Salt Sensitivity
It Is Not Always in the Genes

Paul W. Sanders

Although increases in dietary NaCl (referred to as salt in this article) intake expand extracellular fluid volume and elevate mean arterial pressure (MAP) even in healthy subjects, the magnitude of the response varies with some individuals demonstrating remarkable resistance to the hypertensive effects of salt intake despite ingestion of very high doses.[1] Salt sensitivity therefore refers to the propensity for changes in salt intake to produce meaningful increases in mean arterial pressure (MAP). The endless debate regarding whether the amount of salt ingested affected blood pressure sufficiently to alter life span was effectively curtailed by the Trials of Hypertension Prevention studies, which showed that dietary salt reduction decreased the long-term risk of cardiovascular events by 25% in patients who had prehypertension, confirming an important effect of salt intake on the cardiovascular system.[2] In addition, the landmark work of Weinberger and colleagues provided convincing evidence that normotensive subjects who demonstrated salt sensitivity had a subsequent cumulative mortality that rivaled that of hypertensive patients.[3]

How salt intake alters cardiovascular function remains uncertain but may be related in part to changes in arterial compliance, a known marker of cardiovascular morbidity and mortality. Gates et al[4] demonstrated in a double-blind placebo-controlled crossover experiment that reduction in salt intake in patients with untreated systolic hypertension lowered systolic blood pressure and increased carotid arterial compliance. In that study, the decrease in systolic blood pressure correlated inversely with change in arterial compliance. In rats, an increase in dietary salt intake increased intravascular production of transforming growth factor (TGF)-β1 through shear stress.[5] TGF-β1, a fibrogenic growth factor, may promote decreased conduit artery compliance as well as the development of hypertension.[6]

A genetic predisposition for salt sensitivity and salt-sensitive hypertension was conclusively demonstrated by Dahl, who bred 2 strains of rats that were derived from the Sprague-Dawley line and were either susceptible or resistant to the hypertensive effects of a high salt diet.[7] In recent years, a genetic cause for salt sensitivity has been vigorously pursued, with a particular focus on the kidney, since elegant studies by Guyton and associates showed the integral role of this organ in blood pressure regulation.[8] Indeed, mutations in a large number of genes related to salt transport in the kidney have each been shown to cause monogenic forms of hypertension.[9]

Acquired forms of kidney injury also can produce salt sensitivity in rats. Interesting work from Johnson and associates[10] showed that a variety of insults can damage the tubulo-interstitium and renal microvasculature and result in salt sensitivity, sometimes without producing other clinical manifestations of renal injury. Regardless of the underlying mechanism, the common finding of these studies is the inability of the kidneys to respond appropriately to changes in salt intake.

In the present issue of *Hypertension*, de Boer et al[11] have added to the complexity of salt sensitivity. A group of 27 white, normotensive, nonsmoking adults were examined. All subjects were products of normal pregnancies and gestational periods. The responses of blood pressure to changes in salt intake (60 versus 200 mmol NaCl daily) were determined in standard fashion and compared to birth weights. A striking inverse correlation between change in MAP and birth weight was observed, with lower birth weight associating with salt sensitivity. It is also interesting that those subjects with higher birth weights tended to show no change or even reductions in blood pressure with the increase in salt intake; that is, they demonstrated salt resistance. Additional correlative analyses also identified the expected inverse correlation of birth weight with creatinine clearance, but this parameter did not influence the association with salt sensitivity, perhaps because the small number of subjects in the sample limited the power of the study or because of the reduced accuracy of the Cockroft-Gault method to determine glomerular filtration rate. It is therefore not clear from this study whether salt sensitivity of patients with lower birth weights was related to an intrinsic defect in renal function or more generally to diminished "renal reserve" from a reduced nephron mass.[12] The findings are important because they define a new variable responsible for salt sensitivity and further suggest that genetic or environmental factors that determine birth weight play an important role in the blood pressure response to dietary salt intake in the adult.

Are these data a mandate to restrict dietary salt intake in individuals with lower birth weights? The findings are provocative, but preliminary and more work is required in this area. Because healthy adults were studied, it is not clear whether salt sensitivity was lifelong or developed in adult-

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Division of Nephrology, Department of Medicine, Department of Physiology & Biophysics, and Nephrology Research and Training Center, University of Alabama at Birmingham, and the Department of Veterans Affairs Medical Center, Birmingham.

Correspondence to Paul W. Sanders, MD, Division of Nephrology/Department of Medicine, 642 Lyons-Harrison Research Building, 1530 Third Avenue, South, University of Alabama at Birmingham, Birmingham, AL 35294-0007. E-mail psanders@uab.edu

(*Hypertension*. 2008;51:823-824.)

***Hypertension* is available at http://hypertension.ahajournals.org**
DOI: 10.1161/HYPERTENSIONAHA.107.109652

hood. The effect of increased salt intake was small, but it could impact on cardiovascular morbidity and mortality. The data suggest that there is a previously unrecognized population of patients who have a history of low birth weight and are at risk of developing the morbid complications of salt sensitivity.

Sources of Funding

P.W.S. is supported by grants from the National Institutes of Health (DK46199) and the Medical Research Service of the Department of Veterans Affairs.

Disclosures

None.

References

1. Luft FC, Rankin LI, Bloch R, Weyman AE, Willis LR, Murray RH, Grim CE, Weinberger MH. Cardiovascular and humoral responses to extremes of sodium intake in normal black and white men. *Circulation*. 1979;60: 697–706.
2. Cook NR, Cutler JA, Obarzanek E, Buring JE, Rexrode KM, Kumanyika SK, Appel LJ, Whelton PK. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ*. 2007;334:885.
3. Weinberger MH, Fineberg NS, Fineberg SE, Weinberger M. Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. *Hypertension*. 2001;37:429–432.
4. Gates PE, Tanaka H, Hiatt WR, Seals DR. Dietary sodium restriction rapidly improves large elastic artery compliance in older adults with systolic hypertension. *Hypertension*. 2004;44:35–41.
5. Ying W-Z, Sanders PW. Dietary salt modulates renal production of transforming growth factor-β in rats. *Am J Physiol*. 1998;274(4 Pt 2):F635–F641.
6. Zacchigna L, Vecchione C, Notte A, Cordenonsi M, Dupont S, Maretto S, Cifelli G, Ferrari A, Maffei A, Fabbro C, Braghetta P, Marino G, Selvetella G, Aretini A, Colonnese C, Bettarini U, Russo G, Soligo S, Adorno M, Bonaldo P, Volpin D, Piccolo S, Lembo G, Bressan GM. Emilin1 links TGF-beta maturation to blood pressure homeostasis. *Cell*. 2006;124:929–942.
7. Dahl LK, Heine M, Tassinari L. Role of genetic factors in susceptibility to experimental hypertension due to chronic excess salt ingestion. *Nature*. 1962;194:480–482.
8. Guyton AC, Coleman TG, Cowley AW, Scheel KW, Manning RD, Norman RA. Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. *Am J Med*. 1972; 52:584–594.
9. Lifton R, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. *Cell*. 2001;104:545–556.
10. Johnson RJ, Herrera-Acosta J, Schreiner GF, Rodriguez-Iturbe B. Subtle acquired renal injury as a mechanism of salt-sensitive hypertension. *N Engl J Med*. 2002;346:913–923.
11. de Boer MP, Ijzerman RG, de Jongh RT, Eringa EC, Stehouwer CDA, Smulders YM, Serné EH. Birth weight relates to salt sensitivity of blood pressure in healthy adults. *Hypertension*. 2008;51:928–932.
12. Schmidt IM, Chellakooty M, Boisen KA, Damgaard IN, Mau Kai C, Olgaard K, Main KM. Impaired kidney growth in low-birth-weight children: distinct effects of maturity and weight for gestational age. *Kidney Int*. 2005;68:731–740.

Salt Sensitivity: It Is Not Always in the Genes

Paul W. Sanders

Hypertension. 2008;51:823-824; originally published online February 25, 2008;
doi: 10.1161/HYPERTENSIONAHA.107.109652
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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