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## Brief Review

# Relative Contributions of Dietary Na<sup>+</sup> and Cl<sup>-</sup> to Salt-Sensitive Hypertension

Matthew A. Boegehold and Theodore A. Kotchen

The effect of dietary NaCl on blood pressure has generally been attributed to the sodium ion. However, 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 in several experimental models of salt-sensitive hypertension and in hypertensive humans to selective dietary sodium loading (without chloride) and to selective dietary chloride loading (without sodium). 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 in the susceptible host. (*Hypertension* 1989;14:579–583)

A high dietary intake of NaCl increases arterial pressure in several experimental models of hypertension and in both normotensive and hypertensive humans. Although the prevalence of “salt-sensitive” blood pressure in humans is not known, blood pressure tends to be more salt sensitive in hypertensive than in normotensive individuals, in blacks than in whites, and in older individuals.<sup>1,2</sup> 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. In this review, we describe studies of the separate effects of high dietary intakes of sodium and chloride on blood pressure in both the experimental animal and in humans.

### Animal Studies

In the Dahl salt-sensitive rat (DS), we have demonstrated that selective dietary sodium loading, in the absence of chloride loading, fails to produce hypertension. In an initial study, separate groups of rats were maintained on either low NaCl, high (8%) NaCl, or high sodium–low chloride diets for 5

weeks.<sup>3</sup> The high sodium–low chloride diet was prepared by supplementing low NaCl chow with sodium bicarbonate to achieve a sodium content equivalent to that of the high NaCl diet. Arterial pressure in those rats on high NaCl increased progressively, whereas pressure in the rats maintained on the high sodium–low chloride and low NaCl diets did not. Although this preliminary observation suggested that the development of hypertension in the DS rat depends on the provision of chloride with sodium, the rats on the sodium bicarbonate diet failed to gain weight and were hypochloremic, hypokalemic, and alkalotic. The degree of alkalosis was in excess of that expected from bicarbonate ingestion and presumably was related to chloride deprivation. An identical chloride depletion syndrome had previously been reported in rats and in human infants fed chloride-deficient, but not sodium-deficient, diets.<sup>4,5</sup>

In a subsequent study in the DS rat,<sup>6</sup> the problem of chloride depletion alkalosis was circumvented by selectively sodium loading with addition of a mixture of non-chloride-containing sodium salts (including phosphate, bicarbonate, aspartate, glutamate, and glycinate) to normal rat chow containing 0.19 meq chloride/g. The chloride content of this diet was approximately 100 times greater than that in our earlier sodium bicarbonate study. In contrast to the sodium bicarbonate-fed rats, these rats grew normally and were neither hypokalemic nor alkalotic. However, in agreement with our earlier observations, selective dietary sodium loading, without chloride, failed to increase arterial pressure (Figure 1).

Similar studies in the deoxycorticosterone acetate (DOCA)–salt rat point to the importance of the chloride ion in this model of hypertension as well.

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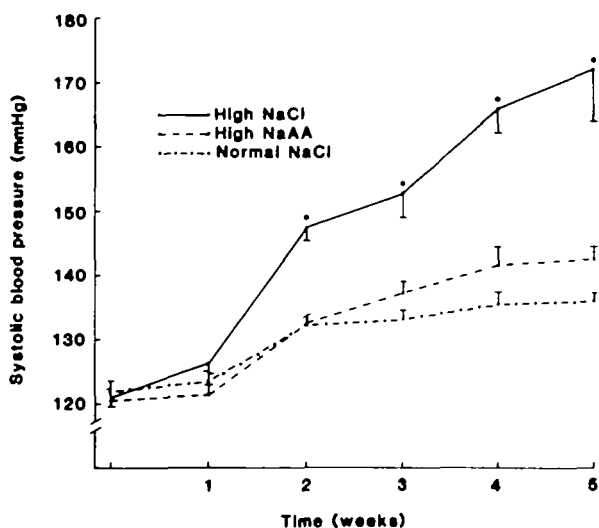


FIGURE 1. Line graph showing blood pressure in Dahl salt-sensitive rats maintained on three different diets: 7% NaCl (High NaCl), 1% NaCl (Normal NaCl), and a diet equimolar in sodium to 7% NaCl (High NaAA). \*Denotes a significant difference from animals receiving 1% NaCl. (Reprinted with permission from Whitescarver et al<sup>6</sup>; Copyright 1984 by the AAAS.)

In uninephrectomized, DOCA-treated rats, Kurtz and Morris<sup>7</sup> reported that both normal and high NaCl intakes produce a greater increase of arterial pressure than equimolar sodium intakes in the form of sodium bicarbonate and sodium ascorbate. Furthermore, hypertension was reversed by switching these rats from a high NaCl intake to a high sodium bicarbonate intake.<sup>8</sup> Passmore et al<sup>9</sup> reported a progressive rise in blood pressure in DOCA-treated rats fed high NaCl, but a much more modest increase when these rats were fed a high sodium-“normal” chloride diet (also prepared by adding sodium phosphate, bicarbonate, aspartate, glutamate, and glycinate to normal chow). However, the high sodium-normal chloride diet did not prevent hypertension in rats with one-kidney, one clip hypertension, indicating that the failure of this diet to increase blood

pressure in two models of salt-sensitive hypertension (DS and DOCA-salt) is related to the absence of a high chloride intake and not to a direct hypotensive effect of the diet itself. Motoyama et al<sup>10</sup> have also reported that this diet attenuates the development of hypertension in the DOCA-salt rat. However, a diet containing a combination of sodium iodide and sodium bromide induces hypertension more readily than other selective high sodium diets in DOCA-treated rats,<sup>11</sup> suggesting that the role played by chloride in the hypertensinogenic effect of NaCl may be related to some property common to halides.

Increased NaCl intake also accelerates the elevation of arterial pressure in the developing spontaneously hypertensive rat (SHR), a strain that is not dependent on salt for the genesis of hypertension.<sup>12,13</sup> Consistent with observations in DS and DOCA-salt rats, Luft et al<sup>14</sup> reported that supplementation of NaCl in drinking water (0.2%) caused a modest but significant increase of arterial pressure in the stroke-prone SHR, whereas an equivalent sodium load primarily in the form of sodium bicarbonate (mineral water) did not.

Thus, in three experimental models (DS rat, DOCA-salt rat, and SHR) the full expression of NaCl-dependent hypertension requires the provision of a high dietary intake of chloride (or bromide) with sodium. Selective dietary sodium loading, in the absence of chloride loading, minimizes or completely prevents the increase of arterial pressure.

To further evaluate the importance of dietary chloride in NaCl-induced hypertension, Whitescarver et al<sup>15</sup> examined the effect of selective chloride loading on blood pressure in the DS rat. Systolic blood pressure was monitored for 11 weeks in DS rats maintained on either 1% NaCl, 4% NaCl, or a normal sodium-high chloride diet (made equimolar in chloride to the 4% NaCl diet by addition of glycine chloride and calcium chloride). After 7 weeks, the rats on 4% NaCl had higher blood pressures than those on either the normal NaCl or normal sodium-high chloride diets, whose pres-

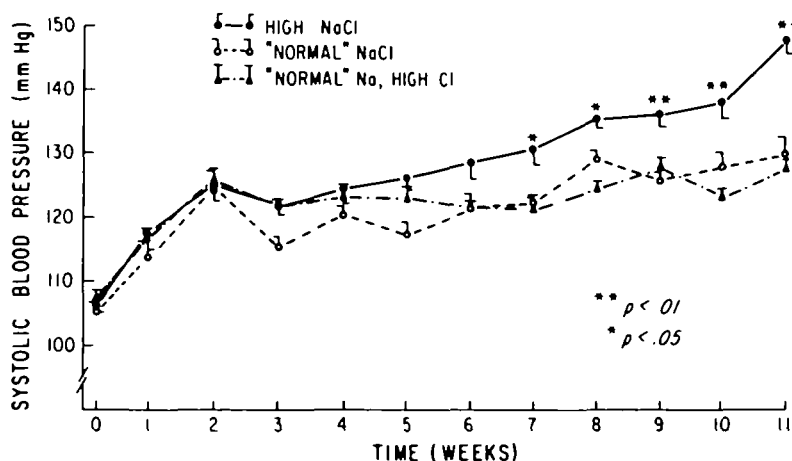


FIGURE 2. Line graph showing effects of dietary NaCl loading and selective chloride loading on blood pressure in Dahl salt-sensitive rats. High NaCl diet contains 4% NaCl, “Normal” NaCl diet contains 1% NaCl, and the “Normal” Na<sup>+</sup>, High Cl<sup>-</sup> diet is equimolar in Cl<sup>-</sup> to 4% NaCl. \*Denotes a significant difference from animals on 1% NaCl. (Reprinted from Whitescarver et al<sup>15</sup> by permission of the American Heart Association, Inc.)

tures were not different from each other (Figure 2). Thus, similar to selective sodium loading, selective chloride loading also failed to produce hypertension in the DS rat.

In the SHR, Wyss et al<sup>16</sup> have reported that a high NaCl (5%) diet increases the severity of hypertension and that the salt-induced rise of blood pressure is delayed by a normal sodium-high chloride diet (addition of glycine chloride and choline chloride to a 1% NaCl diet). However, SHR fed the normal sodium-high chloride diet eventually attained the same blood pressure elevation as SHR on the high NaCl diet.

Taken together, these observations indicate that the expression of experimental salt-sensitive hypertension is dependent on 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 SHR fed a high chloride diet, delays its development.

#### Clinical Studies

Preliminary studies also indicate an important role for dietary chloride in the development of salt-sensitive hypertension in humans. In 1929, Berghoff and Geraci<sup>17</sup> reported that blood pressure increased in seven hypertensive individuals on a high NaCl intake (200 meq/day), but not on a high sodium bicarbonate intake (278 meq/day). This observation has been confirmed by Morgan.<sup>18</sup> In five hypertensive patients, Shore et al<sup>19</sup> reported that NaCl feeding induced a greater rise in blood pressure than sodium phosphate feeding. Similarly, Kurtz et al<sup>20</sup> have recently reported that blood pressure was increased by a high NaCl intake (Figure 3), but not by equimolar sodium loading provided as sodium citrate in five NaCl-deprived men with essential hypertension.<sup>20</sup> Serum concentrations of sodium, potassium, chloride, bicarbonate, and blood pH did not differ after consumption of each of these two sodium salts. Limited evidence suggests that selective dietary chloride loading, in the absence of sodium loading, also does not increase blood pressure in humans. Approximately 40 years ago, Grollman et al<sup>21</sup> and Dole et al<sup>22</sup> observed that dietary supplementation with ammonium chloride failed to increase blood pressure of hypertensive humans after dietary NaCl restriction had decreased blood pressure.

Thus, analogous to results in the experimental animal, selective dietary sodium loading (in the absence of chloride loading) and selective dietary chloride loading (in the absence of sodium loading) also fail to increase blood pressure in salt-sensitive, hypertensive humans. Increases of arterial pressure are dependent on high dietary intakes of both sodium and chloride.

#### Implications for Mechanisms of Salt Sensitivity

Volume mechanisms have been implicated in the pathogenesis of salt-sensitive hypertension.<sup>23</sup> Studies of selective sodium loading support this hypothesis.

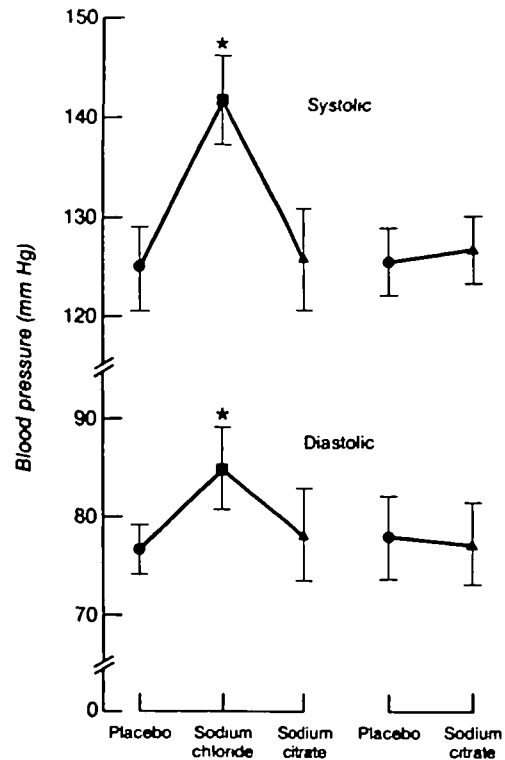


FIGURE 3. Line graph showing effect of dietary sodium chloride and sodium citrate on blood pressure in individuals with essential hypertension. \*Denotes a significant difference from the preceding placebo period. (From Kurtz et al.<sup>20</sup> Reprinted, by permission of the New England Journal of Medicine, 317:1043-1048, 1987.)

In both animals and humans, although net sodium balance is at least as positive on a high sodium-normal chloride diet as on a high NaCl diet,<sup>3,6,7,9,20</sup> the anion provided with sodium influences plasma volume. In the DOCA-salt rat, extracellular fluid volume (inulin space) is expanded by dietary NaCl loading, but not by selective sodium feeding.<sup>9</sup> Similarly, in salt-sensitive hypertensive humans, plasma volume is higher on a high NaCl diet than on a sodium citrate diet.<sup>20</sup> Furthermore, it has been suggested that plasma volume expansion stimulates release of a circulating sodium-potassium adenosine triphosphatase (Na<sup>+</sup>,K<sup>+</sup>-ATPase) inhibitor, which in turn might increase vascular smooth muscle contractility.<sup>24</sup> Luft et al<sup>14</sup> have recently reported that a high NaCl intake decreases erythrocyte Na<sup>+</sup>,K<sup>+</sup>-ATPase activity in the SHR, whereas sodium bicarbonate does not, indirectly suggesting that plasma volume is expanded by NaCl but not by sodium bicarbonate. Thus, despite comparable increases of net positive sodium balance, the failure of nonchloride sodium salts to produce hypertension is associated with their failure to expand plasma volume.

The anion ingested with sodium may affect the distribution of sodium between the intracellular and extracellular compartments. In the rat, sodium bicarbonate, but not NaCl loading, is associated with



increased intracellular sodium concentrations in skeletal muscle.<sup>25</sup> Motoyama et al<sup>10</sup> have recently reported that intramuscular and intra-erythrocyte sodium concentrations are lower in DOCA-treated rats fed NaCl than in those fed equimolar sodium in the form of nonchloride salts.<sup>10</sup> Thus, a greater movement of sodium into the intracellular compartment may explain the absence of volume expansion in rats fed nonchloride sodium salts. Bromide transport closely resembles that of chloride,<sup>26</sup> and conceivably the ability of a high sodium bromide intake to produce hypertension may also be related to plasma volume expansion.

Elevated arterial pressure in salt-loaded hypertensive animals is associated with increased intracellular sodium in vascular smooth muscle.<sup>27,28</sup> Increased vascular smooth muscle sodium may be due to the release of a circulating  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase inhibitor or, in the case of DOCA-salt hypertension, a direct effect of DOCA on the ionic permeability of the membrane.<sup>29</sup> We are unaware of studies of sodium content of vascular smooth muscle in salt-sensitive animals fed nonchloride sodium salts. However, if vascular smooth muscle sodium was increased by these diets, this would suggest that NaCl-induced hypertension is related to an interaction between intracellular sodium and plasma volume.

Neural mechanisms may also contribute to salt-sensitive hypertension.<sup>23</sup> Sympathetic nervous system activity may be increased in salt-sensitive animals, and dietary NaCl loading may have different effects on neural activity in salt-sensitive and salt-resistant animals. NaCl 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. Currently, there is little information in the literature concerning the effects of different sodium and chloride salts on neural activity. Motoyama et al<sup>10</sup> have 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 stimulation of sympathetic nervous system activity by NaCl.

Abnormalities of calcium metabolism have been associated with salt-sensitive hypertension. In both the experimental animal and humans, salt sensitivity is associated with increased urinary calcium excretion and a reduction of serum ionized calcium concentrations.<sup>30</sup> Kurtz and Morris<sup>8</sup> have reported that hypercalciuria in DOCA-treated rats fed a high NaCl intake precedes the onset of hypertension, whereas DOCA-treated animals fed an equivalent sodium load provided as bicarbonate do not exhibit hypercalciuria and do not become hypertensive; furthermore, replacement of dietary NaCl with sodium bicarbonate reversed both the hypercalci-

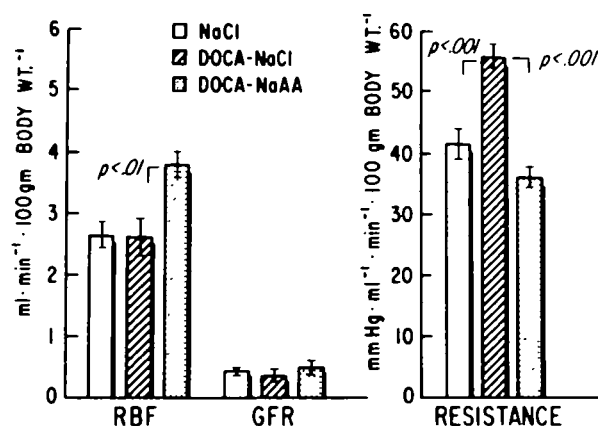


FIGURE 4. Renal blood flow (RBF), glomerular filtration rate (GFR), and renal vascular resistance in untreated rats on a 6% NaCl diet (NaCl), deoxycorticosterone acetate (DOCA)-treated rats on 6% NaCl (DOCA-NaCl), and DOCA-treated rats on a diet equimolar in sodium to 6% NaCl (DOCA-NaAA). (Reprinted from Passmore et al,<sup>9</sup> by permission of the American Heart Association, Inc.)

uria and the hypertension. Similarly, in the DS rat, we have recently reported that dietary NaCl loading increases urinary calcium excretion, whereas provision of sodium without chloride does not.<sup>31</sup> Furthermore, on a high NaCl intake, but not on the non-chloride-containing high sodium intake, DS rats had lower serum calcium and higher parathyroid hormone (PTH) concentrations than respective values in Dahl salt-resistant rats. The hypercalciuric effect of NaCl, with subsequent reduction of serum calcium and elevation of PTH, may be related to a specific effect of sodium chloride on renal tubular calcium transport or to expansion of plasma volume by NaCl. Whatever the mechanism, it is not clear what relation, if any, these alterations of calcium and PTH have to the development of hypertension.

Chloride itself may act as a direct renal vasoconstrictor. Schnermann et al<sup>32</sup> demonstrated that retrograde injections of chloride-containing solutions into the distal tubule elicit a decrease in single nephron glomerular filtration rate, whereas injections of sodium-containing solutions without chloride do not. In the denervated kidney, Wilcox<sup>33</sup> has reported that renal arterial infusion of chloride results in vasoconstriction, whereas sodium infusion without chloride produces renal vasodilation. Consistent with these observations, in the DOCA-salt rat,<sup>9</sup> we have found that renal blood flow is lower and renal vascular resistance is higher in DOCA-treated animals fed NaCl than in DOCA-treated animals fed sodium without chloride (Figure 4). Plasma chloride concentration was significantly higher in the DOCA-NaCl group. Thus, a specific renal hemodynamic effect of chloride, resulting in a decreased filtration fraction and hence, a natriuretic "handicap," might contribute to the expansion of

extracellular fluid volume and hypertension in NaCl-fed animals.

In summary, the concomitant provision of high dietary intakes of both sodium and chloride is necessary for the expression of salt-sensitive hypertension in the experimental animal and in humans. Although other mechanisms may be involved, expansion of extracellular fluid volume or plasma volume by NaCl, but not by nonchloride sodium salts, may contribute to the effect of NaCl on blood pressure. In addition to providing information about mechanisms of salt sensitivity, confirmation of the failure of selective sodium and selective chloride loading to produce hypertension in larger groups of subjects may have implications for food seasoning and food processing.

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KEY WORDS • salt-sensitive hypertension • sodium chloride • blood pressure • deoxycorticosterone • Dahl salt-sensitive rat