Racial and Ethnic Modifiers of the Salt–Blood Pressure Response


The relation between sodium and blood pressure is a centuries-old question. A substantial body of epidemiological and experimental data has accumulated that strongly implicates NaCl as having a causal role in the genesis of arterial hypertension. Prospective studies that have performed in diverse populations that have manipulated NaCl exposure by diet or infusion have repeatedly documented an NaCl pressor effect. Further, similar studies in biracial populations have also demonstrated a greater prevalence of “salt sensitivity” in blacks compared with whites. The reasons for this observation are not entirely clear; however, intrinsic or hypertension-induced renal abnormalities that limit natriuretic capacity, reduced Na⁺,K⁺-ATPase pump activity, other membrane ion transport disturbances, differential exposure to psychological stressors, greater insulin resistance, and dietary factors (reduced Ca⁺ and K⁺ intake) have all been suggested as possibly playing a role. Salt sensitivity appears to be a widespread phenomenon. However, it is critically important to determine what factors account for racial differences in salt sensitivity. Moreover, the prevalence of salt sensitivity in the general population is unknown. Current definitions of salt sensitivity are varied and unidirectional. In comparison with bidirectional criteria (blood pressure increase with salt loading and blood pressure decrease with salt restriction), they are probably inadequate to identify salt-sensitive individuals who manifest less extreme blood pressure change after dietary sodium or plasma volume manipulations. More sensitive criteria for diagnosing salt sensitivity will facilitate a better understanding of racial and ethnic differences in the prevalence of salt sensitivity. (Hypertension 1991;17[suppl I]:I-115–I-121)

Cross-cultural studies support the concept that habitual NaCl intake is related to differences in mean blood pressure levels, hypertension prevalence, and the increasing slope of the blood pressure curve with advancing age among populations.1-3 When considered in aggregate, different populations demonstrate a reasonably consistent relation among observed mean blood pressure, hypertension prevalence, and habitual sodium intake. In unacculturated societies consuming less than 50 meq/day sodium, hypertension is rare, blood pressures are low, there is little rise in blood pressure with advancing age, and blood pressures vary within a remarkably narrow range.2 On the other hand, in more developed societies in which sodium intake is much greater, hypertension prevalence and mean blood pressure levels are much higher, and both increase with advancing age. However, ecological data alone provide insufficient evidence to establish a cause-effect relation between sodium and blood pressure or to define the longitudinal relations between sodium and blood pressure. This report will focus on mechanisms of salt sensitivity and potential modifying factors that affect the sodium–blood pressure relation. These factors also may help explain the apparent greater prevalence of salt sensitivity in blacks compared with whites.

In the United States, salt sensitivity has been studied in both black and white populations.4-10 It has been observed that a larger proportion of both normotensive and hypertensive blacks are salt sensitive compared with similar whites for reasons that are unclear.5,6,8,10 Thus, salt sensitivity is not a unique finding in blacks, although it does appear to be more prevalent compared with whites. Further, salt sensitivity does not seem to be unique to more affluent western cultures.11-14 Although race has been frequently used as a marker for salt sensitivity, skin color is probably an inadequate surrogate measure...
for this condition. Genetic diversity has also been proposed to explain racial and ethnic differences in hypertension prevalence and susceptibility to the pressor effects of sodium.\textsuperscript{15,16} However, specific genetic markers have yet to be established that predict susceptibility to the pressor effects of NaCl.

### Sodium Manipulation Studies

Luft et al\textsuperscript{6} demonstrated a greater rise in both systolic and diastolic blood pressure in normotensive blacks compared with whites across a wide range of escalating dietary sodium intakes (10–1,500 meq/day). There was no difference in creatinine clearance between the two groups, although other differences in renal physiology may have existed. Another study by Luft et al\textsuperscript{17} also made similar observations in a normotensive biracial population after plasma volume expansion with intravenous NaCl; in this study, blacks experienced both a greater rise in blood pressure and a suppression of plasma renin activity compared with whites. In yet another study, these investigators observed an identical 3 mm Hg rise in mean arterial pressure after plasma volume expansion with intravenous NaCl in 94 pairs of age- and sex-matched normotensive blacks and whites, although black subjects demonstrated an exaggerated natriuresis after administration of furosemide compared with white subjects.\textsuperscript{17}

Falkner et al\textsuperscript{8} observed a greater prevalence of salt sensitivity in young (18–23 years of age) black normotensive subjects (53%) compared with young white normotensive subjects (19%). Salt sensitivity was defined as a change in mean arterial pressure of ≥5 mm Hg or more after oral salt loading. In addition, blacks with a positive family history for hypertension gained more weight after dietary NaCl loading than did blacks with a negative family history.

Takeshita et al\textsuperscript{12} found salt sensitivity in 38% (8/21) of hypertensive Japanese subjects. Salt sensitivity was defined as a rise in mean arterial pressure of greater than 10% after switching from a 70 meq/day sodium diet to a 345 meq/day sodium diet. This study suggested that dietary salt loading was associated with reduced venous distensibility in salt-sensitive subjects that did not appear to be mediated by changes in sympathetic nervous system tone. It was hypothesized that this reduced venous distensibility may have been related to venous structural changes induced by dietary NaCl loading. In another study of Japanese hypertensive patients (n=53), Shingu et al\textsuperscript{14} observed positive independent associations between the percent rise in mean arterial pressure after dietary sodium loading with age and the severity of hypertensive retinopathy; negative independent associations were observed for plasma renin activity and the percent change in mean arterial pressure with furosemide.

An increase in salt sensitivity with advancing age and a greater prevalence of salt sensitivity at lower renin levels appear to be common features to all three of the abovementioned racial groups.

### Is Salt Sensitivity a Stable Classification?

The definition of salt sensitivity has been arbitrary and varied. These definitions are usually based on an observed change in systolic, diastolic, or mean arterial blood pressure in the appropriate direction after manipulating sodium by diet or infusion. For example, if the subject has received supplemental dietary sodium, then a diagnosis of salt sensitivity would be made only when there was a rise in blood pressure equal to or greater than a predetermined amount. Random variation of the blood pressure is expected under normal conditions and may occur in the "appropriate" direction after manipulation of salt exposure by diet or infusion, even if the maneuvers had no effect on the blood pressure. If it is assumed that dietary sodium or plasma volume manipulation has an effect on blood pressure, the observed distribution of changes in blood pressure will likely manifest a normal or skewed but quasinormal distribution. This distribution of blood pressure responses is similar to

<table>
<thead>
<tr>
<th>Change in DBP</th>
<th>Directional criteria</th>
<th>Pr(SR)</th>
<th>Pr(A)</th>
<th>Pr(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mm Hg)</td>
<td>Increase only (A)</td>
<td>Decr. only (B)</td>
<td>Either (C)</td>
<td>Both (D)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>0.21</td>
<td>0.35</td>
<td>0.49</td>
<td>0.07</td>
</tr>
<tr>
<td>&gt;3</td>
<td>0.19</td>
<td>0.27</td>
<td>0.41</td>
<td>0.05</td>
</tr>
<tr>
<td>&gt;6</td>
<td>0.13</td>
<td>0.19</td>
<td>0.30</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;8</td>
<td>0.08</td>
<td>0.17</td>
<td>0.24</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Pr(SR), probability of diagnosing salt resistance in same individual after identical repeat dietary sodium manipulations; DBP, diastolic blood pressure; Increase only, rise in DBP during dietary sodium loading; Decrease only, fall in DBP during dietary sodium restriction; Either, directionally appropriate DBP change after adding or restricting dietary sodium; Both, directionally appropriate rise and fall in DBP after respectively adding and restricting dietary sodium.

Assumptions underlying these probabilities are that 1) all DBP responses after dietary sodium manipulations are independent, 2) the observed downward trend in DBP during the latter 4 weeks of the dietary run-in phase is largely regression to the mean and was random, and 3) the random variability of DBP was stable over time. Probabilities (Pr) were calculated as follows: Pr(C)=Pr(A)+Pr(B); Pr(D)=Pr(A)xPr(B). The probability of diagnosing salt sensitivity during the second or repeat dietary sodium manipulation is [1−Pr(SR)]. Pr(Ai) on an identical subsequent experiment=Pr(A)x[1−Pr(A)]; Pr(Bi) on an identical subsequent experiment=Pr(B)x[1−Pr(B)].
the expected spectrum of change associated with chance biological variation of blood pressure. Thus, when attempting to dichotomize salt-sensitive and salt-insensitive individuals by using a solitary blood pressure response to dietary manipulation of NaCl or plasma volume expansion, the most likely observed difference will be a shift in the distribution of the blood pressure responses for salt-sensitive subjects. It is clear, however, that there will be considerable overlap in the observed distribution of blood pressure responses between salt-sensitive and salt-resistant groups on a single experiment. Therefore, it is not possible to achieve maximal separation of these groups by using only a single arbitrary unidirectional blood pressure change. Tables 1 and 2 demonstrate that unidirectional criteria for salt sensitivity should be fairly robust; however, these criteria are probably insensitive since they use extreme blood pressure change to diagnose salt sensitivity. Thus, these definitions have probably underestimated the true prevalence of salt sensitivity in various populations.

It seems more logical to use appropriate bidirectional or even unidirectional blood pressure change during two independent experimental periods as criteria for salt sensitivity. Truly salt sensitive individuals should respond equally well and in the appropriate directions to both salt restriction or supplementation. Support for this recommendation comes from a study that we recently reported.18 The Study of Sodium and Blood Pressure (SNaP) (Figure 1) was a randomized, two-period, placebo-controlled crossover study that examined the effects of adding dietary NaCl on blood pressure in 48 men and women (47 whites, 1 black) with high normal diastolic blood pressure (80–89 mm Hg). From this data, we estimated the chance probabilities of diagnosing salt sensitivity by using diastolic and mean arterial blood pressure changes (Tables 1 and 2). When less extreme blood pressure change is used in bidirectional definitions of salt sensitivity, the estimates are probably more sensitive and have greater negative predictive value compared with unidirectional diagnostic criteria that use more extreme blood pressure change. Eight of 48 subjects were classified as salt sensitive when a bidirectional change of 2 mm Hg or more in diastolic blood pressure was used during the two study periods when dietary sodium was either added or restricted. During the treatment period when supplemental NaCl was given, the observed change in systolic and diastolic blood pressure was 6.7±4.6 and 6.5±4.4 mm Hg, respectively, in salt-sensitive individuals. On the other hand, systolic and diastolic blood pressure change was 1.5±6.7 and −0.7±4.3 mm Hg, respectively, in salt-resistant individuals. Salt-sensitive individuals experienced a slightly greater fall in overnight (8-hour) urinary sodium output than did salt-resistant subjects (19.5 versus 16.5 meq/8 hr).

Regardless of the diagnostic criteria used to identify salt sensitivity, these data emphasize the relative insensitivity of using definitions of salt sensitivity that require only a unidirectional change in blood pressure. At least a portion of the excessive prevalence of salt sensitivity in blacks compared with whites could be artifactual. Greater spontaneous blood pressure variability (random variation) was observed in blacks

**TABLE 2. Probabilities of Diagnosing Salt Sensitivity and Salt Resistance in the Study of Sodium and Blood Pressure (SNaP) Participants**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Probability of chance diagnosis of salt sensitivity</th>
<th>Probability of diagnosing salt resistance on second experiment</th>
<th>Probability of diagnosing salt sensitivity on second experiment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rise in MAP≥5%* (n=13)</td>
<td>0.10</td>
<td>0.09</td>
<td>0.91</td>
</tr>
<tr>
<td>Rise in MAP≥5 mm Hg* (n=5)</td>
<td>0.13</td>
<td>0.11</td>
<td>0.89</td>
</tr>
<tr>
<td>Rise in MAP&gt;10 mm Hgt (n=12)</td>
<td>&lt;0.02</td>
<td>&lt;0.02</td>
<td>0.98</td>
</tr>
<tr>
<td>Fall in MAP≥10 mm Hgt† (n=17)</td>
<td>0.04</td>
<td>0.04</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Common diagnostic criteria was used in the assessment of salt sensitivity. Chance probabilities were calculated based on observed random variation in mean arterial pressure (MAP) (mm Hg) during terminal 4 weeks of the dietary run-in phase.
*After dietary sodium supplementation.
†After dietary sodium restriction.

**FIGURE 1.** Design of the Study of Sodium and Blood Pressure (SNaP). Period A is the 8-week dietary run-in phase, when all SNaP participants received counseling regarding dietary sodium restriction. Eligibility for randomization into the active treatment phase required that overnight urinary sodium excretion was reduced to less than 25 meq/8 hr during period A. During period B, urine eligible subjects were randomly allocated to receive either 100 meq/day sodium given as NaCl or an identical-appearing placebo. Period C was a 2-week placebo washout phase. During period D, participants were given the treatment that they did not receive during period B. The low sodium diet was maintained constant for the duration of the entire study.
compared with whites in the Evans County study. Random error in blood pressure measurement would result in an underestimation of the prevalence of salt sensitivity in blacks and would likewise falsely reduce the black–white differential; however, if blacks systematically manifested a pressor response during blood pressure measurement, then salt-sensitivity estimates for blacks and the black–white differential would be spuriously inflated, particularly during salt-loading experiments. It is not known how racial differences in the prevalence of salt sensitivity will be affected with use of more sensitive bidirectional definitions of salt sensitivity. We do, however, speculate that the prevalence of salt sensitivity will be higher in any racial or ethnic group when bidirectional blood pressure response criteria are used. Therefore, salt sensitivity may ultimately be recognized as a more prevalent metabolic characteristic than is now assumed.

At the present time, the prevalence of salt sensitivity in the general population is unknown. A reanalysis of previous studies in which salt exposure was manipulated during two independent experimental periods using bidirectional criteria similar to ours should provide more accurate prevalence estimates of salt sensitivity. If salt exposure is only manipulated during one experimental period, then extreme blood pressure response criteria are required to separate random blood pressure fluctuations from true blood pressure change (α error < 0.05).

Mechanisms and Modifiers of the Salt–Blood Pressure Response

It is an intuitively appealing hypothesis that the primary mechanism by which NaCl raises blood pressure is through plasma volume expansion. One study involving intravenous NaCl loading and depletion in a biracial group of normotensive and hypertensive subjects found no relation between blood pressure change and sodium balance; this finding suggests that the pressor response may have been mediated by factors other than sodium retention. Circulating plasma volume may be slightly greater in blacks compared with whites, although other studies have found virtually no racial differences in plasma volume. The lack of racial differences in plasma volume does not exclude the possibility of an abnormal pressure–natriuresis curve in black hypertensive patients, in that the presence of an intrinsic or hypertension-induced renal abnormality may require an inappropriately high blood pressure to achieve a given level of natriuresis. Also, salt sensitivity appears to increase with advancing age in both races in parallel with a falling plasma volume. Therefore, it seems unlikely that the greater salt sensitivity observed in the black population is closely linked to a state of chronic plasma volume expansion.

Another possible explanation for the higher prevalence of salt sensitivity in blacks compared with whites might relate to a higher dietary sodium intake in blacks. However, dietary sodium intake and the preference for salty food is similar between both normotensive and hypertensive blacks and whites. Blacks, however, may consume less dietary calcium and potassium than whites. Both these cations may have natriuretic properties, particularly when dietary sodium intake is high. Supplemental dietary calcium has also been shown to stimulate Na⁺,K⁺-ATPase pump activity and to preferentially lower blood pressure in hypertensive patients with reduced levels of serum ionized calcium, who interestingly enough often have "low" plasma renin activity and more frequently manifest salt sensitivity. Other proposed mechanisms for explaining the greater prevalence of salt sensitivity in blacks compared with whites include failure of adrenergic receptors to downregulate and inadequate renal dopamine generation after salt loading, lower Na⁺,K⁺-ATPase pump activity, and reduced intracellular magnesium. Furthermore, black hypertensive patients also have been found to excrete an NaCl load more slowly than their white counterparts, although this has not been an invariable observation. Some of these factors manifest a component of heritability, although there is ample evidence that environmental exposures and, in some instances, even hypertension may modify the phenotypic expression of these heritable traits.

Several trends involving metabolic parameters have been observed in salt-sensitive compared with salt-resistant hypertensives. These trends include lower plasma renin activity and a decreased responsiveness of the renin-angiotensin system after maneuvers that contract the circulating plasma volume; lower serum ionized calcium and higher serum magnesium levels have been observed to be associated with lower levels of plasma renin activity. On the other hand, there appears to be a substantial overlap between salt-sensitive and salt-resistant subjects in these parameters.

A greater prevalence of hyperinsulinemia and insulin resistance could also explain some of the observed racial differential in the prevalence of salt sensitivity. Hyperinsulinemia increases the renal tubular reabsorption of sodium even though peripheral resistance to insulin-mediated glucose uptake may be present. Hyperinsulinemia also appears to increase the activity of the sympathetic nervous system, which may lead to increased renal renin secretion and enhanced renal tubular reabsorption of sodium.

Data from national probability samples show an excess prevalence of obesity in adult blacks compared with whites. Obese subjects are more likely to manifest insulin resistance and to have higher circulating insulin levels compared with nonobese subjects, although hyperinsulinemia and insulin resistance may occur in nonobese subjects as well.
Manolio et al. reported data on a biracial group of young adults aged 18–30 years in the CARDIA study; they found higher mean fasting insulin levels in black men and women compared with their age- and sex-matched white counterparts. Insulin levels, insulin resistance, and circulating catecholamines all fall in parallel with reversal of salt sensitivity after weight loss. Insulin resistance might also influence blood pressure in an indirect way that involves sodium. Reduced Na⁺,K⁺-ATPase pump activity in the arterial wall as a consequence of insulin resistance, or perhaps as a result of the release of the putative Na⁺,K⁺-ATPase inhibitor during plasma volume expansion, could result in intracellular accumulation of sodium and calcium. Raised intracellular sodium and calcium concentrations can sensitize the arterial wall to circulating pressor substances and thereby lead to increased peripheral vascular reactivity, resistance, and ultimately higher blood pressure.

Human studies have also demonstrated that psychological stress causes an increase in circulating plasma renin activity and reduces renal blood flow. Murphy et al. found higher levels of cardiovascular reactivity in black compared with white third graders. Another study by Light et al. found a direct correlation between the magnitude of the reduction in urinary sodium and water excretion and the rise in heart rate in young men who were subjected to mental stress. In animals, identical renal responses to stress appear to be mediated by the sympathetic nervous system. Acute changes in cardiovascular reactivity in humans are also probably mediated via the sympathetic nervous system. Although exposures to psychological stressors are ubiquitous, the intensity, duration, and frequency of such exposure may be greater in blacks compared with whites. Therefore, a differential burden of psychological stress may help explain the greater prevalence of salt sensitivity in blacks, who as a group appear to have equal exposure to dietary salt compared with whites.

The proposed plasma volume, renal, and metabolic derangements in Figure 2 appear to be likely mechanisms mediating salt sensitivity. This schema is a simplified unifying hypothesis for salt sensitivity. Although unproven, it appears that these mechanisms may be operative, to some degree, in all salt-sensitive subjects. However, it is doubtful that salt sensitivity is mediated by identical mechanisms in all salt-sensitive individuals. Racial and ethnic differences in the presence of salt sensitivity could be mediated, or at least modified, by reduced renal natriuretic capacity, genetic factors, obesity, dietary cation (Ca²⁺ and K⁺) intake, differential exposures to psychological stressors, differences in tissue insulin sensitivity or Na⁺,K⁺-ATPase pump activity, or possibly other, as of yet unidentified, factors. A strong bias toward publication of positive results regarding the association of the aforementioned metabolic markers with salt sensitivity may, however, exist. The relation of these biochemical markers to salt sensitivity should, therefore, be systematically reexamined in previously reported data sets by using bidirectional blood pressure response criteria such as ours.

In summary, salt sensitivity appears to be present in various racial and ethnic groups and is probably mediated by multiple but related pathophysiological mechanisms. The apparent greater prevalence of salt sensitivity in blacks compared with whites remains unexplained, yet it seems to be clear that a substantial proportion of both races exhibit an acute pressor response to NaCl. Numerous factors appear to be capable of modifying the blood pressure response to NaCl. Any observed racial and ethnic differences in this response are likely to be strongly influenced by differential environmental exposures. The search for specific genetic markers of salt sensitivity must continue.

Finally, more sensitive bidirectional criteria that use less extreme blood pressure change should be applied in the diagnosis of salt sensitivity. Theoretically, bidirectional definitions will identify a greater number of truly salt-sensitive individuals and should enhance our understanding of observed racial and ethnic differences. Race-specific criteria for diagnosing salt sensitivity based on study-specific random blood pressure variability should be developed to prevent differential misclassification of salt-sensitivity status. Future research should be directed toward uncovering clinically useful criteria that allow for the prospective identification of salt-sensitive and salt-resistant individuals. It may be useful for these studies to use sampling techniques that allow for more accurate estimation of the population prevalence of salt sensitivity.

References


**KEY WORDS**  • sodium-dependent hypertension  • ethnic differences  • blood pressure  • sodium chloride
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