of a patient may be demonstrated by reduction of arterial pressure with sodium withdrawal6; but this concept also has not been tested formally. To my way of thinking, effects of salt need not be defined solely in terms of a patient’s arterial pressure response to salt-loading. It might be more reasonably defined in terms of the overall hypertensive disease process itself or the effects of chronic salt-loading on the target organs of the disease rather than solely by pressure assessment.

Perhaps an analogy for this conundrum may be demonstrated by epidemiological experiences with another hypertension controversy. Consider the remarkable clinical responses to diuretic therapy over the past 50 years. There is no question that a dramatic reduction in deaths from stroke and coronary heart disease (CHD) has occurred7,8; yet, these guidelines acknowledge a continuous increased prevalence of cardiac and renal failure. Perhaps these two observations (ie, reduction in deaths from stroke and CHD coincident with increased cardiac and renal failure) may be explained similarly by specific local target organ responses to therapy as well as long-term dietary salt-loading on certain target organs of the disease rather than solely by their respective effects on arterial pressure.

Personal Investigative and Other Supportive Evidence

Our first salt-loading investigations were concerned with its hemodynamic and cardiac consequences in spontaneously hypertensive (SHR) rats. These rats are remarkably similar to patients with essential hypertension.9 Thus, in our extensive studies over the past 4 decades, we have been able to confirm our clinical hemodynamic observations in patients with essential hypertension with those obtained in the SHR; and, further, we have also been able to translate our clinical observations to those that occur in the SHR.10,11 Although some investigators have believed that the SHR was not salt-sensitive, our findings (and those of others) have clearly demonstrated that these genetically hypertensive rats are, indeed, salt-sensitive.12,13 Moreover, when desoxycorticosterone acetate was added to salt-loading, malignant hypertension developed.12 Thus, in contrast with their normotensive Wistar-Kyoto (WKY) controls that responded to long-term salt-loading with increased cardiac output but unchanged arterial pressure, the SHR demonstrated increased arterial pressure and total peripheral resistance and a normal cardiac output (and, hence, a normal ventricular preload was associated with salt-loading).13 We followed these reports with another study in which long-term low, normal, or 4% salt-loading diets were administered to separate groups of SHR.14 Even before their arterial pressure rose, cardiac mass in-
increased significantly suggesting that salt-loading promoted non-hemodynamic responses, thereby confirming our contemporaneous clinical and experimental findings suggesting that nonhemodynamic as well as hemodynamic mechanisms were responsible for the increased cardiac mass in hypertension.

One possible limitation to these long-term studies could have been lack of 24-hour pressure measurements but, at the time, these long-term measurements were at their infancy for the rat and, more practically, use of these measurements precluded the initially designed goal for determination of other systemic, local, and ventricular hemodynamic structural and functional measurements. Others pursued similar lines of study, and demonstrated that not only were there pressure-independent effects of salt-loading on cardiac, aortic, and renal mass, but they were associated with increased extracellular matrix and perivascular fibrosis of these organs as well as other biological effects. Of particular significance, this 8% salt-loading produced fibrosis in the heart and kidney in the normotensive WKY as well as in the SHR.

These foregoing findings stimulated our suggestion (which was novel at that time) associated with the changes producing left ventricular enlargement in hypertension were nonhemodynamic as well as hemodynamic mechanisms. Among those nonhemodynamic factors we suggested at that time were mechanisms associated with aging, gender, race, genetic, environmental, pharmacological, coexistent morbid and disease factors, as well as participation of humoral (eg, angiotensin II and/or other peptides, catecholamines, and growth factors) thereby contributing to the overall increased ventricular mass that is regularly seen in long-standing hypertensive disease. Indeed, these factors may operate through autocrine, paracrine, or even intracrine mechanisms to promote not only ventricular myocytic hypertrophy, but also mitogenesis of fibrous or fibromuscular cellular elements in the ventricular interstitium as well as perivascularly. More recently, others have suggested that perhaps one humoral factor (ie, angiotensin II) that stimulates growth in the kidney and in the ventricular interstitium as well as perivascularly. More recently, others have suggested that perhaps one humoral factor (ie, angiotensin II) that stimulates growth in the heart may also be necessary to promote ventricular hypertrophy. And one clinical trial has supported the notion that certain genetic factors to also explain development of ventricular hypertrophy.

These foregoing findings prompted us to initiate a number of studies in a long-term series of investigations in which the WKY and SHR were followed longitudinally with weekly echocardiographic measurements during prolonged salt-loading. These studies carefully demonstrated reproducibility of these repeated measurements of ventricular structure, mass, impaired coronary hemodynamics, as well as systolic and diastolic function. Thus, we demonstrated that prolonged salt-loading was associated with a slight, but significant, elevation of arterial pressure in the SHR that was associated with an increased mass and severe fibrosis of the extracellular matrix and perivascular areas of both ventricular chambers, and impaired diastolic function in both the normotensive WKY as well as the SHR. We also demonstrated and validated the systemic hemodynamic and ventricular systolic and diastolic functional measurements as well as the anatomic mensurations of the ventricular chambers. In one of the reports, 2 groups of adult SHRs, younger adults (20 weeks) were given an 8% salt-loading diet for 8 weeks and older adults (52 weeks) were similarly treated. Of great interest, 25% of the younger adults developed overt cardiac failure with impaired left ventricular systolic and diastolic function; the remaining 75% of that group and all of the older adult SHRs developed only left ventricular diastolic dysfunction associated with preserved systolic function. Furthermore, in all of these WKY and SHR rats, both left and right ventricular coronary blood flow and flow reserve became markedly impaired; and all of these salt-loaded rats (younger and older adult SHR) demonstrated impaired diastolic functions, severe fibrosis of both ventricles (increased hydroxyproline content and concentration), as well as increased aortic mass associated with impaired distensibility and pulse wave velocity. Moreover (in another report), when these adult SHR rats were treated with an angiotensin II (type I) receptor blocker (ARB), arterial pressure was not reduced, even though the left ventricular diastolic functions and collagen content were normalized (Figure 1). Furthermore, in that report, salt-loading diminished renal blood flow and produced massive proteinuria, findings that were normalized by the ARB.

These findings prompted our more detailed study of the kidney. Several individual SHR groups were given either 4, 6, or 8% salt-loads. In all salt-loaded groups, 24-hour protein excretion increased by the second week, and cardiac, aortic, and renal mass increased as renal function became severely impaired out of proportion to the minimally, but significantly, increased arterial pressure. Although renal micropuncture was not possible in those rats receiving the 8% salt-load (because of their inability to withstand the prolonged renal investigation under anesthesia), whole kidney renal function of all 3 groups demonstrated diminished renal flow and increased renal filtration fraction. Renal micropuncture, performed in the groups receiving the 4% and 6% salt-loads, demonstrated markedly decreased single-nephron plasma flow and glomerular filtration rate as filtration fraction, afferent, and efferent glomerular resistance, and glomerular hydrostatic pressure increased. In addition, histological studies of the kidneys demonstrated severe glomerular and arteriolar injury associated with all salt-loading maneuvers; and the glomerulosclerosis was most severe in the group receiving an 8% salt-load.

Thus, our experimental findings demonstrated clearly that salt-loading of varying increments increased arterial pressure and mass of the target organs that was associated with increased hydroxyproline concentration and fibrosis and severely impaired cardiac and renal functions. Finally, it was of great importance to demonstrate that these structural and functional changes were also reversed by an ARB without reducing arterial pressure.

Hypothesis

We therefore suggest a hypothesis to explain this conundrum (Figure 2). Salt-loading not only may raise arterial pressure, but it also promotes severe cardiac, vascular, and renal structural and functional derangements that interrelate
through a myriad of factors that involve multifactorially in the salt-hypertension relationship. We, therefore, hypothesize that salt-loading does not simply raise pressure; more complexly and as yet incompletely elucidated, we believe that it may stimulate local renin–angiotensin–aldosterone systems (RAAS) in heart, vessels, and kidney. It is well-established that the classical response of salt-loading is suppression of renal renin release by the juxtaglomerular apparatus; but we postulate that salt excess also stimulates (directly or indirectly) important local RAAS. Compelling experimental and clinical evidence support existence of local cardiac and renal RAAS. Favoring these contentions are our experimental findings that ARB administration coincident with salt-loading failed to reduce arterial pressure while markedly reducing affected organ masses, decreased collagen deposition (extracellular matrix and perivascularly), and dramatically improved cardiac, vascular, and renal functions. Moreover, other studies have also demonstrated improved organ functions in stroke-prone SHR or \( N^\text{G} \)-nitro-L-arginine methyl ester–treated rats with mineralocorticoid inhibition without reducing pressure.

Although intracardiac renin has been difficult to identify, the other components of a local cardiac RAAS have been demonstrated. Compelling experimental and clinical evidence support existence of local cardiac and renal RAAS. Favoring these contentions are our experimental findings that ARB administration coincident with salt-loading failed to reduce arterial pressure while markedly reducing affected organ masses, decreased collagen deposition (extracellular matrix and perivascularly), and dramatically improved cardiac, vascular, and renal functions. Moreover, other studies have also demonstrated improved organ functions in stroke-prone SHR or \( N^\text{G} \)-nitro-L-arginine methyl ester–treated rats with mineralocorticoid inhibition without reducing pressure.

Clinically, several studies demonstrated that salt-loading impaired renal and left ventricular diastolic functions and, further, many large multicenter trials have provided compelling evidence demonstrating efficacy of agents that suppress the RAAS system and remarkably improved cardiac and renal outcomes.

How, then, can we reconcile the above observations involving patients with cardiac and renal failure with those observations obtained in the large numbers of multicenter trials with hypertensive patients treated with a diuretic-based therapy? We suggest that long-term diuretic therapy secondarily promoted an increased generation of renin from the juxtaglomerular apparatus which, in turn, stimulated local RAAS in heart, vessel, and kidney. Recent experimental studies from our laboratory have demonstrated that when the thiazide is administered alone, renal hemodynamics as well as glomerular and arteriolar injury became impaired. However, when that same diuretic was administered with an
ACE-inhibitor or an ARB (or both), these adverse pathophysiological effects were prevented.69 Consequently, we further hypothesize that the reason for the dissociation of the stroke and coronary heart disease benefits from those potential benefits preventing cardiac and renal failure increases with diuretic-based antihypertensive therapy was not solely related to the hypotensive action of diuretics. We suggest that the inability of the many reports and guidelines published over the years demonstrating the ever-increasing cardiac and renal failure end points7,8 was not because the trialists had not yet had the opportunities to analyze and these outcomes, but because the diuretic (by itself or with inadequate doses of angiotensin-inhibiting drugs) stimulated local cardiac, vascular, or renal RAAS. This, in turn, failed to reduce (or prevent the continuous increase in prevalence) cardiac or renal failure. Why, then, should pressure reduction with the diuretic alone and/or other added therapy reduce the stroke and CHD outcomes? These end points are more vulnerable to pressure-reducing mechanisms. In contrast, whereas cardiac and renal failure also are pressure related, they also involve participation of other adverse compensatory mechanisms including the local RAAS, endothelial dysfunction, loss of parenchymal functions, and those that promote fibrosis, apoptosis, and inflammation which could further exacerbate pressure elevation. We, therefore, hypothesize that prolonged dietary salt-excess similarly stimulates these local RAAS and, consequently, local target organ structure and function become impaired.

Perspectives
Salt surfeit is characteristic of industrialized societies and are related directly to prevalence of hypertension; however, only 30% of patients with hypertension are “sodium-sensitive”. We hypothesize that elevated arterial pressure is not the sole consequence of salt-loading; it also results in structural and functional target organ alterations. Our experimental studies have demonstrated that salt-loading results in: increased cardiac, aortic, and renal mass even before pressure increases; severe ventricular fibrosis associated with ventricular diastolic dysfunction; reduced aortic distensibility; and severe nephrosclerosis in proportion to salt-loading magnitude associated with massive proteinuria, ischemia, glomerular hypertension, and tissue damage. ARB and, more recently, prorenin inhibiting therapy reversed these changes without reducing arterial pressure, suggesting that salt-loading produced severe structural and functional changes resulting from local RAAS stimulation which, when inhibited, reversed these derangement. Similar findings have been shown therapeutically in large multicenter clinical trials which prevented and retarded progression of impaired cardiac and renal function. These findings may be analogous to those major trials cited in clinical guidelines which employed diuretic-based therapy and demonstrated profound reductions in stroke and coronary heart disease mortality. In contrast, cardiac and renal failures have continued to increase unabated and may also result from local renal and cardiac RAAS stimulation.

Disclosures
None.

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