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REVIEW ARTICLE

Changing views on the common physiologic abnormality that mediates salt sensitivity and initiation of salt-induced hypertension: Japanese research underpinning the vasodysfunction theory of salt sensitivity

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Abstract

High-salt intake is one of the major dietary determinants of increased blood pressure and cardiovascular disease. Thus, there is scientific and medical interest in understanding the mechanistic abnormalities mediating the pressor effects of salt (salt sensitivity). According to historical theory, salt sensitivity stems from an impairment in renal function (referred to as "abnormal pressure natriuresis" or a "natriuretic handicap"), which causes salt-sensitive subjects to excrete a sodium load more slowly, and retain more of it than salt-resistant normotensive controls. However, this historical view has come under intense scrutiny because of growing awareness that in salt-sensitive subjects, acute salt loading does not usually induce greater increases in sodium balance and cardiac output than those induced by salt loading in salt-resistant normotensive controls. Here we highlight pioneering studies from Japan that challenge the historical thinking and provide insights into a contemporary theory of salt sensitivity termed the "vasodysfunction theory." According to this theory, initiation of salt-induced hypertension usually involves abnormal vascular resistance responses to increased salt intake, not greater renal retention of a salt load in salt-sensitive subjects than in normal subjects. By shifting the focus from the historical theory to a contemporary final common pathway for the pathogenesis of salt sensitivity, research from Japan is building the scientific foundation for more effective approaches to the prevention and treatment of salt-induced hypertension. Among the most promising approaches are dietary strategies for reducing the risk for salt-induced hypertension that do not depend on reducing salt consumption in the population.

Keywords salt · salt sensitivity · sodium · hypertension · vasodysfunction

Introduction

Blood pressure salt sensitivity is a common disorder associated with increased risk for hypertension [1]. Studies by Morimoto et al. [2] from the National Cardiovascular Center in Suita, Japan suggest that salt sensitivity may also be an independent risk factor for elapsed time to a cardiovascular event. Thus, in addition to increasing risk for hypertension, salt sensitivity might signify an underlying disturbance in vascular biology that influences risk for cardiovascular events beyond its effects on blood pressure per se [2]. Of the many different methods that have been explored for assessing salt sensitivity, a carefully controlled dietary protocol similar to that employed by Morimoto et al. [2], provides the highest test–retest reliability for identifying salt-sensitive subjects [3]. While there is ongoing concern about the meaning and practical utility of various methods of testing for salt sensitivity [3–5], the mechanistic abnormalities mediating the pressor effects of salt, and the role of dietary salt restriction in the prevention and management of hypertension, are subjects of major scientific and medical interest [1, 6–11].

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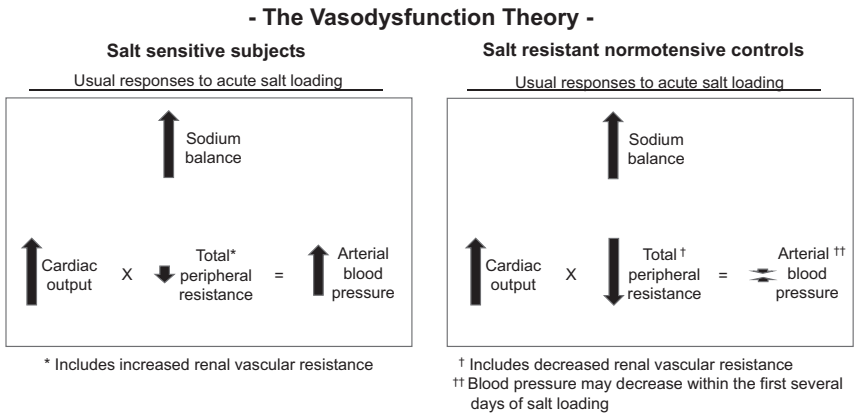

Fig. 1 The vasodysfunction theory for initiation of salt sensitivity and salt-induced hypertension. This diagram shows the usual changes in sodium balance, cardiac output, and vascular resistance that occur with initiation of increased salt intake in salt-sensitive subjects, and in salt-resistant subjects with normal blood pressure. Note that in salt-sensitive subjects, the increases in sodium balance and cardiac output that occur during initiation of salt loading are not abnormal, i.e., not greater than those that occur with salt loading in salt-resistant controls with normal blood pressure. In contrast, the salt-induced changes in vascular resistance that occur in salt-sensitive subjects are distinctly abnormal, i.e., distinctly different from those that occur in normotensive, salt-resistant controls

Disturbances in many molecular, biochemical, neural, immunologic, and other mechanisms have been implicated in the pathogenesis of salt sensitivity [12–45]. It has been proposed that many, if not most, of these disturbances usually mediate salt sensitivity and initiation of salt-induced hypertension through a common physiologic abnormality termed "vasodysfunction" [42, 46]. In the present review, we discuss the vasodysfunction theory of salt sensitivity and highlight pioneering studies from Japan that have been instrumental in elucidating this final common pathway through which a variety of biologic disturbances initiate salt-induced hypertension.

The physiologic abnormality that usually mediates salt sensitivity and initiation of salt-induced hypertension: an abnormal vascular resistance response to increased salt intake

According to the vasodysfunction theory of salt sensitivity, initiation of salt-induced hypertension usually involves subnormal decreases in systemic vascular resistance (total peripheral resistance) in response to salt loading, together with normal salt-induced increases in sodium balance and cardiac output (Fig. 1) [42]. Thus, the theory holds that "vasodysfunction," defined as a subnormal decrease in systemic vascular resistance in response to increases in salt intake, is the physiologic abnormality that initiates most instances of salt-induced hypertension. The abnormal systemic vascular resistance response to salt loading is determined at least in part by an abnormal renal vascular resistance response to salt loading (Fig. 1) [46].

It is important to note that while salt-sensitive subjects undergo increases in sodium balance and cardiac output in response to acute salt loading, the vasodysfunction theory holds that those increases are usually *not* abnormal [42]. That is, the vasodysfunction theory holds that in most salt-sensitive subjects, increases in sodium balance and cardiac output in response to acute salt loading are not greater than those that occur with salt loading in normal controls (salt-resistant subjects with normal blood pressure) (Fig. 1). The theory holds that in contrast to salt-resistant normal controls, most salt-sensitive subjects fail to robustly vasodilate and normally reduce systemic vascular resistance in response to acute salt loading (Fig. 1) [42]. This abnormal vascular resistance response to salt loading causes systemic vascular resistance to be greater in salt-sensitive subjects than in salt-resistant normal controls. With salt loading, the abnormally high (greater) levels of systemic vascular resistance, together with normally increased levels of sodium balance and cardiac output, cause greater increases in blood pressure in salt-sensitive subjects than in salt-resistant normal controls (Fig. 1) [42]. The vasodysfunction theory can apply not only to common forms of salt sensitivity, but also to salt sensitivity that may occur in rare Mendelian forms of hypertension [47].

Questioning the historical view that subnormal sodium excretion is usually involved in the initiation of salt sensitivity and salt-induced hypertension: pioneering studies from Japan

In contrast to the contemporary vasodysfunction theory of salt sensitivity, the historical and still prevailing theory of salt

sensitivity championed by Guyton, Hall, and others [48–59] incorporates the view that initiation of salt-induced hypertension usually involves an impairment in renal function (referred to as a "natriuretic handicap" or "abnormal pressure natriuresis") which causes salt-sensitive subjects to excrete a sodium load more slowly, and retain more of it than salt-resistant subjects with normal blood pressure. This historical theory holds that in response to increased salt intake, the natriuretic handicap causes salt-sensitive subjects to undergo abnormally large increases in sodium balance, cardiac output, and therefore blood pressure. However, in careful metabolic studies conducted at Tokyo University more than 30 years ago, Ishii et al. [60] found that in response to increases in salt intake (from 100 mmol/day to ~275 mmol/day), salt-sensitive subjects usually do not excrete sodium more slowly and undergo greater increases in sodium balance than salt-resistant normal controls (salt-resistant subjects with normal blood pressure). This seminal observation from Japan was subsequently confirmed by investigators in other countries studying humans and animal models [61–67] and provides the foundation for a key tenet of the contemporary vasodysfunction theory: initiation of salt sensitivity does not usually involve subnormal sodium excretion and retention of greater amounts of sodium in salt-sensitive subjects than in salt-resistant normotensive controls.

Salt-sensitive Japanese and non-Japanese may often excrete a sodium load more slowly, and retain more of it when compared with salt-resistant hypertensive subjects [68, 69], but not when compared with normal subjects (salt-resistant subjects with normal blood pressure) [60–63]. Thus, contrary to historical theory, a natriuretic handicap (subnormal sodium excretion in response to salt loading) does not usually account for the initiation of most instances of salt sensitivity and salt-induced hypertension. Note that this view does not conflict with the popular teleologic interpretation of salt sensitivity which holds that in salt-sensitive subjects, increases in blood pressure in response to salt loading are "required" to excrete the salt load [1, 50, 55, 57]. The teleologic interpretation is a statement of the supposed purpose of salt-induced hypertension. It is not a statement about the mechanism of salt sensitivity, and it does not address the abnormality that usually mediates salt-induced increases in blood pressure in the first place.

The key role of the renal blood vessels in mediating salt sensitivity and abnormal vascular resistance responses to increases in salt intake

According to the vasodysfunction theory, the abnormal vascular resistance response to salt loading that usually initiates salt-induced hypertension includes impaired renal vasodilation and abnormally increased renal vascular resistance (greater renal vascular resistance in salt-sensitive subjects than in salt-loaded, salt-resistant subjects with normal blood pressure) (Fig. 1) [46]. Investigators in Japan were among the first to show that in salt-sensitive subjects, renal vascular resistance increases within a week after switching from a low-salt diet to a high-salt diet (Fig. 2) [68, 70, 71]. Salt-induced increases in renal vascular resistance have been reported to occur in both Japanese and non-Japanese subjects with salt sensitivity [68, 70–75]. These findings in humans are consistent with studies from the Department of Pharmacology, Kagawa Medical School by Tomohiro et al. [76] in conscious Dahl salt-sensitive rats (Dahl S rats) showing that salt loading induces large increases in renal vascular resistance.

To determine whether the salt-induced increases in renal vascular resistance that occur in salt-sensitive subjects are abnormal, it is necessary to have an accurate understanding of the effects of salt loading on renal vascular resistance in appropriate normal controls (salt-resistant subjects with normal blood pressure). Figure 2 shows that in salt-resistant subjects with normal blood pressure, but not in salt-sensitive subjects, renal vascular resistance usually decreases within the first week of switching from a low-salt diet to a high-salt diet [74, 77–79]. Thus, in salt-sensitive subjects, the increases in renal vascular resistance that occur in response to salt loading appear distinctly abnormal. Further, in response to short-term salt loading, salt-induced increases in renal vascular resistance are directly correlated with salt-induced increases in blood pressure [74, 75].

As noted above, in response to salt loading, it is well established that renal vascular resistance usually increases in salt-sensitive subjects and decreases in salt-resistant normal controls (salt-resistant subjects with normal blood pressure) [46]. This raises the question: what is the usual effect of salt loading on renal vascular resistance in salt-resistant subjects with hypertension? Investigators in Japan and other countries have found that in salt-resistant subjects with hypertension, renal vascular resistance usually undergoes relatively little or no change in response to short-term increases in salt intake [68, 70–73]. Thus, within the first week of switching from a low-salt diet to a high-salt diet, renal vascular resistance increases in salt-sensitive subjects (with or without hypertension), decreases in normal subjects (salt-resistant subjects with normal blood pressure), and undergoes relatively little or no change in salt-resistant subjects with hypertension.

The usual mechanism whereby salt-induced increases in renal vascular resistance initiate salt-induced hypertension

In salt-sensitive subjects, the abnormal renal vascular resistance response to salt loading does not usually initiate

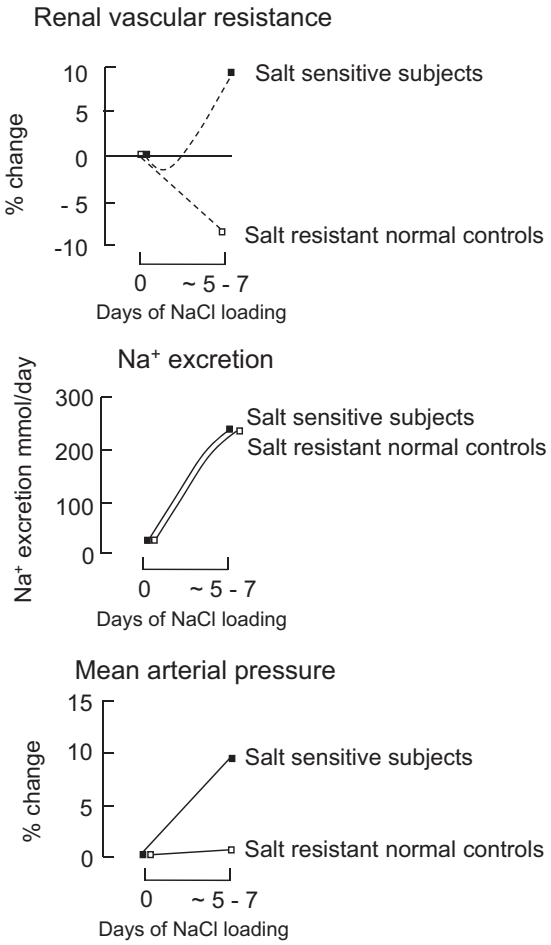

Fig. 2 Changes in renal vascular resistance, sodium excretion, and blood pressure that occur with initiation of increased salt intake in humans. These results are based on salt-loading studies in salt-sensitive subjects [63, 68, 70, 72–75] and in salt-resistant normal controls (salt-resistant subjects with normal blood pressure) [63, 74, 77–79]. The dotted lines indicate that with initiation of salt-induced increases in blood pressure (within the first few days of salt loading), the exact time courses for the salt-induced changes in renal vascular resistance are unknown. Adapted from Kurtz et al. [46] with permission

hypertension by causing greater sodium retention than in salt-loaded normal controls (salt-resistant subjects with normal blood pressure). In salt-sensitive subjects, the abnormal increase in renal vascular resistance with salt loading may constrain salt-sensitive subjects from excreting more of a sodium load than normal subjects (salt-resistant subjects with normal blood pressure) [46]. However, it does not cause salt-sensitive subjects to excrete the sodium load less rapidly and retain more of it than salt-loaded normal subjects [46, 60–63]. As discussed earlier, in light of the pioneering work of Ishii and colleagues, and of confirmatory studies by others, it is apparent that salt-sensitive subjects usually do not retain more of a salt load than normal subjects, acutely or chronically [46, 60–63]. Accordingly, the vasodysfunction theory holds that in salt-sensitive subjects, the abnormal renal vascular resistance response to salt loading contributes to initiation of salt-induced hypertension by promoting greater systemic vascular resistance in salt-sensitive subjects than in salt-loaded normal subjects, not by causing greater retention of sodium than in salt-loaded normal controls (Fig. 1) [42, 46].

In salt-sensitive subjects, further research is required to precisely establish the roles of various segments of the renal circulation in determining the abnormal renal vascular resistance responses to salt loading. It has been suggested that in salt-sensitive subjects, increases in salt intake induce increases in afferent and efferent arteriolar resistance [72, 73, 75]. Salt-induced decreases in preglomerular resistance may largely account for the decreases in renal vascular resistance that occur in response to salt loading in salt-resistant normal controls [74, 79]. Furthermore, studies by Fujita and colleagues, Takeshita et al, and others suggest that in salt-sensitive subjects, salt loading may also promote increases in arterial resistance in non-renal vascular beds [28, 68, 80–84]. Thus, in salt-sensitive subjects, abnormal vascular resistance responses to salt loading appear to involve more than just the renal circulation.

In salt-sensitive subjects, what mechanisms mediate abnormal renal vascular resistance responses to increases in salt intake?

According to the vasodysfunction theory of salt sensitivity, the abnormal vascular resistance response to salt loading that is usually involved in initiation of salt-induced hypertension can be mediated by disturbances in a variety of molecular, biochemical, neural, immunologic, and other pathways [12–45, 85]. Figure 3 depicts this final common pathway through which an assortment of mechanistic disturbances may enable salt loading to initiate hypertension. The underlying mechanistic disturbances involved in causing abnormal vascular resistance responses to salt loading and salt sensitivity may vary according to genetic, environmental, and demographic factors. Such mechanistic disturbances may cause abnormal vascular resistance responses to salt loading by increasing activity of pathways promoting vasoconstriction, impairing activity of pathways promoting vasodilation, or both. While many mechanisms can be involved in mediating abnormal vascular resistance responses to increases in salt intake, here we highlight the role of disturbances in the nitric oxide (NO) system in the vasculature, and single out key studies from Japan pertaining to this topic.

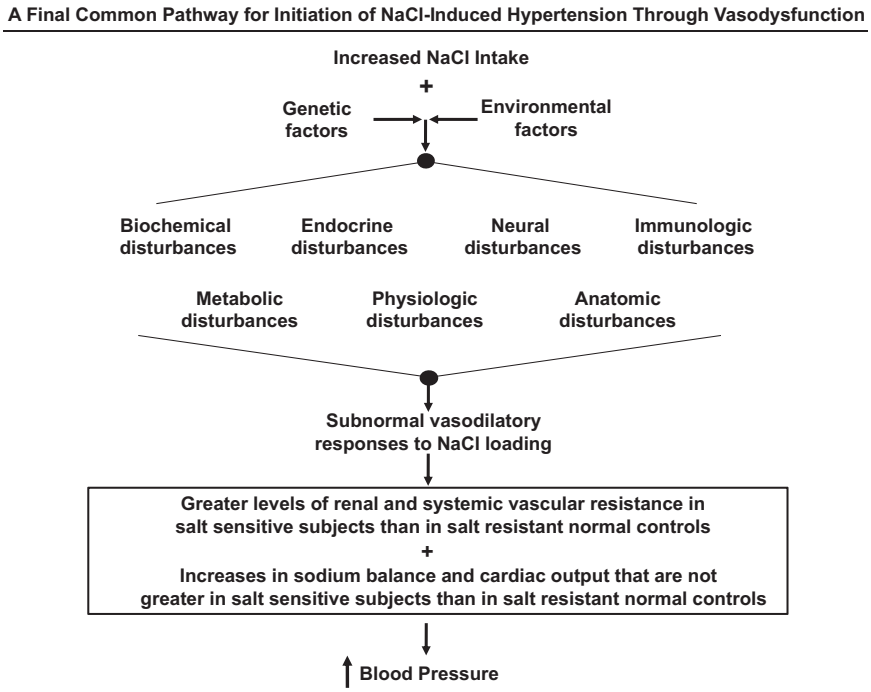

Fig. 3 A final common pathway through which a variety of mechanistic disturbances enable increased salt intake to initiate hypertension. For a discussion of the factors that chronically maintain salt-induced increases in blood pressure, see Kurtz et al. [11]. The mechanistic disturbances mediating the abnormal vascular resistance responses to a high-salt diet that initiate hypertension may also mediate the abnormalities in vascular resistance that characterize sustained hypertension

Highlighting the role of disturbances in nitric oxide activity in mediating the vasodysfunction that initiates salt-induced hypertension

With respect to the pathogenesis of salt sensitivity, we are particularly interested in disturbances that impair activity of vasodilation pathways involved in the flow-mediated decreases in vascular resistance that normally occur in response to increased salt intake. NO plays a major role in flow-mediated vasodilation, and increased NO activity is an important determinant of the reductions in renal and systemic vascular resistance that normally occur in response to a high-salt diet [79]. While other factors besides NO can be involved in flow-induced dilation, Matic et al. [86] have suggested that in the setting of a high-salt diet, the dependence of flow-induced dilation on NO becomes particularly prominent. In 1991, Chen and Sanders [29] proposed that abnormalities in NO activity are involved in the pathogenesis of salt sensitivity and reported that in Dahl S rats, subnormal NO responses to increased salt intake may initiate disturbances in vascular resistance and hypertension.

Asymmetrical dimethylarginine as a mechanism of salt-induced disturbances in NO activity mediating renal vasodysfunction and salt sensitivity

Shortly after the landmark study by Chen and Sanders [29], investigators from Japan [40, 41, 70, 87–90] and elsewhere [91–95] began to explore mechanisms mediating abnormal NO responses to increased salt intake. Consistent with the hypothesis proposed by Chen and Sanders, Tolins and Shultz [94] found that inhibition of NO synthesis induces salt sensitivity in Sprague Dawley rats that are otherwise resistant to the pressor effects of a high-salt diet. Pioneering work by Japanese investigators indicated that in salt-sensitive subjects, impaired NO activity in response to a high-salt diet may be mediated by endogenous inhibitors of NO synthase and by various factors that impair NO bioavailability. Specifically, Matsuoka et al. [40] from Kurume University School of Medicine reported that the failure of Dahl S rats to normally increase NO activity in response to increases in salt intake is mediated by abnormally increased levels of asymmetrical dimethylarginine (ADMA). ADMA substantially inhibits NO activity by inhibiting NO synthase activity and by increasing oxidative stress [96–99]. Oxidative stress impairs NO bioavailability and also increases ADMA levels, and has been proposed to be a key determinant of salt sensitivity [43, 44, 99–101]. Suda et al. [97] from the School of Medicine of the University of Occupational and Environmental Health in Kitakyushu reported that in mice, ADMA can induce vascular oxidative stress and vascular damage in the presence or absence of endothelial nitric oxide synthase, possibly by increasing vascular levels of angiotensin-converting enzyme and activity of the vascular renin angiotensin system (RAS).

In agreement with the experimental findings in animal models, studies in both Japanese and non-Japanese humans have demonstrated that in salt-sensitive subjects, but not in salt-resistant subjects [31, 41, 63, 102–104], increases in

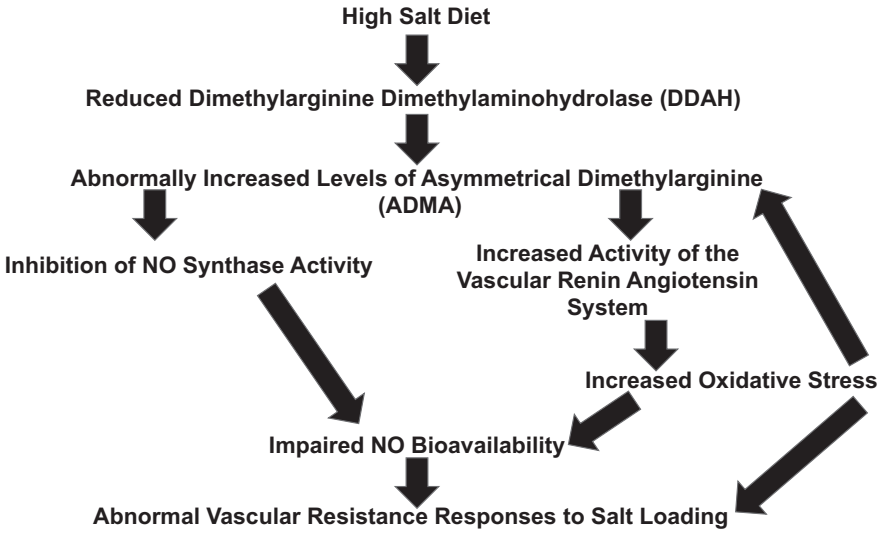

Fig. 4 Impaired NO bioavailability mediated by increases in ADMA in response to salt loading

salt intake: (1) reduce vascular activity of the enzyme dimethylarginine dimethylaminohydrolase (DDAH) that degrades ADMA; (2) induce increases in plasma ADMA and urinary excretion of ADMA; and (3) reduce biomarkers of NO in plasma. In key studies in hypertensive and normotensive Japanese, Fujiwara et al. [41] at Hirosaki University found that salt-induced changes in blood pressure correlated inversely with salt-induced changes in plasma nitrate/nitrite levels, which correlated inversely with salt-induced changes in plasma levels of ADMA. Based on these and other observations, the investigators concluded that "Modulation of NO synthesis by salt intake may be involved in a mechanism for salt sensitivity in human hypertension, presumably via the change in ADMA" [41]. Figure 4 illustrates the proposed involvement of ADMA in salt-induced disturbances in NO activity mediating vasodysfunction in salt-sensitive subjects.

Consistent with the role for ADMA in salt sensitivity proposed by Fujiwara et al. [41], Schmidlin et al. [63] found that in salt-sensitive African Americans, increases in plasma levels of ADMA occur within 24 h of initiating increased salt intake. In normal, salt-resistant African-American control subjects, the same salt loading does not increase ADMA levels [63]. In salt-sensitive subjects, the early salt-induced increases in ADMA levels precede the initiation of salt-induced increases in blood pressure and are not simply a consequence of salt-induced hypertension [63].

Although many mechanisms may mediate the disturbances in renal vascular resistance involved in the pathogenesis of salt sensitivity, the role of abnormal ADMA activity is of particular interest because it is one of the few mechanisms that might explain why the trait of salt-sensitivity does *not* always "follow the kidney" in transplantation studies [105]. As we have discussed elsewhere [42], it is conceivable that non-renal production of ADMA, or renal production of ADMA, or both could bring about salt-sensitivity. Specifically, intrarenal disturbances in NO activity in salt-sensitive animals caused by salt-induced increases in circulating ADMA from extra-renal sources could explain why transplanting a kidney from a Dahl salt-resistant rat into a bilaterally nephrectomized salt-sensitive recipient fails to correct salt-sensitivity in the recipient [105]. In addition, intrarenal disturbances in NO activity caused by salt-induced increases in renal production of ADMA and decreases in renal clearance of ADMA could account for the observation that transplantation of a kidney from a Dahl salt-sensitive donor into a bilaterally nephrectomized salt-resistant recipient induces salt-sensitivity in the recipient [105].

Additional mechanisms of salt-induced disturbances in NO activity mediating renal vasodysfunction and salt sensitivity

Many factors in addition to ADMA may be involved in mediating salt-induced disturbances in oxidative stress and NO activity that promote renal vasodysfunction and salt sensitivity [30, 43, 45, 106, 107]. For example, Kobori et al. [108, 109] reported that in Dahl S rats, increased salt intake causes a paradoxical increase in intrarenal levels of angiotensinogen and fails to normally suppress angiotensin II in the kidney. With salt loading, greater levels of angiotensin II in renal tissue in salt-sensitive rats versus salt-resistant rats could generate greater NADPH oxidase activity and abnormally high levels of renal oxidative stress that can interfere with NO bioactivity [44]. The observations of

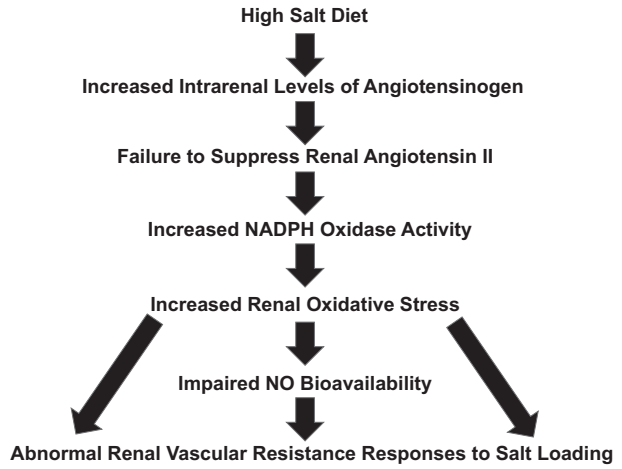

Fig. 5 Impaired NO bioavailability mediated by increased intrarenal activity of the renin angiotensin system in response to salt loading

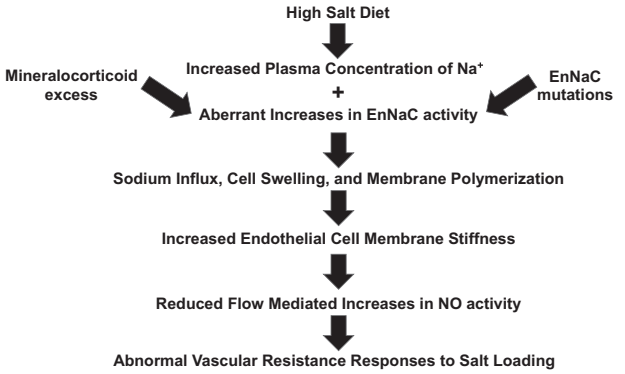

Fig. 6 Impaired flow-mediated increases in NO activity mediated by increases in EnNaC activity and endothelial cell stiffness in response to salt loading

Kobori et al. in Dahl rats [108] are consistent with the clinical studies of Konishi et al. [110] and others [74, 111, 112], which suggest that abnormal responses of the intrarenal RAS to salt loading may mediate salt-induced disturbances in oxidative stress, renal vascular resistance, and salt sensitivity in humans. Because the balance between NO activity and angiotensin II activity is a key determinant of vascular tone [101, 113, 114], interactions between the NO system and the RAS should be considered when assessing the mechanisms underlying renal vasodysfunction and salt sensitivity. Figure 5 illustrates a role for the intrarenal RAS in mediating impaired NO bioavailability, abnormal renal vascular resistance, and increased blood pressure in response to salt loading.

Based on the work of Oberleithner and others [36, 39, 115–118], it has been proposed that impairment of NO-mediated vasodilation in response to a high-salt diet may also be caused by increases in endothelial cell stiffness mediated by salt-induced increases in plasma sodium concentrations, together with aberrant increases in the activity of epithelial-like sodium channels in endothelial cells (termed "EnNaCs") [118]. Increases in EnNaC activity promote increased endothelial cell membrane stiffness by promoting sodium influx, cell swelling, and membrane actin polymerization [36, 116–118]. By reducing membrane deformability, increased endothelial cell stiffness may interfere with flow-mediated activation of mechanoreceptors and signaling pathways that promote increases in NO activity and vasodilation in response to increases in salt intake [36, 117, 118]. Figure 6 illustrates a role for increases in EnNaC activity and endothelial stiffness in mediating impaired NO bioavailability and abnormal vascular resistance in response to salt loading. Because increases in EnNaC activity may be caused by mineralocorticoid excess, or by certain genetic mutations, this mechanism of salt-induced vasodysfunction may be of particular importance in patients with hyperaldosteronism, the syndrome of apparent mineralocorticoid excess, Liddle syndrome, or some forms of congenital adrenal hyperplasia [47, 116, 118].

Implications of the vasodysfunction theory of salt sensitivity for prevention and treatment of salt-induced hypertension

As we have emphasized, initiation of salt-induced hypertension usually involves the combination of (1) abnormal vascular resistance responses to acute salt loading that cause renal vascular resistance to become greater in salt-sensitive subjects than in salt-resistant normal controls and (2) normal increases in sodium retention in response to acute salt loading that do not cause greater increases in sodium balance and cardiac output in salt-sensitive subjects than in salt-resistant normal controls. Thus, in salt-sensitive subjects, prevention of either the abnormal vascular resistance responses to salt loading, or the normal increases in sodium balance and cardiac output in response to salt loading, can help prevent the initiation of salt-induced hypertension.

While restriction of dietary intake of salt is routinely recommended for prevention or treatment of salt-induced hypertension, many individuals may not wish, or be able, to reduce their intake of salt to the levels recommended by medical authorities in Japan (<6 g NaCl per day) [7] or to even lower dietary targets recommended in other countries such as the United States and Germany (<3.8 g NaCl per day) [119, 120]. Thus, additional strategies are needed for prevention and management of salt sensitivity and salt-induced hypertension.

Ideally, interventions to prevent or treat salt-induced hypertension should be primarily directed at the abnormal

physiologic mechanisms that usually mediate salt sensitivity, i.e., the abnormal vascular resistance responses to salt loading, including those involving the renal vasculature. In patients in whom the salt sensitivity is due to functional disturbances in vascular resistance mediated by low NO activity, excess activity of the RAS, or excess activity of other vasoconstrictors, use of angiotensin receptor blockers (ARBs), calcium channel blockers, or both may be sufficient to treat salt sensitivity. For example, in cases of salt sensitivity mediated by subnormal NO responses to increases in salt intake, interventions aimed at improving NO bioavailability in the renal vasculature would represent a targeted approach to prevention and treatment of salt-induced hypertension. However, in salt-sensitive subjects with noncompliant blood vessels (e.g. advanced arteriolar nephrosclerosis) in whom subnormal vasodilatory responses to salt loading may be mediated by structural changes in the vasculature, treatments aimed at promoting vasodilation may have limited effectiveness in reducing vascular resistance and attenuating salt-induced hypertension. Accordingly, in those subjects, salt restriction and or diuretic therapy will be required in the management of salt sensitivity.

Pharmacologic approaches to preventing salt sensitivity mediated by subnormal NO responses to a high-salt diet

In subjects with salt sensitivity mediated by subnormal NO responses to a high-salt diet, pharmacologic correction of mechanistic abnormalities that cause oxidative stress and impair NO bioactivity may attenuate salt sensitivity and reduce the risk for salt-induced hypertension. Consistent with this view, Imanishi et al. [111] proposed that in some patient subgroups, treatment with ARBs to attenuate salt-induced increases in renal oxidative stress and support NO activity may protect against salt sensitivity. Specifically, the investigators found that in diabetic patients with microalbuminuria, salt sensitivity is associated with reduced urinary excretion of NO metabolites (nitrate and nitrite, NOx) in response to salt loading [111]. Treatment with an ARB reduced renal excretion of a marker of oxidative stress (8-hydroxy-2′-deoxyguanosine), increased NOx excretion, and reduced salt sensitivity (defined by the blood pressure effects of switching NaCl intake from 60 mmol/day for one week to 180 mmol/day for one week) [111]. As noted by Imanishi et al. [111], these observations suggest that the protective effect of ARB treatment on salt sensitivity may be mediated through antioxidative mechanisms that restore NO bioavailability in the kidney.

In studies in which blood pressure has been directly measured through arterial catheters in unanesthetized animals, blockade of the RAS has also been found to significantly attenuate salt-induced hypertension in classic animal models of salt sensitivity including in Dahl S rats [121–123] and in rodents with reduced renal mass [67]. Recently, Hatanaka et al. [124], from Osaka University Graduate School of Medicine, speculated that in partially nephrectomized mice, the ARB azilsartan attenuates salt sensitivity by inhibiting proximal tubule reabsorption of sodium. However, in those studies, no measurements were reported of the effects of azilsartan on the changes in sodium balance induced by salt loading. Furthermore, Kanagy and Fink [67] found that in partially nephrectomized rats, the ARB losartan prevents salt-induced hypertension without attenuating salt-induced increases in sodium balance. The present discussion focuses on the possibility that RAS inhibitors attenuate salt sensitivity by inhibiting activity of the intrarenal RAS, reducing renal oxidative stress, and maintaining NO bioavailability. However, it should be noted that effects of RAS inhibitors on the central nervous system and sympathoexcitation may also mediate the capacity of these inhibitors to protect against abnormal vascular resistance responses to salt loading that initiate salt-induced hypertension [125, 126].

As previously discussed, some cases of salt sensitivity involve impaired NO activity caused by increases in endothelial cell stiffness mediated by mineralocorticoid excess, or by other factors that stimulate activity of EnNaCs [39, 118]. In those cases, pharmacologic treatment would rationally include agents that attenuate EnNaC activity (e.g., mineralocorticoid receptor (MR) blockers or epithelial sodium channel blockers) [127, 128]. Such agents might be expected to protect against salt-induced increases in blood pressure not only by ameliorating abnormal vascular resistance responses to salt loading but also by attenuating salt-induced increases in sodium balance. However, we are unaware of any published studies which have compared the effects of salt loading on sodium balance, cardiac output, and vascular resistance in salt-sensitive subjects treated with MR blockers or epithelial sodium channel blockers to those in placebo-treated salt-sensitive controls. It should also be noted that the capacity of MR blockers or epithelial sodium channel blockers to affect vascular resistance responses to salt loading and attenuate salt sensitivity may be related to effects of these drugs on central nervous system activity [129, 130].

Unfortunately, in clinical practice, we do not have efficient tests for readily identifying patients with salt sensitivity and we do not have effective tests for readily determining the primary abnormalities causing salt sensitivity in most affected individuals. Thus, from a practical point of view, it is currently difficult to target pharmacologic therapy to the primary mechanistic abnormalities mediating salt sensitivity. As we continue to gain a better

understanding of the mechanisms of salt sensitivity, it may become possible to develop better tests for identifying salt-sensitive patients and for guiding the choice of pharmacologic therapy in the future.

Dietary approaches to augmenting NO activity and preventing salt sensitivity

The use of dietary approaches to prevent salt sensitivity by augmenting NO activity was originally tested in animals by Chen and Sanders [29] more than 25 years ago. In studies using Dahl S rats, the investigators found that increased intake of the NO precursor L-arginine could prevent salt-induced hypertension [29]. However, patients with endothelial dysfunction have a reduced ability to convert L-arginine to NO [131]. As an example, Higashi et al. [70], at the Hiroshima University School of Medicine, found that in Japanese in-patients with mild to moderate essential hypertension and salt sensitivity, salt loading may impair the ability of L-arginine to increase endothelial NO synthesis in the renal vasculature and decrease renal vascular resistance. For these and other reasons, we have advocated alternative dietary approaches to preventing salt-induced hypertension based on increased intake of vegetables with a high content of nitrate which can augment generation of NO without the need to increase NO synthase activity [132].

In humans and in animals, NO can be generated by reduction of nitrite derived from dietary or non-dietary sources of nitrate [133]. In addition, supplemental administration of nitrate or nitrite has been reported to reduce blood pressure in humans and animals [133]. Gao et al. [134] have suggested that the renal microvasculature is a primary target for blood pressure regulation by nitrite and nitrate because preglomerular resistance vessels are particularly sensitive to the capacity of nitrite to promote vasodilation and to inhibit vasoconstriction induced by angiotensin II. While angiotensin II is known to promote efferent arteriolar constriction, it can also increase afferent arteriolar tone [110]. According to Gao et al. [134], "nitrate and nitrite dilate renal afferent arterioles and counteract angiotensin II-induced vasoconstriction by generating NO-like bioactivity and reducing NADPH oxidase activity".

The high concentration of nitrate in leafy green vegetables is considered to be an important determinant of the antihypertensive effect of traditional Japanese diets [135] and of the Dietary Approaches to Stop Hypertension (DASH) diet [136–140]. In normal subjects fed a diet containing traditional Japanese vegetables with a high nitrate content, Sobko et al. [135] from the Kyorin University School of Medicine in Tokyo found that plasma levels of nitrate and nitrite were higher, and blood pressure was lower than in subjects fed a control diet lacking those vegetables. Blood pressure of Japanese vegetarians is also lower than that of non-vegetarians [141]. Furthermore, Japanese longevity is among the highest in the world [142, 143], which might be explained, in part, by high consumption of a diet rich in green leafy vegetables associated with reduced risk of cardiovascular diseases [135, 144].

In unilaterally nephrectomized rats, supplemental dietary nitrate has been reported to attenuate salt-induced hypertension [145], and in normotensive or hypertensive humans, the DASH diet has also been found to attenuate salt-induced increases in blood pressure [146]. Vegetable-rich diets such as the DASH diet and the DASH-Japan Ube Modified diet Program (DASH-JUMP) not only can contain large amounts of nitrate, they can also contain substantial amounts of potassium, both of which could contribute to protection from salt-induced increases in blood pressure [146, 147]. In fact, potassium is a nutrient recognized by the Japanese government in the evaluation of foods with functional claims for maintaining healthy blood pressure. Although potassium may reduce blood pressure partly by increasing urinary excretion of sodium, the antihypertensive effects of potassium also appear to involve effects on the NO system [103, 148]. For example, studies in normotensive salt-sensitive humans by Fang et al. [103] indicate that the capacity of supplemental potassium to protect against salt-induced increases in blood pressure is related, at least in part, to its capacity to prevent salt-induced increases in plasma levels of ADMA and decreases in plasma levels of nitrate and nitrite. The beneficial effects of nitrate and potassium on NO activity and blood pressure provide scientific support for efforts by Japanese and other governmental agencies to encourage greater consumption of vegetables in the general population.

Summary

According to the vasodysfunction theory of salt sensitivity, the initiation of salt-induced hypertension usually involves abnormal renal vascular resistance responses to increases in salt intake, not greater renal retention of a salt load in salt-sensitive subjects than in salt-resistant normal controls. The scientific foundation of this theory is based heavily on pioneering studies from Japan that have provided critical insights into the mechanisms that normally mediate resistance to the pressor effects of a high-salt diet, and the abnormalities commonly involved in the pathogenesis of salt-induced hypertension. In addition to shifting the focus away from historical theories of salt sensitivity, research from Japan has pointed to new dietary strategies for reducing the risk for salt-induced hypertension that are based on enhancing NO activity and that do not depend on reducing salt consumption in the population.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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