How Does High Salt Intake Cause Hypertension?

Vasodysfunction That Involves Renal Vasodysfunction, Not Abnormally Increased Renal Retention of Sodium, Accounts for the Initiation of Salt-Induced Hypertension

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It has long been recognized that in some people substantially increasing dietary intake of salt (NaCl) increases blood pressure, whereas in others, “salt loading” has little or no effect on blood pressure. Blood pressure so affected by salt has been called salt sensitive and salt resistant, respectively. Although the blood pressure response to salt is a continuous variable and the trait of salt sensitivity, like that of hypertension, is arbitrarily defined, it has been estimated that 30% to 50% of hypertensive humans are salt sensitive and 25% of normotensive humans are salt sensitive. Salt sensitivity confers an increased risk for the occurrence of hypertension and cardiovascular disease. Furthermore, pathophysiological mechanisms mediating salt sensitivity may contribute to the risk for cardiovascular disease beyond their effects on blood pressure. Accordingly, the mechanisms of salt sensitivity continue to be studied intensively with the hope that better understanding of those mechanisms could lead to improved approaches to the prevention and treatment of salt-induced increases in blood pressure and cardiovascular disease.

Response by Hall on p 893

Prevailing Theory of Initiation of Salt Sensitivity and Salt-Induced Hypertension

Prevailing theory holds that an abnormally large increase in renal retention of salt is an early pathophysiological event in the causation of salt sensitivity and salt-induced hypertension. In accord with this theory, it is held that a substantial increase in dietary salt does not induce a pressor effect in salt-resistant subjects because they excrete a salt load more rapidly and retain less sodium than salt-sensitive individuals. In the present analysis, we challenge this conventional view of salt sensitivity/salt resistance and make the case for a “vasodysfunction” theory for the initiation of salt-induced hypertension: An abnormal vascular resistance response to increases in salt intake, in the absence of an abnormally large increase in renal retention of sodium, usually mediates the initiation of salt-induced increases in blood pressure.

We focus this analysis on the initiation of salt-induced increases in blood pressure because we are interested in how increases in salt intake cause increased blood pressure from the outset and why individuals vary in their blood pressure responses to the initiation of a high-salt diet. Furthermore, it is possible that the mechanisms mediating abnormalities...
in vascular resistance during the initiation of salt-induced hypertension may also contribute to the abnormally increased systemic vascular resistance that characterizes sustained hypertension.

According to prevailing theory, salt-sensitive subjects have an impaired renal ability to excrete a salt load that usually causes them to retain more sodium than normal salt-resistant subjects. The retention of abnormally large amounts of salt and water is held to cause abnormally large increases in sodium balance, blood volume, and a transient, abnormally large increase in cardiac output that contributes importantly to the hemodynamic initiation of increased blood pressure. Many investigators also note a role for abnormalities in the control of systemic vascular resistance in the hemodynamic initiation of salt-induced increases in blood pressure; that is, they do not contend that only an abnormally large increase in cardiac output induced by abnormally large increases in renal retention of sodium causes an impaired renal ability to excrete a salt load that usually causes them to retain more sodium than normal salt-resistant subjects. The retention of abnormally large amounts of sodium is said to initiate and sustain salt-induced hypertension.

It should be noted that views holding that abnormal levels of both cardiac output and systemic vascular resistance contribute to the hemodynamic initiation of salt-induced hypertension differ from the view championed by Lifton et al. This view shown in Figure 1 holds that during the initiation of salt-induced hypertension, systemic vascular resistance is "normal" and pathogenically uninvolved in the initial pressor effect of salt. Abnormal systemic vascular resistance is held to be secondary only to increases in cardiac output and blood pressure caused by abnormal increases in renal retention of sodium and water. This volume-loading theory also describes the sequence of events through which the phenomenon of abnormal pressure natriuresis is said to initiate and sustain salt-induced hypertension. Most theories of salt-induced hypertension share 2 core tenets: (1) Salt-sensitive subjects have a subnormal ability to excrete a salt load that causes them to retain more sodium than normal salt-resistant subjects, and (2) such an abnormally increased renal retention of sodium causes an abnormally large increase in cardiac output and thereby contributes importantly to the hemodynamic initiation of salt-induced increases in blood pressure. Here, we challenge the validity of both these tenets.

**Pro Position: Vasodysfunction Theory for the Initiation of Salt-Induced Hypertension**

We first define key terms as they are used in this analysis. We use the term vasodysfunction to indicate a subnormal decrease in systemic vascular resistance in response to increases in salt intake. For all variables, we define normal responses to increases in salt intake as the responses to increases in salt intake observed in normal subjects, that is, salt-resistant subjects with normal blood pressure. We define substantial increases in salt intake as increases equivalent to 200 mmol/d or more occurring within the dietary range of salt intake reported in humans (a range of 10–350 mmol/d). The terms systemic vascular resistance and total peripheral resistance are used interchangeably.

We take the position that vasodysfunction, that is, a subnormal decrease in systemic vascular resistance in response to increases in salt intake, is the hemodynamic abnormality that mediates initiation of most instances of salt-induced hypertension. Furthermore, in contrast to most theories of salt-induced hypertension, the vasodysfunction theory holds that the initiation of increased blood pressure by increased salt intake does not usually involve either: (1) abnormally large increases in renal sodium retention, that is, does not usually involve retention of sodium in an amount greater than that retained during salt loading in normal controls, or (2) abnormally large increases in cardiac output, that is, does not usually involve an increase in cardiac output greater than that occurring during salt loading in normal control subjects.

The Normal Natriuretic and Hemodynamic Responses to Increases in Salt Intake

To determine which responses of salt-sensitive subjects to salt loading are normal or abnormal, it is first necessary to establish the responses of normal subjects to salt-loading. In normal salt-resistant humans, substantial increases in salt intake usually induce substantial renal sodium retention and substantial increases in blood volume, plasma volume, stroke volume, and cardiac output. In response to increases in salt intake, it takes considerable time (days) for normal humans to increase sodium excretion enough to achieve sodium balance (sodium excretion equals sodium intake), and thus, normal humans retain substantial amounts of sodium in response to substantial increases in salt intake.

In normal humans, substantial increases in salt intake, renal sodium retention, fluid volumes, and cardiac output induce little or no increase in blood pressure because normal humans rapidly undergo substantial decreases in systemic vascular resistance in response to such increases in salt intake. In normal humans, the decreases in systemic vascular resistance induced by salt are usually great enough to offset the pressor effects that would otherwise be expected to result from the substantial salt-induced increases in cardiac output. The normal decrease in systemic vascular resistance on NaCl loading appears to involve an early decrease in renal vascular resistance.

In normal animals (salt-resistant animals with normal blood pressure), increases in salt intake also usually induce increases in renal sodium retention, but induce little or no increase in blood pressure because normal animals also vasodilate and substantially reduce systemic vascular resistance in response to such increases in salt intake. These observations in normal humans and animals contradict the contention that normal subjects resist the pressor effects of increased...
salt intake because they excrete sodium chloride “almost as rapidly as it can be infused or drunk”17 and their “blood volume is hardly altered.”12

The Lack of Appropriate Normal Control Subjects in Studies of Salt-Induced Increases in Blood Pressure

We know of no publications that show that during the period when salt loading initiates increases in blood pressure in salt-sensitive subjects, they both retain more sodium and have greater levels of cardiac output than do salt-loaded normal control subjects. The volume-loading theory (Figure 1) that: (1) salt-induced hypertension is initiated by abnormally large increases in sodium retention and cardiac output, and (2) systemic vascular resistance becomes abnormal only when it increases above baseline, is based on publications28–30,57–66 that lack reference to appropriate normal control subjects. Specifically, the studies cited in support of the volume-loading theory28–30,57–66 do not compare salt-sensitive subjects with normal control subjects with respect to the observed changes in sodium balance, cardiac output, and systemic vascular resistance that occur during salt loading. Without such comparisons with salt-loaded normal control subjects, one cannot judge whether the changes observed to occur in salt-sensitive subjects during salt loading are normal or abnormal.

Salt-sensitive hypertensive subjects have been reported to have greater salt-induced increases in sodium balance and cardiac output than salt-resistant hypertensive subjects.60,61 However, as cautioned by Campese et al.,67 such increases cannot be judged to be abnormal without comparing them with results of salt-loading studies in proper normal control subjects, that is, salt-resistant subjects with normal blood pressure (salt-resistant normotensive controls). Indeed, in a salt-loading study by Ishii et al.,35 salt-sensitive hypertensive subjects did not have greater salt-induced increases in sodium balance than those observed in salt-resistant normotensive control subjects. It remains to be determined whether the mechanisms that contribute to salt resistance in normal subjects also contribute to salt resistance in hypertensive subjects.

The Natriuretic and Hemodynamic Responses of Salt-Sensitive Subjects to Increases in Salt Intake

Figure 2 shows the results of studies from our group demonstrating that at no time during initiation of salt-induced increases in blood pressure in normotensive salt-sensitive humans do salt-sensitive subjects usually retain more sodium or have greater increases in cardiac output than do salt-loaded normal control subjects.37,38 The results of these and all other relevant, properly controlled studies demonstrate that in normal...
subjects, salt-loading usually induces increases in sodium retention\textsuperscript{35–38,48–51} and cardiac output\textsuperscript{7,38,44,53,55,56} that are just as great as those observed with salt loading in salt-sensitive subjects (Figure 2). Thus, the finding that blood pressure during salt loading is substantially greater in salt-sensitive subjects than in normal control subjects cannot be attributed to abnormal (greater) increases in sodium retention and cardiac output in the salt-sensitive subjects.

Note that we do not dispute that sodium retention and increases in cardiac output occur during salt loading in salt-sensitive subjects. Rather, we emphasize that the increases in cumulative sodium retention\textsuperscript{35–38,48–51} and cardiac output\textsuperscript{7,38,44,53,55,56} that usually occur in salt-sensitive subjects when salt loading increases blood pressure are not abnormally large, that is, not greater than those that occur during salt loading in normal controls (Figure 2).

**Systemic Vascular Resistance Is Abnormal Throughout Initiation of Salt-Induced Increases in Blood Pressure**

With respect to changes in systemic vascular resistance induced by increases in salt intake, Figure 2 shows results from our laboratory demonstrating that during initiation of salt loading, normal salt-resistant humans vasodilate and reduce systemic vascular resistance, whereas salt-sensitive humans fail to vasodilate and reduce systemic vascular resistance normally.\textsuperscript{37,38} Specifically, the salt-sensitive subjects fail to vasodilate and reduce systemic vascular resistance to the same extent as that observed during the initiation of salt loading in normal control subjects. In studies in salt-sensitive humans and in animals that have included salt-loaded normal controls, it has consistently been observed that salt-sensitive subjects fail to decrease systemic vascular resistance to a normal extent in response to increases in salt intake.\textsuperscript{37,38,44,53,55,56} In salt-sensitive subjects, this failure of systemic vascular resistance to robustly decrease during the initiation of salt-loading is clearly abnormal.

Given that in normal salt-resistant humans a robust decrease in systemic vascular resistance begins within 12 to 24 hours of initiating salt loading (Figure 2), the failure of systemic vascular resistance to decrease to the same extent in the salt-sensitive subjects as in the normal control subjects indicates the occurrence of a very early salt-induced abnormality in vascular resistance. This vasodysfunction, that is, this subnormal decrease in systemic vascular resistance in response to salt loading, is a critical pathogenic event in the initiation of the salt-induced increase in blood pressure. Without this vasodysfunction, the normal increase in cardiac output induced by salt in the salt-sensitive subjects would not have elicited a pressor effect, just as it did not in the salt-resistant normal control subjects (Figure 2). Furthermore, in salt-sensitive subjects, the failure of systemic vascular resistance to normally decrease in response to increases in salt intake occurs before blood pressure increases above baseline. Thus, the abnormal vascular resistance response to salt loading cannot be a

![Figure 2. Time course of NaCl-induced changes in cumulative sodium balance and hemodynamic variables in salt-sensitive subjects and normal, salt-resistant control subjects. Results of studies in normotensive blacks in which Schmidlin et al\textsuperscript{38} continually monitored blood pressure, cardiac output, systemic vascular resistance, and cumulative sodium retention before and after increasing dietary intake of NaCl from 30 to 250 mmol/d (adapted from Schmidlin et al\textsuperscript{38} with permission from the publisher). Hemodynamic values are shown as percentage age of change from the period of low NaCl intake (average of values during the last 3 days of the 1-week period in which the low-NaCl diet was consumed). During the last 3 days of the low-NaCl diet, the salt-sensitive subjects (n=19) did not differ from the salt-resistant subjects (n=18) with respect to absolute levels of mean arterial pressure, systemic vascular resistance, cardiac output, or cumulative sodium balance. The changes in cardiac output are secondary to changes in stroke volume, not in heart rate. Changes in hemodynamic values are shown at 4-hour intervals for the first 72 hours and then at 24-hour intervals thereafter. Results are displayed as means and 95% confidence intervals. †Significant difference between salt-sensitive subjects and salt-resistant control subjects for salt-induced changes in blood pressure on day 1 of high NaCl intake (P<0.05) and on days 2 to 7 of high NaCl intake (P<0.001). §§Significant difference between salt-sensitive subjects and salt-resistant control subjects for salt-induced changes in blood pressure on day 1 of high NaCl intake (P<0.05) and on days 2 to 7 of high NaCl intake (P<0.001). ns indicates no significant differences between salt-sensitive subjects and salt-resistant control subjects.
consequence of the salt-induced increases in blood pressure (Figure 2).

The Vasodysfunction Theory for the Initiation of Salt-Induced Hypertension
We propose the vasodysfunction theory (Figure 3), which has 2 tenets. First, substantial increases in salt intake induce little or no increase in blood pressure in salt-resistant normal subjects because they substantially reduce systemic vascular resistance in response to salt loading, not because they excrete sodium more rapidly, retain less sodium, and undergo smaller increases in cardiac output than do salt-loaded salt-sensitive subjects. Second, substantial increases in salt intake induce substantial increases in blood pressure in salt-sensitive subjects because they undergo vasodysfunction; that is, they fail to normally reduce systemic vascular resistance in response to salt loading, not because they retain a greater salt load and have greater increases in cardiac output than do salt-loaded normal subjects.

The observations of many investigators indicate that vasodysfunction, that is, a failure to normally decrease systemic vascular resistance in response to salt loading, can contribute to the initiation of salt-induced increases in blood pressure in salt-sensitive subjects. The roots of this concept extend back to at least 1975 when Mark et al noted that in normotensive salt-resistant subjects ingesting a low-salt diet, increases in dietary salt induced decreases in forearm vascular resistance, whereas in salt-sensitive subjects, such salt loading induced increases in forearm vascular resistance.

It should be noted that in salt-sensitive subjects, the failure of systemic vascular resistance (total peripheral resistance) to decrease normally in response to the initiation of increased salt intake does not necessarily require the occurrence of a subnormal decrease in vascular resistance in all organs/tissues. For example, vascular resistance may substantially decrease in some organs/tissues, whereas vascular resistance may fail to decrease or may even substantially increase in other organs/tissues. The inability of salt-sensitive subjects to normally decrease systemic vascular resistance during initial NaCl loading may include unchanged or even increased renal vascular resistance. Thus, the vasodysfunction theory depicted in Figure 3 allows for the view that an abnormal renal vascular resistance response to salt loading contributes to the development of an abnormal systemic vascular resistance response to salt loading that, together with normal salt-induced increases in cardiac output, initiates the increase in arterial pressure (Figure 3). The abnormal renal vascular resistance response to salt does not cause salt-sensitive subjects to retain a greater salt load than salt-resistant normal control subjects.

We do not intend to imply that in salt-sensitive subjects the kidney is uninvolved in the initiation of salt-induced increases in blood pressure. Rather, we contend that during salt loading in salt-sensitive subjects, (1) the level of renal vascular resistance is abnormally high, that is, is greater than that in salt-loaded normal subjects, and this contributes to the abnormally high level of systemic vascular resistance that hemodynamically initiates salt-induced hypertension, and (2) the level of renal sodium retention is not abnormally high, that is, is not greater than that in salt-loaded normal subjects and thus abnormally increased renal sodium retention is not involved in the initiation of salt-induced hypertension.

Vasodysfunction Is Likely Involved in the Initiation of All Forms of Salt Sensitivity and Salt-Induced Hypertension
We have previously proposed that the vasodysfunction theory likely accounts for the initiation of salt-induced increases in blood pressure that might occur in rare mendelian forms of human hypertension, including those characterized by high mineralocorticoid levels. With 1 exception, all mendelian disorders of hypertension have been found to be caused by mutations that are associated with increased renal tubular reabsorption of sodium. However, the association of these disorders of hypertension with mutations that increase renal tubular sodium reabsorption does not necessarily mean that mutation-dependent increased renal tubular reabsorption of sodium causes the salt-induced hypertension. The initiation of salt-induced hypertension in humans or animals with such mutations has not been demonstrated to be caused by greater increases in sodium retention and cardiac output in the mutant subjects than in salt-loaded normal control subjects. In experimental models relevant to the Liddle syndrome, deficiency of 11β-hydroxysteroid dehydrogenase type 2, familial hyperkalemic hypertension, and states of mineralocorticoid excess, many studies have indicated that initiation of salt-induced hypertension may not be simply a sodium-retention/volume-loading phenomenon. As discussed in detail elsewhere, most if not all mutations affecting sodium transport in mendelian disorders of hypertension have the potential to cause salt-induced vasodysfunction by affecting neural, hormonal, or vascular mechanisms that influence vascular resistance.

In the present analysis, we have reviewed information indicating that the vasodysfunction theory likely accounts for the hemodynamic initiation of common forms of salt sensitivity. Thus, we contend that the vasodysfunction theory accounts for the hemodynamic initiation of salt-induced increases in blood pressure in most instances of salt sensitivity. Even in animals rendered salt sensitive by surgical reduction of renal mass, that is, even in a model of hypertension that was classically thought to be "caused by pure excess volume loading," the initiation of salt-induced increases in blood pressure does not appear to be due to retention of greater amounts of sodium in the salt-sensitive subjects than in salt-loaded normal control subjects.

Mechanisms Mediating Normal and Abnormal Vascular Resistance Responses to Increases in Salt Intake
In salt-sensitive subjects, increases in salt intake usually induce normal increases in sodium retention and cardiac output and
subnormal decreases in systemic vascular resistance. What mediates this hemodynamic abnormality, that is, the subnormal decrease in systemic vascular resistance in response to increased salt intake, that initiates the salt-induced increase in blood pressure? Multiple factors can affect arterial vascular resistance (Table), and the relative importance of different mechanisms in mediating failure to normally vasodilate in response to increases in salt intake remains to be established. Among the many candidate factors, it may be worthwhile to first consider those recognized to be involved in mediating the normal decrease in vascular resistance that occurs in normotensive, salt-resistant control subjects. For example, nitric oxide (NO) is a powerful vasodilator, and it has been proposed that increases in salt intake normally cause increases in blood volume/blood flow that result in shear stress–mediated release of NO from
endothelial cells that may mediate vasodilation in response to increased salt intake.46

**The Role of NO Mechanisms in Mediating Normal and Abnormal Vascular Resistance Responses to Increases in Salt Intake**

In Figure 4, we focus on several NO-related mechanisms influencing salt sensitivity because of the apparent role of NO in contributing to normal vasodilatory responses to increases in salt intake and because many studies have indicated that disturbances in NO activity play a major role in the pathogenesis of salt-induced hypertension,95 an idea proposed by Chen and Sanders72 at least 25 years ago. Recent studies from Schmidlin et al88 and from Jeggle et al,84 Oberleithner et al,93 and others84,89,98,103,104 have provided new insights into abnormalities in the regulation of NO activity that likely contribute to the abnormal vascular resistance responses to salt that initiate various forms of salt-induced hypertension.

Salt-induced increases in blood pressure vary inversely with salt-induced increases in plasma105,106 and urinary107 biomarkers of NO and vary directly with salt-induced increases in plasma88,89,105,106 and urinary97 levels of asymmetrical dimethylarginine (ADMA), a major endogenous inhibitor of NO bioavailability, through its capacity to inhibit NO synthase and to increase oxidative stress.100–102 Intravenously administered ADMA has been shown to acutely increase systemic vascular resistance and blood pressure in humans.109 In salt-sensitive humans, we have found that increases in plasma levels of ADMA occur within 24 hours of the initiation of increased salt intake, whereas in normal salt-resistant control subjects, the same salt loading does not increase ADMA levels.38 In salt-sensitive subjects, increases in salt intake may induce increases in ADMA levels by promoting both oxidative stress-induced decreases of ADMA metabolism and increases in ADMA synthesis.100

The role of ADMA-mediated decreases in NO activity in the abnormal vascular resistance response to salt is of particular interest because the involvement of ADMA might help to explain why the trait of salt sensitivity does not always “follow the kidney” in transplantation studies.110 For example, the classic renal cross-transplantation studies by Morgan et al110 indicate that the trait of salt sensitivity in the Dahl rat model is determined not only by renal factors but also by extrarenal factors (Figure 5).110 ADMA is generated by multiple cell types in the cardiovascular system,108 and circulating ADMA may originate from both extrarenal and intrarenal sources. Thus, in salt-sensitive animals, disturbances in NO activity caused by salt-induced increases in circulating ADMA from extrarenal sources could help explain why transplanting a kidney from a Dahl salt-resistant rat into a bilaterally nephrectomized recipient (Figure 5).110 Conversely, disturbances in NO activity caused by salt-induced increases in renal production of ADMA and decreases in renal clearance of ADMA could help explain why transplanting a kidney from a Dahl salt-sensitive donor into a bilaterally nephrectomized salt-resistant recipient induces salt sensitivity in the recipient (Figure 5).110 It should also be noted that in humans, supplemental potassium appears to attenuate salt sensitivity in part by preventing salt-induced increases in ADMA levels and decreases in NO activity.106

Emerging evidence from studies by Oberleithner et al84 and others84,89,98,103,104 has indicated that in some salt-sensitive models, the initiation of salt-induced hypertension is determined by decreases in vascular NO activity that are mediated by aberrant increases in the activity of epithelium-like sodium channels in endothelial cells (EnNaCs).99 Specifically, it has been proposed that in some forms of salt sensitivity, salt-induced increases in plasma sodium, together with aberrant increases in EnNaC activity, induce increases in endothelial cell membrane stiffness by promoting sodium influx, cell swelling, and membrane actin polymerization (Figure 4).84,93,98,99 The increases in endothelial cell membrane stiffness are said to reduce membrane deformability in a manner that interferes with the normal capacity of increases in pulsatile flow/shear stress to activate signaling pathways that promote increases in NO activity and vasodilation (Figure 4).93,98,99 Such increases in EnNaC activity that promote endothelial cell stiffness in response to salt loading may be determined by increases in mineralocorticoid levels or by variants in genes that code for EnNaC subunits or other proteins that affect EnNaC activity.99 Accordingly, this novel mechanism for impairing normal vasodilatory responses to increases in salt intake may be particularly relevant to the initiation of salt-induced hypertension in patients with hyperaldosteronism, certain forms of

**Table. Examples of Systems/Factors That Affect Vascular Resistance**

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<th>System/Factor</th>
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<tr>
<td><strong>NO system</strong></td>
<td>Sympathetic nervous system</td>
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<td>Renin-angiotensin system</td>
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<td>Adrenal hormone systems</td>
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<td>Kallikrein-kinin system</td>
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<td><strong>CGRP, substance P, adrenomedullin</strong></td>
<td><strong>γ-MSH and other neuropeptide systems</strong></td>
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<tr>
<td><strong>γ-MSH and other neuropeptide systems</strong></td>
<td><strong>Transient receptor potential vanilloid channels</strong></td>
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<tr>
<td><strong>CGRP, substance P, adrenomedullin</strong></td>
<td><strong>Structural factors affecting vessel mechanics and function</strong></td>
</tr>
<tr>
<td><strong>CGRP, substance P, adrenomedullin</strong></td>
<td><strong>Various ion channels and cell signaling systems regulating MLC function</strong></td>
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CGRP indicates calcitonin gene related peptide; γ-MSH, γ-melanocyte-stimulating hormone; MLC, myosin light chain; and NO, nitric oxide.
Exposure of endothelial cells to increases in potassium levels in the physiological range can reduce endothelial cell stiffness and increase NO release. This phenomenon might contribute to the ability of supplemental dietary potassium to increase plasma biomarkers of NO and to attenuate salt-induced increases in blood pressure. Conversely, in subjects with a low potassium intake and suboptimal plasma levels of potassium, the risk for salt sensitivity may be increased owing to increases in endothelial stiffness and decreases in NO activity mediated by both salt loading and decreases in plasma concentrations of potassium.

We recognize that disturbances in NO activity, and in many other factors that could influence vascular resistance responses to salt loading, may also influence renal tubular reabsorption of sodium. However, during the initiation of salt loading, the effects of these factors on renal tubular sodium transport usually do not cause greater increases in sodium retention and cardiac output in salt-sensitive subjects than in salt-loaded normal subjects. Thus, effects of these factors on renal tubular sodium transport do not mechanistically account for the hemodynamic initiation of greater salt-induced increases in blood pressure in salt-sensitive subjects than in salt-loaded normal subjects.

The Role of the Sympathetic Nervous System and Other Mechanisms in Mediating Normal and Abnormal Vascular Resistance Responses to Increases in Salt Intake

We have highlighted disturbances in several mechanisms regulating NO pathways in the vasculature of salt-sensitive subjects compared with normal subjects (Figure 4). However, we recognize that in salt-sensitive humans and animal models, a variety of factors, both neural and nonneural (Table), likely play important roles in the abnormal vascular resistance response to initiation of salt loading. Among these other mechanisms, some that have received the most attention include alterations in sympathetic nervous activity, activity of the local and circulating renin-angiotensin systems, and activities of transient receptor potential vanilloid channels. In addition to research on the many well-known pathways involved in regulation of vascular resistance (Table), novel mechanisms involved in subnormal vasodilatory responses to increases in salt intake may be revealed by studies in which genetic alterations are selectively targeted to the vasculature.

Figure 4. Nitric oxide–related mechanisms mediating vascular resistance responses to initiation of increased salt intake. A, In normal subjects (normotensive, salt-resistant subjects), increases in salt intake cause volume-induced increases in cardiac output, resulting in shear stress–mediated release of nitric oxide from endothelial cells. The increases in nitric oxide activity contribute to vasodilation and decreases in systemic vascular resistance (SVR) that help offset potential pressor effects of the salt-induced increases in cardiac output so that blood pressure does not increase. This normal decrease in SVR on NaCl loading includes a decrease in renal vascular resistance (RVR). B, In salt-sensitive subjects, increases in salt intake induce normal increases in cardiac output but subnormal decreases in SVR and RVR, in part because of subnormal increases in nitric oxide activity caused by salt-induced increases in asymmetrical dimethyl arginine (ADMA) and endothelial cell stiffness. Increases in cellular and plasma ADMA may be caused by several mechanisms, including abnormally large salt-induced increases in oxidative stress that affect cellular export of ADMA and enzymatic production and clearance of ADMA. Note that increases in ADMA can also cause increases in vascular activity of the renin-angiotensin system (RAS) that promote oxidative stress. Increases in endothelial cell stiffness may be caused by the combination of increases in plasma sodium concentrations with decreases in activity of epithelial sodium channels (ENaCs) in the endothelium.
It should also be noted that the sodium and chloride components of salt each may have an independent capacity to affect vascular resistance and blood pressure. It is possible that in some salt-sensitive subjects, not only might the sodium or chloride components fail to cause a normal decrease in vascular resistance, but either or both ionic components of salt might provoke an increase in vascular resistance. It is also possible that alterations in the amount of sodium or chloride stored in skin or other tissues including the vasculature or the brain, might play a role in abnormal vascular resistance responses to salt.

The Relevance of Acute Salt-Loading Studies to the Initiation of Sustained Hypertension

In the present analysis, we draw inferences about the initiation of short-term salt-induced increases in blood pressure and the initiation of sustained hypertension from acute salt-loading studies in salt-sensitive and salt-resistant normotensive humans. The rationale for this is based on data indicating that properly controlled acute salt-loading studies are predictive of the occurrence of sustained hypertension and cardiovascular disease in humans. It is possible that in some salt-sensitive subjects, not only might the sodium or chloride components fail to cause a normal decrease in vascular resistance, but either or both ionic components of salt might provoke an increase in vascular resistance. It is also possible that alterations in the amount of sodium or chloride stored in skin or other tissues including the vasculature or the brain, might play a role in abnormal vascular resistance responses to salt.

The present analysis focuses on hemodynamic abnormalities that mediate the initiation of salt-induced hypertension and is not intended to discuss the hemodynamic abnormalities involved in sustaining salt-induced hypertension. However, it should be noted that in chronic forms of salt-sensitive hypertension (eg, primary aldosteronism), the level of systemic vascular resistance, not the level of cardiac output, is greater than that in normotensive control subjects. In addition, in long-term salt-loading studies in humans, Titze’s group has reported that variations in blood pressure are associated with variations in salt intake but are not associated with variations in total body sodium.

Conclusions

A large body of evidence now exists that demonstrates that a subnormal vasodilatory response to increased salt intake, not abnormally large increases in renal sodium retention and cardiac output in response to increased salt intake, accounts for the hemodynamic initiation of most instances of salt-induced hypertension. Multiple mechanisms, including disturbances in NO activity, sympathetic nervous system activity, and activity of other pathways regulating vascular resistance, likely mediate the impaired vasodilatory response to salt that hemodynamically initiates salt-induced increases in blood pressure. This conclusion shifts the pathophysiological focus to disturbances in the regulation of vascular resistance and away from the conventional view that salt-induced hypertension is mediated by increases in renal retention of sodium in amounts greater than those that occur during salt loading in normal control subjects. We believe that a better understanding of the mechanisms of salt sensitivity and salt resistance will lead to more precisely targeted, and hence more effective, approaches to the prevention and treatment of hypertension and cardiovascular disease.
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Disclosures

None.

References


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Response to Morris et al
John E. Hall, PhD

Morris and colleagues argue that vascular dysfunction causes salt sensitivity of blood pressure (BP). However, they fail to cite any studies showing that primary increases in nonrenal vascular resistance can actually cause BP salt sensitivity. In contrast, many studies have shown that genetic or acquired kidney-specific disorders that enhance NaCl reabsorption or induce nephron injury also increase BP salt sensitivity. The simplistic view of Morris et al that BP fails to increase in salt-resistant subjects because they acutely vasodilate during high salt intake whereas salt-sensitive subjects vasoconstrict does not take into account (1) overwhelming evidence that kidney dysfunction, reflected by impaired pressure natriuresis, is required for increased salt intake to raise BP chronically in all types of genetic or acquired salt-sensitive hypertension studied thus far; (2) that vasodilation in salt-resistant subjects is transient and does not persist after the kidneys re-establish salt balance; (3) that vasoconstriction in salt-sensitive hypertension usually follows rather than precedes increased BP, suggesting that vascular dysfunction is secondary to increased BP; (4) that vasoconstriction of nonrenal blood vessels, induced experimentally or by genetic mutations, has not been shown to increase BP salt sensitivity; and (5) that treatments which specifically improve renal excretory function (eg, diuretics or kidney transplantation) reduce BP and reverse hypertension-induced vascular changes. Morris et al focus mainly on selected short-term studies of salt loading, failing to consider that mechanisms of chronic hypertension differ from those activated to buffer BP effects of large, short-term salt loads. They also fail to recognize that although salt-sensitive subjects may excrete a sodium load as rapidly as salt-resistant subjects, they do so at the expense of higher BP, indicating impaired renal-pressure natriuresis. Nephrologists are keenly aware that BP becomes extremely salt/volume sensitive as kidney function declines. More attention should be focused on the mechanism by which long-term (rather than just short-term) increases in salt intake cause progressive renal and cardiovascular injury.
Vasodysfunction That Involves Renal Vasodysfunction, Not Abnormally Increased Renal Retention of Sodium, Accounts for the Initiation of Salt-Induced Hypertension
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