Importance of Dietary Chloride for Salt Sensitivity of Blood Pressure

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Recent evidence indicates that the anion accompanying sodium plays an important role in determining the magnitude of the blood pressure increase in response to a high dietary intake of NaCl. The purpose of this review is to describe studies of blood pressure responses to selective dietary sodium loading (without chloride) and to selective dietary chloride loading (without sodium) in several experimental models of salt-sensitive hypertension and in hypertensive humans. The full expression of salt sensitivity depends on high dietary intakes of both sodium and chloride. This observation has implications for understanding mechanisms contributing to NaCl-induced hypertension. (Hypertension 1991:17[suppl I]:I-158–I-161)

It has generally been assumed that salt sensitivity of blood pressure is related to dietary sodium intake; however, increasing evidence suggests that the anion ingested with sodium has an important impact on the subsequent blood pressure response. Recognition of the contribution of the anion to the development of NaCl-induced hypertension has practical implications as well as implications for understanding the mechanism by which a high dietary NaCl intake increases arterial pressure in the susceptible host.

Animal Studies

In the Dahl salt-sensitive rat, we have demonstrated that selective dietary sodium loading, in the absence of chloride loading, fails to produce hypertension.1,2 Although animals fed a high NaCl diet (8%) developed hypertension within several weeks, in animals fed an identical sodium load provided as sodium bicarbonate or other nonchloride salts of sodium (NaAA), arterial pressure did not increase above that in control animals on a "normal" (1%) NaCl intake (Figure 1). The failure of selective dietary sodium loading to produce hypertension was not related to differences of body weight, net sodium balance, or blood pH or serum concentrations of sodium, potassium, or chloride. Compared with respective values in animals fed a normal NaCl diet, plasma renin activity and plasma aldosterone were each similarly suppressed by dietary NaCl loading and NaAA. Urinary calcium excretion was increased to a greater extent by NaCl than by NaAA feeding.3

Similar observations have been made in other models of experimental hypertension. Luft et al4 reported that supplementation of NaCl in drinking water caused a modest but significant increase of arterial pressure in the stroke-prone spontaneously hypertensive rat (SHRSP), whereas an equivalent sodium load, primarily in the form of sodium bicarbonate, did not. Hypertension also does not develop in the deoxycorticosterone acetate (DOCA)-salt rat fed sodium bicarbonate or NaAA, in contrast to animals fed NaCl.5–7 However, a diet containing a combination of sodium iodide and sodium bromide induces hypertension more readily than other nonchloride sodium salts in DOCA-treated rats, suggesting that the role of chloride in the effect of NaCl on blood pressure may be related to some property common to halides.8 Additionally, in the Dahl salt-sensitive rat and in the SHRSP, the blood pressure of animals fed chloride without sodium is less than that of animals fed NaCl.9,10

Thus, in three experimental models (Dahl salt-sensitive rat, DOCA-salt rat, and SHRSP), the full expression of NaCl-dependent hypertension requires the concomitant provision of high dietary intakes of both sodium and chloride. Selective feeding of sodium without chloride or chloride without sodium either fails to produce hypertension, or in the case of the SHRSP fed a high chloride diet, delays its development.

Clinical Studies

Limited evidence suggests that high dietary intakes of both sodium and chloride are also required to increase blood pressure in humans. Approximately 40 years ago, Grollman et al11 and Dole et al12 observed that dietary supplementation with ammonium chlo-
ride failed to increase blood pressure of hypertensive humans after dietary NaCl restriction had decreased blood pressure. In 1929, Berghoff et al. reported that blood pressure increased in seven hypertensive individuals on a high NaCl intake, but not on a high sodium bicarbonate intake. This observation has subsequently been confirmed. In five hypertensive patients, Shore et al. recently reported that NaCl feeding induced a greater rise in blood pressure than sodium phosphate feeding (Figure 2). Similarly, Kurtz et al. reported that blood pressure is increased by a high NaCl intake but not by equimolar sodium loading provided as sodium citrate in five NaCl-deprived men with essential hypertension (Figure 3).

Volume Mechanisms

The development of hypertension in the Dahl salt-sensitive rat may be related to an impaired capacity to excrete sodium in response to the challenge of an NaCl load. We have previously reported that plasma volume is greater in Dahl salt-sensitive than in Dahl salt-resistant rats maintained on a "normal" NaCl diet. Other investigators have also found either transient or sustained elevations of plasma volume in the Dahl salt-sensitive rat.

Studies of selective sodium loading support the hypothesis that volume mechanisms contribute to the pathogenesis of salt-sensitive hypertension. In the DOCA-salt rat, extracellular fluid volume is expanded by dietary NaCl loading (Figure 4) but not by selective sodium feeding. Similarly, in salt-sensitive hypertensive humans, plasma volume is higher on a high NaCl diet than on a high sodium citrate diet.

In the Dahl salt-sensitive rat, the DOCA-salt rat, and humans, although extracellular fluid volume is not expanded by selective dietary sodium loading, net sodium balance is at least as positive on a high sodium-normal chloride diet as on a high NaCl diet. This suggests that the anion ingested with sodium affects the distribution of sodium between the intracellular and extracellular compartments. There is some experimental evidence to support this hypothesis. In the rat, in contrast to NaCl, sodium bicarbonate loading is associated with increased intracellular fluid volume.
cellular sodium concentrations in skeletal muscle.\textsuperscript{21} Motoyama et al\textsuperscript{7} recently reported that intramuscular and intraerythrocyte sodium concentrations are lower in DOCA-treated rats fed NaCl than in those fed equimolar sodium in the form of nonchloride salts. We are unaware of the effects of these diets on intracellular sodium concentrations in vascular smooth muscle. However, these results suggest that an elevation of intracellular sodium concentration per se, in the absence of an expanded extracellular fluid volume, does not cause vasoconstriction.

**Neural Mechanisms**

Increased sympathetic nervous system activity and alterations of both high pressure and low pressure baroreceptor reflexes may also contribute to NaCl-induced elevations of arterial pressure.\textsuperscript{22} Sodium chloride loading in the salt-sensitive host may affect neural activity indirectly via an effect on plasma volume or directly via a central nervous system effect of NaCl.

There is little information in the literature concerning the effects of different sodium and chloride salts on neural activity. Motoyama et al\textsuperscript{7} recently reported that norepinephrine turnover rates in the heart and spleen are higher in DOCA rats fed high NaCl than those in either DOCA rats fed high sodium–normal chloride or normotensive controls, which have similar turnover rates. This raises the possibility that the different effects of high NaCl and selective sodium loading on arterial pressure in this model result from the stimulation of sympathetic nervous system activity by NaCl.

It has been suggested that an increase in cerebral spinal fluid (CSF) sodium concentration is the signal by which a high dietary NaCl intake increases sympathetic nervous system activity.\textsuperscript{23} Experimental elevation of CSF sodium content activates the central nervous system and raises arterial pressure.\textsuperscript{24} Nakamura and Cowley\textsuperscript{26} recently reported that a high NaCl diet increases CSF sodium content in Dahl salt-sensitive rats but not in salt-resistant controls. We are unaware of the effect of selective dietary sodium loading (without chloride) on CSF sodium concentrations. Such a study would answer the question about a direct effect of sodium on neural activity in the absence of expansion of the extracellular fluid volume.

In conclusion, studies in both the experimental animal and in humans demonstrate that high dietary intakes of both sodium and chloride are necessary for the development of hypertension in the susceptible host. These studies also demonstrate the importance of expansion of the extracellular fluid volume for NaCl-sensitive hypertension, since extracellular fluid or plasma volumes are expanded by dietary NaCl but not by nonchloride salts of sodium. Further studies with these diets should provide additional information about mechanisms by which dietary NaCl increases arterial pressure.

**Acknowledgment**

We appreciate the secretarial assistance of Vickie Zahradnik.
References


Key Words • NaCl-dependent hypertension • sodium chloride • chlorides • deoxycorticosterone • blood pressure • Dahl rats
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Hypertension. 1991;17:I158
doi: 10.1161/01.HYP.17.1_Suppl.I158

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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/17/1_Suppl/I158

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