Heterogeneous responses to changes in dietary salt intake: the salt-sensitivity paradigm\(^1,2\)

Friedrich C Luft and Myron H Weinberger

**ABSTRACT** Blood pressure responses to increases and decreases in dietary salt intake are heterogeneous. In some hypertensive individuals, decreases in blood pressure with salt restriction are clinically significant and approach that achieved with medication. In others, little or no change in blood pressure occurs, whereas in still others, blood pressure may actually increase with salt restriction. The heterogeneous responses are partly acquired and involve the influences of age, the intake of other electrolytes, and the influence of certain medications. Genetic predisposition may also play a substantial role because salt sensitivity is increased in black individuals and in persons with non-insulin-dependent diabetes mellitus. Some uncommon but readily diagnosed salt-sensitive genetic syndromes, such as glucocorticoid-remediable aldosteronism and Liddle syndrome, have been identified. Short-term volume expansion and contraction and longer-term dietary interventions appear to be reproducible and may be used to identify salt-sensitive and salt-resistant individuals; however, these maneuvers are cumbersome and cannot be used on a large scale. Molecular genetic techniques for identifying individuals with salt-sensitive and salt-resistant essential hypertension are not yet available, but if the putative gene polymorphisms are identified, such techniques may replace the current trial-and-error methods. *Am J Clin Nutr* 1997;65(suppl):612S–7S.

**KEY WORDS** Sodium, salt, salt sensitivity, hypertension, nutrition, diet

**INTRODUCTION**

Epidemiologic studies have suggested a link between dietary salt intake and blood pressure, increases in blood pressure with increasing age, and the prevalence and complications of hypertension. However, interventional studies have often failed to show a convincing effect of reduced salt intake on alterations in blood pressure. Because of these discrepant observations, the salt–blood pressure hypothesis has been vigorously debated and remains controversial. Proponents of the hypothesis have noted that many studies were relatively short, did not use large differences in the amount of salt ingested, and were conducted in borderline-hypertensive or normotensive individuals with possible diminished susceptibility to pressor effects or who lacked a genetically predisposed sensitivity to the effects of salt.

A paradigm that may reconcile the salt–blood pressure hypothesis with the data available is the proposal that humans vary in their responses to alterations in salt intake with respect to extracellular fluid balance and blood pressure (1–3). Termined salt sensitivity, this notion implies that some individuals respond to a high salt intake with an increase in blood pressure and that others (salt-resistant individuals) do not. Were that the case, no simple relation between dietary salt intake and blood pressure would exist within a population composed of individuals exhibiting these varied responses. Salt sensitivity and resistance to blood pressure increases could also explain the normal distribution of blood pressure values observed in response to a reduced-salt diet, although random variability provides an alternative explanation.

**DOES SALT SENSITIVITY EXIST?**

Watt (4) and Grobbee (5) criticized the notion of salt sensitivity on methodologic grounds. Watt (4) drew attention to three fatal flaws frequently made by investigators in this area, the most common of which is the flaw of the normal distribution (Figure 1). The post hoc selection of an arbitrary definition of salt sensitivity results in the pitfall of confusing the random variation of blood pressure measurements with salt sensitivity of blood pressure. Blood pressure tends to decrease with time and with repeated measurements in many subjects, a phenomenon termed regression to the mean. The “white coat” phenomenon (blood pressure elevation evoked by the stress of having to deal with a physician) generally does not dissipate with time. The error is in the absence of a concurrent, placebo-treated control group. Interestingly, the initial study of salt sensitivity suffered from this flaw (6). However, other studies have used multiple measurements to minimize the effect of this factor (7).

A second theoretical flaw is engendered by the assumption that although a desirable decrease in blood pressure with salt restriction occurs in salt-sensitive patients, there cannot be a deleterious blood pressure increase in salt-resistant patients (the “might help, can’t hurt” argument). Because a rise in blood pressure may occur in some patients and could thus have risk potential, the phenomenon of salt-resistance requires further study.

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1 From the Franz Volhard Clinic, Rudolf Virchow University Hospital, Free University of Berlin, and the Hypertension Research Center, Department of Medicine, Indiana University School of Medicine, Indianapolis.

2 Address reprint requests to FC Luft, Franz Volhard Clinic, Wilberg Strasse 50, 13122 Berlin, Germany. E-mail: fluft@mdc-berlin.de.
A third faulty assumption is engendered by the trial-and-error method of determining the salt sensitivity of blood pressure in medical practice. Patients commonly have their blood pressure measured by their physician and are then instructed about a low-salt diet. The advent of a clinically significant decrease in blood pressure in such patients cannot necessarily be equated with a diagnosis of salt sensitivity because blood pressure tends to fall with repeated observation. Thus, salt sensitivity of blood pressure is convincing only when the protocol used has been shown to provide reproducible information or when randomized, placebo-controlled study designs are used.

IS THE SALT-SENSITIVITY PHENOMENON REPRODUCIBLE?

Four protocols have been reported that were used in salt-sensitive and salt-resistant subjects more than once. These diverse protocols, involving acute salt loading and salt and volume depletion, dietary interventions, or a combination of both, support the notion that salt sensitivity of blood pressure is a real phenomenon on the basis of observed reproducibility.

Weinberger et al (8) used a short-term protocol involving intravenous saline loading to achieve volume expansion followed by provision of a low-salt diet and furosemide to achieve volume contraction. They performed this protocol on > 700 normotensive and hypertensive subjects. This protocol was conducted twice within 12 mo in additional subjects and blood pressure responses correlated significantly with salt and volume changes (9). In a subsequent study these investigators also showed that the blood pressure response to the volume expansion-contraction protocol was significantly correlated with the changes in blood pressure observed in response to a low-sodium diet (Figure 2) (10). This is the only published study to have compared two different techniques for the assessment of salt responses of blood pressure in the same persons.

Sharma et al (11) studied normotensive medical students with a randomized, placebo-controlled dietary protocol. This protocol had the advantage of avoiding order effects and was repeated in a relatively small number of subjects 1 y later.

There was a significant correlation between the response of blood pressure and changes in dietary salt intake in both studies.

Williams et al (12) studied hypertensive patients in whom aldosterone secretion rate did not increase appropriately in response to angiotensin II or to a low-salt diet and a diuretic. Renal blood flow in these patients (nonmodulators) also does not increase appropriately in response to a high-salt diet. In a previous study Hollenberg et al (13) found that nonmodulators were salt-sensitive. They studied some of these subjects twice and were able to show a significant concordance in the renal and adrenal responses (12). These investigators did not report blood pressure responses to manipulation of salt and volume balance in these subjects, however.

Ruppert et al (14) studied normotensive men and women receiving 20 or 300 mmol NaCl/d for 1 wk in random order. A change in blood pressure of 5 mm Hg was used to define salt sensitivity or resistance. Resistance, indicated by a 5-mm Hg decrease in blood pressure with high salt intake, is termed counterregulation. This protocol was performed twice in a limited number of subjects and a significant degree of reproducibility was described (15).

These four divergent protocols, with differing definitions of salt sensitivity, suggest that salt sensitivity of blood pressure is a reproducible phenomenon and that a statistical accord exists between short-term volume loading and depletion and a longer dietary intervention. Nevertheless, the definition of salt sensitivity remains arbitrary and a clinically useful definition, as well as a clinically practical means to identify it, have not as yet been found.

DEMографIC CHARACTERISTICS ASSOCIATED WITH SALT SENSITIVITY

Race and age

We and others have observed that salt sensitivity is more frequently observed in hypertensive than normotensive subjects, in black than in white subjects, and in older than in younger subjects (16, 17). In fact, we recently observed that even among normotensive subjects, the prior finding of salt
sensitivity predicts a significantly greater increase in blood pressure over a ≥ 10-yr follow-up period than does salt resistance (9). This finding has obvious implications for our understanding of the age-related increase in blood pressure and perhaps for the primary prevention of this disorder.

Family history of hypertension and sex may be related to salt responsiveness of blood pressure. When the blood pressure responses of 174 Japanese hypertensive patients were examined after the patients received 15 g salt/d for 1 wk and < 3 g/d for 1 wk, a relation between family history of hypertension and change in blood pressure during the low-salt diet was observed in women but not in men (18). However, because < 25% of this hypertensive population had a negative family history of hypertension (the absence of known hypertension in both parents and siblings), the significance of this observation is unclear.

Renal function

We observed that the age-related increase in salt sensitivity in our study subjects (9) was paralleled by a similar age-related decrease in creatinine clearance in both normotensive and hypertensive subjects (19). This was also associated with an age-related increase in the natriuretic response during the intravenous saline load (19). In a study of 13 hypertensive subjects, a correlation was observed between salt sensitivity and urinary sodium excretion at baseline but not after manipulation of dietary sodium intake (20). In response to dietary salt restriction, we found that salt-sensitive subjects had a significantly reduced capacity to achieve sodium balance during a low-sodium diet after dietary sodium loading (a longer half time of urinary sodium excretion than for those who were salt resistant) (10). Finally, we also found that the accumulation half-life for sodium increases with increasing salt intake and that this phenomenon is significantly greater in blacks than in whites (21).

Brenner and Anderson (22) suggested that this could have been predicted on the basis of the reduced-nephron hypothesis, which would limit urinary sodium excretion and favor salt retention and salt sensitivity of blood pressure. However, the observation of an exaggerated natriuretic response to salt loading seen in salt-sensitive subjects (8) would not necessarily be explained by this hypothesis. Alternatively, Kimura et al (23) reexamined the pressure-natriuresis feedback relation of Selkurt and Guyton and suggested that the slope of the relation is determined by the difference between the whole-kidney ultrafiltration coefficient ($K_f$) and the rate of renal tubular sodium reabsorption. They reason that a decrease in the whole-kidney ultrafiltration coefficient, an increase in sodium reabsorption, or both would depress the slope of the pressure-natriuresis relation, thereby making a person more salt sensitive. This novel interpretation explains the salt sensitivity of decreased renal function and chronic glomerulonephritis and also provides a framework in which to examine the salt sensitivity found in obesity, diabetes mellitus, and essential hypertension in black patients. Obviously, numerous acquired or inherited factors could also influence $K_f$ and sodium reabsorption. One interesting example is the recently observed effects of dopamine on sodium transport in different renal tubular segments (24). Finally, microalbuminuria has been associated with salt-sensitive hypertension (25). This observation may imply a particular propensity to endothelial damage in salt-sensitive hypertension, which is manifest within the kidneys, or it could reflect glomerular hyperfiltration.

Sympathetic nervous system

Several earlier studies implied a role for the sympathetic nervous system in the mediation of salt-sensitivity in humans.
(16). New information supports these earlier findings. In a study of nonmodulators, both plasma norepinephrine concentrations and urinary sodium excretion were higher than values observed in salt-resistant modulators (26). In a study of 15 Japanese hypertensive patients subjected to 7 d each of 16–18 and 1–3 g salt/d, salt-sensitive hypertensive patients had less suppression of plasma epinephrine and plasma renin concentrations than did salt-resistant patients (27). In this study of a small number of subjects, the renin suppression in salt-sensitive subjects that others reported (16) was not observed.

Although norepinephrine is recognized to have both vascular and renal effects relevant to salt-sensitive hypertension, dopamine has also been implicated. These two agents appear to have opposing effects on renal sodium excretion: norepinephrine favors sodium retention, presumably via an a-adrenergic receptor-mediated action, and dopamine promotes an increase in urinary sodium excretion, believed to be due to a specific dopaminergic receptor (28). Gill et al (29) observed decreased dopamine excretion in salt-sensitive individuals, which supports a role for dopaminergic mechanisms in salt sensitivity. To explore the role of adrenergic receptors further, Kotanko et al (30) studied cultured skin fibroblasts obtained from 20 normotensive subjects after 1-wk periods of normal (180 mmol/d) and restricted (60 mmol/d) sodium (chloride) intakes. Persons defined as salt sensitive had a reduced number of β2-adrenergic receptors, and the change in blood pressure associated with the high sodium intake was correlated with the density of β2-adrenergic receptors. Feldman (31) evaluated β-adrenergic receptor activity by measuring maximal isoproterenol-mediated vasodilation in 10 older normotensive subjects during sodium intakes of 400 and 10 mol/d. In comparison with younger subjects, older individuals had reduced vasodilator responses on the high-sodium diet that were increased with the low-sodium diet. Thus, it appears that dietary salt restriction corrects the β-adrenergic receptor defect seen with aging in both vasculature and lymphocytes (31). This observation further strengthens the link between the sympathetic nervous system and salt responsiveness of blood pressure.

Insulin and lipoproteins

Falkner et al (32) studied a group of young, adult black subjects after 2 wk of high salt intake (> 10 g/d) and found no correlation between fasting insulin concentrations and blood pressure or salt responsiveness. However, they did observe a relation between the insulin response to oral glucose loading at 1 h and salt sensitivity of blood pressure as well as the change in mean arterial pressure with time over a 5-y follow-up. Lind et al (33) studied 10 hypertensive subjects after 1 wk of 20 g salt/d and after 1 wk of < 3 g salt/d. Salt sensitivity was significantly correlated with high-density lipoprotein concentrations as well as insulin sensitivity and fasting insulin concentrations. Thus, in this study, low high-density lipoprotein concentrations and insulin resistance were associated with decreased salt sensitivity of blood pressure. A putative mechanism may be an increased activity in pressor systems affecting glucose and lipid metabolism. In collaboration with Goodfriend et al (34), we also observed a decrease in plasma insulin concentrations and an increase in plasma fatty acid concentration with salt loading induced either by increased dietary sodium intake or by intravenous saline administration. Finally, Sharma et al found impaired glucose tolerance (35) and insulin resistance (36) in salt-sensitive compared with salt-resistant normotensive subjects. Rocchini et al (37) noted that salt sensitivity is associated with obesity and is reversible if weight is lost. Tuck (38) reviewed the evidence that in terms of blood pressure, obese patients and those with non-insulin-dependent diabetes mellitus are salt sensitive rather than salt resistant.

Interaction among sodium, calcium, and potassium

Using a protocol of 1 wk each of high- and low-sodium intake as described previously (33), Lind et al (39) found a correlation between salt-sensitive blood pressure responses and both ionized and total serum calcium concentrations. They also observed a 95% increase in urinary calcium excretion and a decrease in total serum calcium concentration with the high-salt diet. In a group of 14 hypertensive subjects studied for 9 d while consuming 20 mmol Na/d and then for 14 d while consuming 200 mmol Na/d, Alexiewicz et al (40) found that 7 salt-sensitive subjects had increased leukocyte calcium contents during the high-salt period that were not seen in those who did not have a rise in blood pressure during the high-salt period. In another study we found increased urinary calcium excretion in salt-sensitive compared with salt-resistant subjects (41). We also identified a decrease in blood pressure with calcium supplementation in salt-sensitive and in black subjects (41).

Potassium intake also has an impressive influence on blood pressure response to dietary sodium intake. Krishna et al (42, 43) studied subjects consuming high and low amounts of potassium. Low potassium intake was associated with greater sodium retention, increased salt intake, and a concomitant blood pressure increase. With high potassium intake, a state of relative salt resistance was achieved. These effects could well be clinically important.

Interaction with indomethacin

Ferri et al (44) studied 25 essential hypertensive subjects who were randomly assigned to receive placebo or indomethacin while consuming a high-sodium (220 mmol/d) or a low-sodium diet (20 mmol/d) for 10 d each. Blood pressure did not change in salt-resistant subjects when taking indomethacin, but did in salt-sensitive subjects. The investigators thus suggested that the increase in blood pressure seen with some nonsteroidal anti-inflammatory agents may be confined to salt-sensitive individuals.

Genetics of salt sensitivity

We found that the haptoglobin phenotype Hp 1 was associated with salt sensitivity whereas the Hp 2 phenotype was associated with salt resistance (45). We have no reason to believe that haptoglobin is involved in the pathogenesis of hypertension; however, a gene close to this locus could conceivably be involved. Rare, autosomal dominant syndromes have been identified that feature salt-sensitive hypertension. An example is glucocorticoid-remediable aldosteronism, which involves a chimeric gene in which the promoter consists of the 11β-hydroxylase gene and the structural portion consists of the aldosterone synthase gene (46). As a result, adrenocorticotrophic hormone stimulates the release of aldosterone in this disease, which can be suppressed by the exogenous adminis-
tation of glucocorticoid. The condition can now be diagnosed readily and specifically by means of the polymerase chain reaction. Another autosomal dominant form of salt-sensitive hypertension is Liddle syndrome (47). In this disease, sodium is avidly reabsorbed in the distal tubule by hyperactivity of the ‘‘fast’’ sodium channel. The molecular basis of this disease is being elucidated.

Work is in progress on essential salt-sensitive and -resistant hypertension (12). Candidate genes are being studied in association studies (48) and families are being recruited in linkage investigations (49). It is highly likely that the condition will prove to be polygenic, but several genes or a combination of genes that are associated with salt sensitivity may be identified. Thus, a single blood specimen may suffice in the future for identifying individuals who possess the genotypic polymorphisms associated with salt-sensitive hypertension.

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