Dietary sodium chloride and potassium have effects on the pathophysiology of hypertension in humans and animals\textsuperscript{1–3}

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\textbf{ABSTRACT}  A diet high in NaCl can raise blood pressure in susceptible people and animals, probably by similar mechanisms. The possibly harmful effects of a high-NaCl diet are not unexpected because both prehistoric humans and mammals evolved in a low-NaCl environment. Evolutionary forces molded mammals to adapt well to a low sodium intake; modern high NaCl intakes go against this adaptation. A high-NaCl diet can cause premature mortality by raising blood pressure in susceptible people. We have new evidence that in hypertension, a high-NaCl diet can cause a great increase in mortality even though it does not cause a further blood pressure rise, partially because of multiple small cerebral infarcts. Recent evidence also indicates that a high-potassium diet reduces the rise of blood pressure caused by a high-NaCl diet, whereas a low-normal potassium intake encourages an NaCl-induced blood pressure rise. The combination of a tendency by the kidneys to retain NaCl together with a high NaCl intake can produce a blood pressure rise. This combination tends to cause NaCl retention, which can trigger blood pressure rises in susceptible humans and animals. Such blood pressure rises can augment renal NaCl excretion and regain the previous NaCl balance. In Dahl salt-sensitive rats several renal abnormalities encourage sodium retention. By analogy, renal "abnormalities" are probably present in people susceptible to hypertension. \textit{Am J Clin Nutr} 1997;65(suppl):606S–11S.

\textbf{KEY WORDS}  Salt, NaCl, potassium, blood pressure, hypertension, cardiovascular morbidity

\textbf{INTRODUCTION}  Human essential hypertension appears to be a salt-related disease. Societies consuming low amounts of salt have no hypertension, yet if such people migrate to a society with high salt intakes, \textasciitilde30\% of them will show a significant rise in blood pressure. Similarly, certain strains of rats develop a significant rise in blood pressure when placed on a high-salt diet. Dogs with reduced renal mass also get salt-induced hypertension. It is likely that the mechanisms that cause a high NaCl intake to raise blood pressure in animals are the same mechanisms that cause a high-NaCl diet to raise blood pressure in susceptible people. Thus, these animal models may teach us much about human hypertension.

Humans have been on Earth for 3.5 million y; for the first 99.8\% of that time, every human except those who lived by the edge of the sea consumed a low-sodium diet and also, incidentally, a low-fat and high-potassium diet. According to the principles of Darwin, the body has been fashioned by evolution to function efficiently with this low-sodium, low-fat, high-potassium diet. Our ancestors ate \textasciitilde690 mg Na/d whereas we average \textasciitilde4000 mg/d (equivalent to 10 g NaCl/d) \textsuperscript{(1)}. There is also a big difference in potassium intake: 284 mmol/d then compared with 64 mmol/d now \textsuperscript{(1)}. Many studies show blood pressure will rise in certain kinds of animals fed a high-NaCl diet. Americans eating 10 g NaCl/d have \textasciitilde2\% NaCl in their diet. In a previous study we found that Dahl salt-sensitive (S) rats fed a low-NaCl diet have a small rise in blood pressure with age, but that if these rats eat a 2\%-NaCl diet the rise in blood pressure is greater (177 compared with 159 mm Hg mean pressure) \textsuperscript{(2)}. Hence, just the amount of NaCl that is common in an American diet is enough to raise blood pressure in these NaCl-sensitive animals.

\textbf{CAN NaCl INCREASE MORTALITY IN A HYPERTENSIVE SETTING WITHOUT RAISING BLOOD PRESSURE?}  From working with stroke-prone hypertensive rats and considering the high stroke rate and hypertension prevalence in northern Japan, where a lot of NaCl is consumed \textsuperscript{(3)}, we had a hunch that NaCl could damage arteries even if it did not raise blood pressure. Once hypertension is established in humans, some people will experience a significant rise in blood pressure when switching from a low-salt to a high-salt diet, whereas others will experience only a minimal change in blood pressure. These latter persons have been termed salt-resistant hypertensive individuals, and it could be said that they would gain little from restricting NaCl in their diet. We have always been somewhat skeptical of this proposition. This skepticism was greatly strengthened when we observed that stroke-prone spontaneously hypertensive rats developed few strokes when fed a low-NaCl diet and developed a high incidence of strokes when eating a high-NaCl diet \textsuperscript{(4)}. However, these observations were not conclusive because the high-NaCl diets also considerably raised the blood pressure of these stroke-prone hypertensive

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rats. To test the proposition that a high-salt diet causes strokes without increasing blood pressure, we needed a hypertensive model in which blood pressure did not rise with consumption of a high-NaCl diet. We believed that Dahl salt-resistant (R) rats might be just right for such a study. These rats have been specifically bred to be highly resistant to NaCl-induced hypertension.

Thus, to test our theory we removed one kidney from 100 Dahl R rats and allowed them to drink only a solution containing 1% NaCl and 0.2% KCl for 6 wk. At the time of the nephrectomy each rat received a subcutaneous silicone implant containing 250 mg deoxycorticosterone acetate (DOCA)/kg wt; DOCA administration and the high-NaCl drink were continued for the next 6 wk. The silicone implant containing the DOCA was then completely removed from under the skin and the drink was switched from 1% NaCl to tap water. The diet was also changed from regular pellets to a low-NaCl pellet containing only 0.3% NaCl. The rats ate this low-NaCl diet for 4 wk as they recovered from the effects of the DOCA and high-NaCl regimen. At the end of this 4-wk recovery period, every Dahl R rat in the study underwent an intraluminal measurement of mean blood pressure under light ether anesthesia. Without the DOCA, all Dahl R rats have virtually no rise in blood pressure when eating a high-NaCl diet (5).

On the basis of this initial blood pressure measurement, the entire pool of rats was divided into two matched groups of ~50 rats each with equal average blood pressures (average mean intraluminal blood pressure: 160 mm Hg) (Figure 1). One group of rats continued to eat the 0.3% low-NaCl diet whereas the other group was switched to an 8% high-NaCl diet. After 5 wk of these diets, mean intraluminal blood pressure was again measured under light ether anesthesia. Because all were Dahl R rats, we were not surprised that the 8% high-NaCl diet did not raise the average blood pressure (158 mm Hg in both groups). This amounts to a mild degree of hypertension in both groups.

At the end of 8 wk of these two diets, 26 of 49 rats eating the 8% high-NaCl diet had died (a 53% mortality rate), whereas during this same period of time no rat eating the low-NaCl diet had died ($P < 0.000001$). After another 7 wk of the 8% high-NaCl diet, all rats (49 of 49) in the 8% NaCl group had died whereas 44 of 50 rats (88%) eating the 0.3% low-NaCl diet were still alive (5). Thus, the mortality rate in these mildly hypertensive rats eating the high-NaCl diet was high whereas that in rats with the same degree of hypertension and eating the low-NaCl diet was low.

Uremia was not the cause of death in the high-NaCl group. In the Dahl R rats eating the high-NaCl diet, no cerebral hemorrhage was obvious when the brain was grossly examined. Moreover, in the rats eating the high-NaCl diet, there was no evidence of mesenteric arteritis with local mesenteric bleeding. Early in the diet regimens both groups gained weight equally.

We weighed the rats weekly and noted that most of the rats eating the high-NaCl diet underwent a marked loss of weight just before their death. Sagittal sections of the brain hemispheres in such rats showed many small brain infarcts. Thus, from both a clinical and a microscopic standpoint, it appeared that most of the rats eating the high-NaCl diet died as a result of cerebrovascular disease with brain infarction and possible brain edema (5).

Whatever the form of cardiovascular disease, the high-NaCl feeding caused it to be severe enough to bring about the premature death of all the rats in this group even though their blood pressures were in the mildly hypertensive range. On the basis of these findings, salt’s infamy seems to go beyond blood pressure. The high-salt diet increased stroke and mortality rates even though it did not raise blood pressure above that found in rats fed the low-NaCl diet (6).

The same mechanisms may well be operating in hypertensive patients who are NaCl resistant. Such patients might be spared some vascular injury if they ate a moderately low-NaCl diet and might show aggravated vascular lesions if they ate a high-NaCl diet. The northern Japanese, who in the past have almost uniformly consumed a very-high-NaCl diet, had a high incidence of death from stroke when they ate such a diet (3). In past years this was the leading cause of death in Japan. However, there is a high prevalence of hypertension in this region, so it is possible that salt and high blood pressure contribute to the high incidence of strokes.

![FIGURE 1. Cumulative survival curves for post-deoxycorticosterone acetate (DOCA) hypertensive Dahl salt-resistant rats fed either a low- or a high-NaCl diet. BP, blood pressure.](https://academic.oup.com/ajcn/article-abstract/65/2/606S/4655379)
EFFECT OF POTASSIUM ON NaCl SENSITIVITY

Potassium has an effect on NaCl sensitivity. The Charles River–Kingston strain of spontaneously hypertensive rats (SHRs) are considered to be NaCl resistant. We confirmed that when these animals are fed a high-potassium diet, they are relatively NaCl resistant after 4 wk of a high-NaCl diet (Figure 2) (7). However, when these rats are not fed a high-potassium diet but are fed a low-to-normal potassium diet with 0.5% K, which is about the same as found in the average American diet, blood pressure increases strikingly when rats are switched from a low-salt to a high-salt diet (Figure 2). After 4 wk on the high-salt diet, there was an increase in blood pressure of 36 mm Hg in rats consuming a normal-potassium diet compared with a 9–mm Hg increase in rats eating a high-potassium diet. After 14 wk mortality was 90% with the high-NaCl, normal-potassium diet compared with 5% for the high-NaCl, high-potassium diet (7). Thus, in this strain of rats, the potassium concentration in the diet markedly influences NaCl sensitivity.

RENAI DYSFUNCTION IN NaCl-INDUCED HYPERTENSION

Various forms of renal dysfunction are closely related to NaCl-induced hypertension. In the Dahl strains of rats, the R rats are resistant to NaCl hypertension and the S rats are sensitive to NaCl hypertension. With a low-salt diet, the pressure natriuresis curve (inflow pressure versus NaCl output) of isolated kidneys from normotensive S rats is shifted to the right (Figure 3). It requires more pressure for the S rat to excrete a given millimole of sodium compared to equal inflow pressures; the S kidneys excrete half as much sodium as do the R kidneys (8). However, a rise in blood pressure to 160 mm Hg cures the natriuretic defect, which may be one reason why these rats become hypertensive. Even when S and R rats are matched for blood pressure, there is still a large significant difference in the pressure natriuresis curves.

FIGURE 3. Sodium excretion of isolated kidneys from Dahl salt-sensitive (S) and salt-resistant (R) rats at various inflow pressures. The distance between the large black dot (the mean value) and the tip of the arrowhead represents SE.

Why does the S kidney tend to retain NaCl? In prehypertensive Dahl S rats there are several demonstrated abnormalities that could lead to an increased tendency for sodium retention. In the prehypertensive state, Dahl S rats show no increase in the glomerular filtration rate (GFR) after an infusion of amino acids, indicating that there is no reserve capacity for increasing glomerular filtration (9). With this defect in glomerular filtration, maximum hemodynamic adaptations are required to barely achieve a normal GFR. However, Dahl R rats increase their GFR by 81% after the same amino acid infusion, indicating that these rats are a great reserve capacity for increasing GFR. When both types of kidneys are perfused with blood at an inflow pressure of 100 mm Hg, the isolated kidneys from prehypertensive Dahl S rats have a 33% reduction in GFR compared with that in Dahl R rats (8). Lithium clearance is also diminished in Dahl S rats, suggesting a reduced rate of sodium reabsorption from the proximal convoluted tubule.

Prostaglandin E2 concentrations are reduced in the cortex and in the outer and inner medullas of quick-frozen kidneys from prehypertensive Dahl S rats. This reduction leads to excessive sodium reabsorption from the ascending thick limb of Henle’s loop as well as from the cortical collecting tubule and the inner medullary collecting duct (10, 11). All these actions encourage sodium retention. Moreover, the quick-frozen outer medullas of Dahl S rats have about a one-third reduction in the concentrations of prostaglandins E2, I2, and D2, all of which are vasodilator prostaglandins, and a 50% increase in the concentration of thromboxane, which is a vasoconstrictor prostaglandin (11). The deficit in vasodilator prostaglandins and the excess of a vasoconstrictor prostaglandin would tend to cause vasoconstriction in the descending vasa recta, which should lead to a diminished papillary plasma flow. In fact, in prehypertensive Dahl S rats fed a low-NaCl diet, we measured a 25% reduction in plasma flow to the renal papilla (12). Both the vasoconstriction of the descending vasa recta and the diminished papillary plasma flow would encourage Na retention.

FIGURE 2. Effect of dietary potassium concentrations on the susceptibility to NaCl-induced hypertension in Charles River spontaneously hypertensive rats after 4 wk of diets. BP, blood pressure. n = 20 (low NaCl, high K), 20 (high NaCl, high K), 20 (low NaCl, normal K), and 33 (high NaCl, normal K).
HOW IS THE NaCl SIGNAL TRANSMITTED?

When the combination of a high-NaCl diet plus a kidney with sluggish sodium excretion brings on hypertension in susceptible humans or rats, it is still a mystery as to how the NaCl signal is perceived. In certain people this NaCl signal may not be perceived at all. We see signs of this in persons who gradually go into renal failure with no hypertension whatsoever and in whom a large expansion of extracellular fluid volume for 4 wk under dialysis conditions leads to no rise of blood pressure (13). This lack of reception of the NaCl signal may be present in as many as 20% of people.

The juxtaglomerular cells in the walls of the renal afferent arterioles are one possible NaCl receptor. An increased extracellular volume and an increased concentration of NaCl in plasma both diminish renin secretion (14, 15). The signal for excess NaCl in the body may also be perceived in the central nervous system (CNS). Various lesions in the CNS of Dahl S rats can greatly attenuate NaCl-induced hypertension. 6-Hydroxydopamine injected into the lateral brain ventricle destroys many catecholamine-containing neurons and reduces NaCl hypertension by 50% (16). Bilateral lesions of the paraventricular nuclei also reduce NaCl hypertension by 50% (17). A thermal lesion at the anterior end of the third brain ventricle (AV3V area) reduces NaCl hypertension by 60% (18). Moreover, a bilateral lesion of the suprachiasmatic nuclei, which are at the bottom of the third brain ventricle, actually increases NaCl hypertension by 15 mm Hg and ratios of heart weight to body weight by 15% (16). Thus, it is essential to have certain CNS systems intact to get the full expression of NaCl-induced hypertension. This raises the possibility that the NaCl signal is somehow received in the brain.

If such is the case it would be helpful to know just how the NaCl signal is received. It is well-known that hypertonic NaCl introduced into the lateral brain ventricle induces a pressor response, and such pressor responses are greatly exaggerated in prehypertensive Dahl S rats (19). When an excessive amount of NaCl is incorporated in food, a meal would transiently increase the NaCl concentration and tonicity of extracellular fluid and the signal could be perceived in this way. To investigate this, we prepared a high-NaCl liquid diet to be fed to Dahl S rats for 12 wk with no additional water offered. These liquid diets contain 0.08 g NaCl/g soluble nutrients; components were dissolved either in a minimal amount of water to produce a hypertonic liquid diet (1.4% NaCl) or in a much greater volume of water to produce a hypotonic (0.45% NaCl) diet. Eleven Dahl S rats ate the hypertonic 1.4%-NaCl diet and 12 other Dahl S rats ate the hypotonic 0.45%-NaCl diet. After 12 wk, average intraarterial mean blood pressure was 195 mm Hg for both the hypertonic and hypotonic groups. Because the same rise in blood pressure occurred when NaCl was introduced hypotonically, it is unlikely that a high NaCl concentration is the signal that causes a rise in blood pressure.

If a rise in NaCl concentration is not the signal, the most likely alternative signal would be a rise in extracellular fluid volume in some specialized receptor area. Many control systems involving body water are located in nuclei surrounding the third brain ventricle, which is a vertical, slit-like structure. It is conceivable that a high-NaCl diet could bring on some excessive extracellular fluid volume in the local tissues on either side of the slit that constitutes the third brain ventricle. This localized extracellular fluid swelling of tissue on either side of the slit could cause the ependymal cells and nerve fibers in the walls of the slit to touch one another, which could give off a neurogenic or humoral signal indicating an increased extracellular fluid volume.

We tested this hypothesis by blocking the aqueduct of Sylvius stereotaxically with an inert silicone material in various Dahl S rats. Such a block creates hydrocephalus with a fourfold widening of the third brain ventricle in formalin-fixed brains, thereby partially preventing ependymal cells or nerve fibers from touching one another in response to a high-NaCl diet. Twenty Dahl S rats fed a 0.23% low-NaCl diet had a verified block of the aqueduct whereas 26 other Dahl S rats fed the same low-NaCl diet had a sham aqueduct block. After 6 wk, both groups had an average intraarterial mean blood pressure of 130 mm Hg. Thus, the block of the aqueduct had no influence on the blood pressure of Dahl S rats as long as they were consuming a very-low-NaCl diet.

Thirty-four other Dahl S rats underwent a sham aqueduct block and then began eating a 6% high-NaCl diet. After 6 wk, the intraarterial mean blood pressure of these rats averaged 177 mm Hg, indicating a rise in blood pressure of 47 mm Hg caused by the high-NaCl diet. In contrast with this, 17 other Dahl S rats underwent a subsequently verified aqueduct block and then began eating the 6% high-NaCl diet. After 6 wk the average blood pressure of this group was 149 mm Hg, indicating an increase of 19 mm Hg because of the high-NaCl diet. Thus, the aqueduct block abolished 60% of the NaCl-induced rise in blood pressure (P < 0.001) (20).

After 12 wk of the 6% high-NaCl diet, the mortality rate for the 34 Dahl S rats with the sham aqueduct block was 64% whereas the mortality rate for the 17 Dahl S rats with the true aqueduct block was only 6% (20). Thus, blocking the aqueduct resulted in a 90% reduction in mortality rate (P < 0.001). There were no deaths in either group of Dahl S rats fed the 0.23% low-NaCl diet. Cumulative survival curves in Figure 4 indicate the striking increase in survival among the S rats with the verified aqueduct block. At week 11 after surgery, none of the high-NaCl rats with the true aqueduct block had died whereas 50% of those with the sham aqueduct block had died (20). Albumin concentrations in 24-h urine samples were also reduced 54% in the high-NaCl S rats with the true aqueduct block compared with those with the sham aqueduct block (P < 0.001).

When the aqueduct is blocked with silicone, some of the periaqueductal fibers of passage and nuclei may be destroyed by the pressure of the silicone; such a periaqueductal lesion could cause the large reduction of blood pressure and mortality rate observed in the S rats fed the high-NaCl diet. To examine this possibility, we made discrete thermal lesions stereotaxically in the periaqueductal structures of other S rats just before they began eating the 6% high-NaCl diet for 6 wk. These rats were compared with another group of S rats fed the same diet who underwent sham thermal lesions. The average mean intraarterial blood pressures of 25 rats with true thermal lesions and 13 rats with sham thermal lesions were 176 and 166 mm Hg, respectively. With the thermal lesion, blood pressure actually tended to be higher than with the sham lesion (P < 0.16). Thus, a thermal lesion of periaqueductal fibers of passage did not reduce the degree of NaCl-induced hypertension in the Dahl S rats, which strengthens the notion that hydrocephalus of
the third brain ventricle is reducing the hypertension and mortality in these NaCl-fed S rats.

In Dahl R rats given mild post-DOCA hypertension, mortality was 53% without a rise in blood pressure within 8 wk of consuming a high-NaCl diet (21). In this study, 42 Dahl R rats were given DOCA in silicone (250 mg/kg) and 1% NaCl to drink. After 4 wk the DOCA and 1% saline were removed and replaced with a low-NaCl diet and tap water. One week later, the rats were divided into two groups perfectly matched for blood pressure (154 mm Hg). One group had the aqueduct blocked with silicone and epoxy materials; the other group had a sham block. After 4 more recovery weeks with a low-NaCl diet, blood pressure averaged 171 mm Hg in sham-blocked rats and 147 mm Hg in truly blocked rats ($P < 0.0001$). Thus, the aqueduct block prevented most of the post-DOCA hypertension and permitted a strong post-DOCA recovery from the acute DOCA hypertension. The rats with the sham block had an actual rise in blood pressure during the post-DOCA recovery period. The vicious cycle leading to permanent post-DOCA-NaCl hypertension was broken by the aqueduct block.

Both groups next began an 8% high-NaCl diet and after 4 wk blood pressure averaged 184 mm Hg in sham-blocked and 155 mm Hg in truly blocked rats ($P < 0.0001$). After 12 wk of 8% NaCl, all 28 sham-blocked rats had died whereas only 1 of 14 truly blocked rats had died (93% reduction in mortality; $P < 0.0001$). The ratio of urinary albumin to creatinine was 36 in sham-blocked rats compared with only 14 in truly blocked rats, ($-62%; P < 0.0001$). Dry heart weights averaged 431 mg in sham-blocked rats compared with 310 mg in truly blocked rats ($-28%; P < 0.05$) even though the body weight of the sham-blocked rats averaged 6% less with the high-NaCl diet. In the post-DOCA-NaCl period it is likely that structural changes linger in the third brain ventricle region, leading to post-DOCA hypertension and progression of renal lesions. An aqueduct block produces hydrocephalus of the third ventricle and thereby reverses the lingering post-DOCA structural effects, greatly reducing blood pressure, mortality rate, cardiac hypertrophy, and urinary albumin (21).

There are several theories to explain how an aqueduct block protects Dahl S and post-DOCA Dahl R rats from a rise in blood pressure and a high mortality rate. However, it appears that the block of the aqueduct with subsequent hydrocephalus produces some change in the CNS that greatly reduces NaCl hypertension and the death rate resulting from it. These studies provide further evidence that the CNS is involved in the process of NaCl hypertension.

REFERENCES