

# Dietary Salt Intake, Salt Sensitivity, and Cardiovascular Health

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The controversial issue of the relationship between dietary NaCl (referred to as “salt” in this article) intake and health was framed nicely in the superb review by Prof Eberhard Ritz.<sup>1</sup> When salt was not readily available, it was a relatively essential commodity, but in the modern world salt has become plentiful, and it is actually difficult to achieve a low salt intake without exerting a significant amount of effort.<sup>2</sup> One of the effects of higher salt intake is increased blood pressure, which was clearly illustrated in chimpanzees fed with a diet containing 35 versus 120 mmol of sodium per day. In contrast, after providing a diet containing  $\approx$ 248 mmol of sodium per day for 2 years, subsequent reduction in daily dietary salt intake to  $\approx$ 126 mmol reduced blood pressure compared with animals that were continued on the increased salt diet.<sup>3</sup> Other than affecting blood pressure, excess salt in the modern diet is increasingly recognized as an additional health risk, particularly for those individuals who demonstrate salt sensitivity, defined basically as an abnormal increase in blood pressure in response to increased salt intake. Japanese patients initially found to have salt-sensitive hypertension subsequently had a greater incidence of left ventricular hypertrophy and rate of nonfatal and fatal cardiovascular events compared with hypertensive patients who were not salt sensitive.<sup>4</sup> Weinberger et al<sup>5</sup> observed a similar trend in a cohort of patients in the United States, but another striking finding of this study was that salt-sensitive patients who were initially normotensive at the time of study had an impressive increase in mortality rate on follow-up evaluation compared with normotensive salt-resistant patients. These studies provide the impetus to understand the underlying mechanisms of salt sensitivity and to identify and perhaps quantify this cardiovascular risk factor in the population.

## Salt Sensitivity: Genes and the Environment

Salt sensitivity occurs with either hereditary or acquired defects in renal function. Genetic causes of salt sensitivity include single gene mutations that promote salt retention through a defect in renal sodium handling. Patients with these disorders are often identified by the significant family history of hypertension and hypokalemia, although the latter is not a prerequisite for the diagnosis.<sup>6,7</sup> Recent publications in

*Hypertension* are expanding the already extensive list of monogenic forms of hypertension that were reviewed by Lifton et al<sup>6</sup> and directly impact renal sodium excretion to promote salt sensitivity. Polymorphic genetic markers of a number of cytochrome P450 enzymes associate with salt-sensitive hypertension. These genes include *CYP11B2*, which encodes aldosterone synthase<sup>8</sup>; the ATP-binding cassette, subfamily B, member 1 (*ABCB1*), either alone or in concert with variants of cytochrome P450 3A5 (*CYP3A5*)<sup>9</sup>; and *CYP4A11*, which converts arachidonic acid into 20-hydroxy-eicosatetraenoic acid.<sup>10</sup> Another area of investigation involves dopamine, dopamine receptors (particularly type-1 dopamine receptor), and G-protein-coupled receptor kinase 4 (GRK4). Dopamine-mediated activation of type-1 dopamine receptor in the proximal tubule facilitates salt excretion by inhibiting sodium and chloride transport. GRK4 $\gamma$  phosphorylates ligand-bound G protein-coupled receptors, such as type-1 dopamine receptor, permitting binding to  $\beta$ -arrestin and subsequent G protein-coupled receptor internalization and inactivation.<sup>11</sup> Transgenic mice overexpressing an activating GRK4 $\gamma$  mutation (A142V) are hypertensive,<sup>12</sup> and renal interstitial instillation of GRK4 antisense oligodeoxynucleotides promoted natriuresis and lowered blood pressure in spontaneously hypertensive rats.<sup>13</sup> Staessen et al<sup>14</sup> demonstrated an association of renal sodium handling and blood pressure with genetic variation in the type-1 dopamine receptor promoter, but not the *GRK4* variant (A142V), in a family based random sampling of a white Flemish population. However, the phenotypic measurements were obtained without control of dietary salt intake, perhaps confounding the findings of the study.

Genetic association analysis represents a powerful tool for identification of genetic intervals controlling variability of studied phenotypes. However, interpretation is typically hampered by the intrinsic lack of demonstration of a causal link between specific genotypes and the phenotype. Additional confounding occurs with the difficulties of producing a precise, reproducible phenotype. Overcoming challenges associated with accurately phenotyping salt sensitivity in large cohorts is a particularly formidable task but essential to ensuring that valid insights are derived from genetic analyses.

Received November 17, 2008; first decision November 30, 2008; revision accepted December 20, 2008.

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(*Hypertension*. 2009;53:00-00.)

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*Hypertension* is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.108.120303

Because candidate gene polymorphisms that associate with the hypertension trait are typically not confirmed in subsequent studies, genetic association studies should, therefore, be validated in several well-characterized populations. An example of this approach is a recent study by Turner et al,<sup>15</sup> which described a genome-wide analysis of the blood pressure response to thiazide diuretic. The investigators identified a candidate blood pressure-modifying interval on chromosome 12q15 by interrogating 100 000 single nucleotide polymorphisms of 2 populations at the phenotypic extremes. Additional single nucleotide polymorphism analyses in that region detected 3 novel candidate genes that were associated with the diastolic blood pressure response to the thiazide diuretic. The authors then used another population to reinforce this association, supporting the need for additional studies to establish the causal link. This study illustrates challenges of performing genome-wide association analyses and pharmacogenomic studies in general.

Interpretation of genetic studies can also be complicated when a specific phenotype is associated with DNA sequences outside “gene-coding” intervals. An example is a gene-wide association study of the *SCNN1G* gene, which encodes the  $\gamma$ -subunit of the epithelial sodium channel. Three of 21 tested single nucleotide polymorphisms were associated with extreme values of systolic blood pressure, and all 3 mapped into introns 5 and 6. Because a sequence variation was not identified in the intervening exon 6, a difference in the amino acid sequence of the  $\gamma$ -subunit was considered an unlikely explanation of the findings.<sup>16</sup> The corresponding review<sup>17</sup> appropriately delineated the potential limitations of the article, but the possibility that a single gene might exert variable effects on systolic blood pressure through noncoding variations that modify gene expression is an interesting and testable hypothesis.

Finally, monogenic forms of hypertension are rare, and it is generally accepted that human hypertension is usually a polygenic trait for which phenotypic manifestations are further complicated by complex interactions among genes and the environment. Animal models and human genetic association studies have validated this concept. For example, in a Chinese population, heritability of blood pressure (systolic, diastolic, and mean) responses to dietary salt intake was 0.49 to 0.51.<sup>18</sup> These data suggest that, in this population, variation in blood pressure responses to salt intake is influenced almost equally by genetic and environmental factors. Therefore, genetic factors are not the only predisposing influences that determine salt sensitivity.

Rodent studies have provided insights into salt sensitivity, which can develop after a reduction in renal mass or injury that may be subtle. A variety of insults can damage the tubulointerstitium and renal microvasculature and result in salt sensitivity, sometimes without producing other clinical manifestations of renal injury.<sup>19,20</sup> Salazar et al<sup>21</sup> orally administered an angiotensin receptor antagonist to newborn rats, which, in adulthood, manifested angiotensin-dependent hypertension that was exacerbated by an increase in salt intake. Thus, in addition to genetic factors, the combined studies underscore the finding that an acquired decrease in kidney mass and function from an environmental stress

results in an inability to respond appropriately to changes in salt intake.

### Salt Sensitivity: Populations at Risk

Until analyses of genetic and environmental risk factors reach fruition, perhaps other surrogate markers will suffice to identify salt sensitivity in the clinical setting. Salt sensitivity is prevalent in black patients who are normotensive<sup>22</sup> and in those with hypertension<sup>23,24</sup> compared with white patients. Subjects of African descent who excrete sodium less efficiently during the daytime also have an associated increase in systolic blood pressure and blunted nocturnal systolic blood pressure dipping response.<sup>25</sup> Chun et al<sup>26</sup> used intravenous furosemide as a pharmacological probe of function of the thick ascending limb in a careful balance study to observe changes in renal handling of calcium and magnesium suggestive of increased activity of the sodium-potassium-chloride cotransporter (NKCC2) in black, but not white, subjects. The findings suggest that enhanced tubular reabsorption of sodium by the kidney is responsible for the observed ethnic susceptibility to salt sensitivity.

Low birth weight is associated with salt sensitivity. de Boer et al<sup>27</sup> observed in a group of 27 white, normotensive, nonsmoking adults that the responses of blood pressure to changes in salt intake (60 versus 200 mmol NaCl daily) correlated with birth weight; ie, lower birth weight was associated with salt sensitivity. It is interesting that events that occur in the prenatal period can affect the response of blood pressure to dietary salt intake in the adult. The study could not determine whether salt sensitivity was related to an intrinsic defect in renal function or more generally to diminished “renal reserve” from a reduced nephron mass.<sup>28</sup> Both possibilities are supported by data derived from animal models and the observation that patients with chronic kidney disease have salt-sensitive hypertension.

Patients with drug-resistant hypertension represent another group likely to benefit from salt restriction. This population has blood pressure that remains above target levels despite concurrent use of 3 antihypertensive agents of different classes.<sup>29</sup> These patients frequently have hyperaldosteronism<sup>30</sup> that, when combined with high salt intake, manifests target organ injury in the form of proteinuria.<sup>31</sup>

### Dietary Salt and Vascular Structure

A mechanistic link between salt sensitivity and mortality has not yet been identified but presumably is related to alteration in vascular structure and function. Evidence supports a direct effect of salt intake on the endothelium mediated through changes in shear stress, which modulates the production of transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) and NO. TGF- $\beta$ 1 is a locally acting growth factor that plays an integral role in the development of vascular and glomerular fibrosis.<sup>32–36</sup> TGF- $\beta$ 1 promotes the development of hypertension, because mice lacking emilin1, an inhibitor of TGF- $\beta$ 1 activation, demonstrated peripheral vasoconstriction and arterial hypertension, which was prevented by inactivation of 1 *TGFBI* allele.<sup>37</sup> The initial event that stimulates endothelial TGF- $\beta$ 1 production by increased salt intake appears to be the opening of a tetraethylammonium-inhibitable potassium channel,<sup>38,39</sup>

followed by a dose-dependent activation of proline-rich tyrosine kinase-2, a cytoplasmic tyrosine kinase that recruited and activated c-Src. These kinases functioned in concert to activate the mitogen-activated protein kinase pathways that increased the endothelial production of TGF- $\beta$ 1.<sup>40</sup> Activation of proline-rich tyrosine kinase-2, c-Src, and another binding partner, phosphatidylinositol 3-kinase, also promoted protein kinase B (Akt) activation and phosphorylation of the endothelial isoform of NO synthase (NOS3) at S1176, which increased NO production in rats.<sup>41</sup> Proline-rich tyrosine kinase-2, therefore, becomes a key signaling molecule in the vascular response to dietary salt intake, because NO also serves an important compensatory response that mitigates the effects of TGF- $\beta$ 1.<sup>42</sup> The reductive state of the endothelium is likely an important consideration, because conditions that generate oxidative stress and inflammation, such as hypertension,<sup>20,43</sup> would promote the attendant loss of the countervailing influence of NO and exacerbate vascular alterations in structure and function mediated through TGF- $\beta$ 1. Changes in conduit artery compliance and resistance vessels can occur.

A major benefit of limiting salt intake might, therefore, be a decrease in endothelial cell production of TGF- $\beta$ 1, a regulator of arterial stiffness, which is a risk factor associated with cardiovascular events.<sup>44</sup> In a double-blind, placebo-controlled, crossover study, dietary salt intake was manipulated by consumption of either placebo or salt tablets for 4 weeks in 12 untreated patients with stage I systolic hypertension. The low salt intake increased carotid arterial compliance by 27% by week 1, and the improvement stabilized at 46% by week 2. Systolic blood pressure fell by 5 mm Hg by week 1 and 12 mm Hg by week 2, correlating well with changes in carotid artery compliance.<sup>45</sup>

### Salt Sensitivity: Perspectives

Dietary salt intake promotes intrinsic changes in compliance and resistance vessels; the effects are intensified by congenital and acquired sodium retentive states. The simplest and perhaps ideal approach would be to limit salt in the diet of the population as a whole.<sup>46</sup> Absent this generalized approach, the observations support the need to identify individuals with salt sensitivity and the associated underlying risk factors and determine whether lifelong reduction in salt intake improves cardiovascular mortality in this population. Although formal protocols define salt sensitivity, which occurs in  $\approx$ 40% to 50% of all patients with hypertension,<sup>4,5</sup> perhaps the initial focus should be on susceptible populations. Specifically, salt intake should be reduced in patients with defined monogenic forms of hypertension, with congenital and acquired reductions in renal mass and function, with drug-resistant hypertension, and with ethnic susceptibility. Because the pathogenesis of salt-induced cardiovascular morbidity and mortality is complex, salt intake should be reduced in these susceptible populations even in the absence of hypertension, which alone is important but not necessarily a sufficient explanation for the excess cardiovascular morbidity and mortality induced by salt.

### Sources of Funding

P.W.S. is supported by grants from the National Institutes of Health (DK46199), a George M. O'Brien Kidney and Urological Research

Centers Program (P30 DK079337), and the Medical Research Service of the Department of Veterans' Affairs.

### Disclosures

None.

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*Hypertension*. published online January 19, 2009;

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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