High Sodium Chloride Diets Injure Arteries and Raise Mortality Without Changing Blood Pressure

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High NaCl diets often increase blood pressure and thereby accelerate lesions in arterial walls. Could high NaCl diets increase arterial lesions without raising blood pressure? To test this, 100 uninephrectomized Dahl salt-resistant (DR) rats (highly resistant to NaCl hypertension) were administered deoxycorticosterone acetate (DOCA) (250 mg/kg) in silicone implants and drinking water containing 1% NaCl for 6 weeks. Then the DOCA and saline were removed, and the rats were allowed to recover for 4 weeks. Intra-arterial mean blood pressures on all rats allowed division of the rats into two matched groups, each group with an average blood pressure of 160 mm Hg. One group continued on a 0.3% NaCl diet, whereas the other group began an 8% NaCl diet for 8 weeks. After 5 weeks on these two diets, the intra-arterial blood pressure averaged 158 mm Hg in both groups. Thus, the 8% NaCl diet produced no further increase in blood pressure in the DR rats. Nevertheless, after 8 weeks on the 8% NaCl diet, 53% of the rats (26 of 49) had died; whereas in the group on the 0.3% NaCl diet, not one rat (0 of 51) had died ($p<0.000001$). After 7 more weeks on the 8% NaCl diet, all the rats in this group had died. The chief cause of death in the group of rats on the 8% NaCl diet was likely cerebral infarction because small cerebral infarcts were observed in rats that died on this diet. Uremia, congestive failure, cerebral hemorrhage, and arrhythmia were not likely causes of death. Thus, it appears that a high NaCl diet in mildly hypertensive DR rats can greatly accelerate cerebral arterial disease with brain infarction and very high mortality, even when the high NaCl diet causes no increase in blood pressure whatsoever. Seemingly, salt’s infamy goes beyond blood pressure. It is even possible that “salt-resistant” hypertensive humans could reduce vascular complications by adhering to a low NaCl diet. *(Hypertension* 1990;15:900–903)

Ambard and Beaujard showed in 1904 that some hypertensive patients will have a large decrease in blood pressure when they reduce the amount of NaCl in their diets. With dietary intakes as low as 10 meq/day, investigators such as Kempner and Watkin et al found that a sizable percentage of hypertensive patients would show a decrease in blood pressure. Even modest reductions in NaCl intake of approximately 60–100 meq/day can lower blood pressure in many hypertensive patients. For this reason, most hypertensive patients are advised to limit their NaCl intake to lower blood pressure, which then reduces hypertensive complications. Recent well-controlled studies have confirmed that reducing the level of NaCl intake to 50 meq/day is accompanied by a decrease in blood pressure, and resuming the higher NaCl intake is associated with a return of blood pressure to the previous higher levels.

Several very short-term studies, however, have shown that when hypertensive patients are placed on a low NaCl diet for 5 days and are then switched for a second 5 days to a high NaCl diet, not all of the hypertensive patients show a big difference in blood pressure on the two contrasting NaCl levels. If a patient’s diastolic blood pressure does not change more than 5 mm Hg, the patient is considered NaCl-resistant, whereas if the blood pressure changes more than 10 mm Hg, the patient is considered NaCl-sensitive. Moreover, there have been recent suggestions in the literature that those patients who are NaCl-resistant should not bother to reduce their intake of dietary NaCl. Most of these studies are very short-term, generally not extending longer than 10 days. It is possible that prolonged NaCl restriction might have results quite different from the results of the 10-day trials.
Moreover, it is possible that almost all people with essential hypertension were NaCl-sensitive at the beginning of their hypertension. For example, Page et al. have found that, in unacculturated societies, there is virtually no hypertension because these unacculturated peoples consume a low fat, low NaCl, and high potassium diet. In contrast, when these unacculturated peoples leave their native villages, migrate to a "civilized" city, and begin to eat the high NaCl diet characteristic of civilized cities, as many as 30% of them begin to show hypertensive levels of blood pressure. Because 30% of these people do become hypertensive after the migration, one can reason that as many as 30% of them have the genetic susceptibility to develop essential hypertension. As long as this 30% remain in their primitive-village environment, however, with a low fat and low NaCl intake, none of them develop high blood pressure. This phenomenon has been observed repeatedly and provides evidence that nearly all people with essential hypertension were originally NaCl-sensitive. After many years on a relatively high NaCl diet and after many years of high blood pressure, however, such hypertensive individuals can be divided into two groups, that is, those who are relatively NaCl-sensitive and those who are relatively NaCl-resistant. Thus, it appears that in many hypertensive people, the presence of high blood pressure for many years causes some irreversible changes that convert a hypertensive person from NaCl-sensitive at the start to NaCl-resistant after many years of hypertension. In such NaCl-resistant people, one wonders whether NaCl restriction provides any benefit because blood pressure does not increase much when these people increase their NaCl intake.

In the last 5 years, we have performed several studies with stroke prone spontaneously hypertensive rats (SHRSP) that clearly indicate that these SHRSP fed a "normal" NaCl diet have virtually no strokes although they have a mild hypertension. In contrast, when this same strain of SHRSP is fed a 4-6% high NaCl diet, the rats have a very high percentage of premature death from strokes. Of course, the blood pressures also became higher in these rats when they were fed the high NaCl diet. Where there was an overlap of blood pressure, however, strokes appeared to be rare in rats on low NaCl diets and very common in rats on high NaCl diets. We sought to design a study in which a high NaCl diet could be compared with a low NaCl diet in mildly hypertensive rats, without having the high NaCl diet increase the blood pressure. We elected to use a different strain of rats that was specifically bred to be extremely NaCl-resistant with regard to blood pressure, that is, the Dahl salt-resistant (DR) rat. We have performed many such studies in DR rats, and we know they can be fed 8% NaCl diets without any increase in blood pressure. We wished to investigate whether a high NaCl diet might increase arterial lesions in rats with mild hypertension although it does not increase blood pressure.

Methods

One hundred DR rats each had one kidney removed and were allowed to drink only a solution containing 1% NaCl and 0.2% KCl for 6 weeks. At the time of the nephrectomy, each rat received a subcutaneous silicone implant that contained 250 mg deoxycorticosterone acetate (DOCA)/kg body wt. These rats were fed regular Purina (St. Louis, Missouri) Rat Chow (0.8% NaCl). The uninephrectomy and implantation of DOCA took place when the rats were 6.5 weeks old, and the DOCA administration and high NaCl drink were continued for the next 6 weeks.

Then the silicone implant containing the DOCA was completely removed from under the skin, and the drink was switched from 1% NaCl to tap water. The diet was also changed from regular Purina Rat Chow to a low NaCl Purina rat chow that contains only 0.3% NaCl. The rats were fed this 0.3% NaCl diet for 4 weeks while they recovered from the effects of the DOCA and high NaCl regimen.

At the end of this 4-week recovery period, every DR rat in the study underwent an intra-arterial measurement of mean blood pressure under light ether anesthesia. For many years, we have noted that variations in vasoconstriction in the rats' tails caused unreliable blood pressure readings. For this reason, we used intra-arterial blood pressure measurements for greater accuracy and reliability. This limited us to two blood pressure readings, cannulating one of the femoral arteries for each mean blood pressure determination. On the basis of this initial blood pressure measurement, the entire pool of rats was divided into two matched groups of about 50 rats each with precisely equal average blood pressures. The average mean intra-arterial blood pressure was 160 mm Hg for both groups.

At this time, one group of rats continued to be fed the 0.3% NaCl Purina diet, whereas the other group was switched to an 8% NaCl Purina diet. Each rat was also weighed weekly. At the end of 5 weeks, the mean intra-arterial blood pressure of each rat was again ascertained under light ether anesthesia.

Results

Because all these rats were DR rats, we were not surprised that the 8% NaCl diet did not raise the average blood pressure at all. At the beginning of the 5-week feeding period, the average blood pressure was 160 mm Hg in the group of rats on the high NaCl (8% NaCl) diet, whereas at the end of 5 weeks, the blood pressures averaged 158.8 mm Hg.

Eighty-eight percent of the rats were alive at the time of this 5-week blood pressure reading. At the end of 8 weeks on these two dietary regimens, 26 of 49 (53%) rats fed the 8% NaCl diet had died, whereas during the same time, not one rat (0 of 51) fed the 0.3% NaCl diet had died (p<0.000001)* (See Figure 1). After 7 more weeks, all the rats (49 of 49)
fed the 8% NaCl diet had died. After 15 weeks, 44 of 50 rats (88%) fed the 0.3% NaCl diet were still alive.

At the end of 5 weeks on these two diets, the average blood pressures of the two groups of rats were very similar, 158.4 mm Hg in the group of rats on the 0.3% NaCl diet and 158.8 in the group of rats on the 8% NaCl diet. This constitutes a mild degree of hypertension in both groups. Thus, we had a very pronounced mortality rate in these mildly hypertensive rats fed the 8% NaCl diet, whereas there was a very low mortality rate in rats with the same degree of hypertension but fed the 0.3% NaCl diet. The variability of blood pressure after 5 weeks on the special diets was greater for the group of rats on the 8% NaCl diet. The coefficient of variation (SD/mean x 100) was 15.7% for the group of rats on the 8% NaCl diet as compared with the group of rats on the 0.3% NaCl diet.

In both groups, blood pressure changed in both directions during the weeks of being fed the special diets, but with a greater variance in the group of rats on the 8% NaCl diet as compared with the group of rats on the 0.3% NaCl diet. By using the blood pressures obtained after 5 weeks on the 8% NaCl diet, we divided the rats fed the 8% NaCl diet into two groups, one group of rats with the highest blood pressures and the other group of rats with the lowest blood pressures. Their respective mortality rates after 8 weeks on the diet were 44% and 58%, a difference that was not significant. The rats on the 8% NaCl diet had a high death rate in high, low, and middle levels of blood pressure, using the 5-week blood pressure readings.

Uremia was not the cause of death in the group of rats on the 8% NaCl diet. The normal creatinine level of a DR rat is about 0.6 mg/dl; after 5 or more weeks on the 8% NaCl diet, none of the rats fed the 8% NaCl diet had a creatinine level above 1.0 mg/dl, although many of them already had undergone the weight loss that preceded their death. In the DR rats eating the 8% NaCl diet, not one rat had had an obvious cerebral hemorrhage when the brain was grossly examined. Moreover, among the rats fed the 8% NaCl diet, there was no evidence of mesenteric arteritis with local mesenteric bleeding on postmortem examination.

We weighed the rats weekly, and we noted that most of the rats fed the 8% NaCl diet underwent a pronounced loss of weight just before death. After 8 weeks of being fed the 8% NaCl diet, whenever a rat had lost 50 g of body weight within a 2-week period, it was anticipated that the rat would soon die. Such rats were killed and autopsied. Sagittal sections of the brain hemispheres in these rats showed many small brain infarcts. This finding might partially explain the high susceptibility to convulsive seizures in these rats, although brain edema could explain these seizures and could also contribute to the deaths of some of the rats. Even if these rats had other causes of premature death, these small brain infarcts would also be considered a partial cause of death.

The cannulation of the femoral artery after 5 weeks on the diet could possibly interact with the 8% NaCl diet to cause death. This femoral artery cannulation procedure, however, takes about 4 minutes under light ether anesthesia; it is not likely to be a major cause of death. Blood pressure was measured after 5 weeks on the diets because most of the rats were still reasonably healthy at that time. Even at that 5-week point in the diets, the mortality rate was significantly higher in the group of rats on the 8% NaCl diet as compared with the group of rats on the 0.3% NaCl diet (p<0.02). After 5 weeks on the diets, no further blood pressures were taken because so many rats had died. A high NaCl diet, however, will generally increase blood pressure in rats close to the full response during the first 5 weeks of NaCl feeding.

**Discussion**

During the past 4 years, we have completed several studies with SHRSP10,11 and have noted a typical syndrome when rats develop cerebral vascular disease. Their rate of weight gain becomes slower, then there is a period of leveling off when there is no weight gain at all, and this is followed by a period of weight loss that usually precedes and presages the death of the rat. As this weight loss pattern becomes evident, the rats become very prone to convulsive behavior whenever they are handled. Of the 49 DR rats with post-DOCA hypertension that were fed the high NaCl diet, 86% (42 of 49) showed this pattern of weight loss and pronounced susceptibility to convulsions whenever they were handled and even when not handled. Thus, from a clinical viewpoint, it appeared that most of the rats fed the high NaCl diet died as a result of cerebral vascular disease with brain infarction or brain edema.

We could predict a rat's death on the basis of the weight loss that preceded death. In such rats, we found many small cerebral infarcts in sagittal sections of the brain hemispheres. On postmortem examination, we did not observe mesenteric arteritis with
bleeding into the mesentery, and we could not find any pulmonary edema that might have been indicative of congestive heart failure. We cannot rule out the possibility that some of these rats died of sudden ventricular fibrillation. In rats with a ligation of the anterior descending coronary artery, during the next several months there was a very high incidence of sudden death as a result of cardiac arrhythmia. Weight loss is not seen in rats that are about to die of sudden ventricular fibrillation. Thus, if some of our rats did die of a sudden ventricular fibrillation, it would likely have been in addition to a serious degree of cerebral vascular disease because 86% of the rats showed the typical syndrome associated with cerebral vascular disease. We believe the evidence supports the conclusion that most of the deaths were at least partially the result of cerebral vascular disease with infarction. It appears that the deaths of the rats fed the high NaCl diet was at least some type of cardiovascular death.

We believe the relative rarity of cerebral hemorrhage can be related to the fact that these DR rats had only a mild form of hypertension, whereas the NaCl-fed SHRSP generally have severely elevated levels of blood pressure.10,11 Regardless of the form of cardiovascular disease, the high NaCl feeding caused it to be severe enough to effect the premature deaths of all the NaCl-fed rats although their blood pressures were only in the mild hypertension range. Limas et al12 also noted that a high NaCl diet increased vascular lesions in the aorta and kidney for a given level of high blood pressure in SHR rats (supplied by Taconic Farms).

Our current study was performed with the most salt-resistant strain of rats that has ever been developed. We have shown that the DR rat will not develop any increase in blood pressure when fed a 6% NaCl (high) diet, even when the potassium intake is in the low-normal range.13 On this same type of diet, the SHR rats that are relatively NaCl-resistant (from the Charles River Company) definitely show a pronounced hypertension and an increased mortality rate.13 Nevertheless, these extremely NaCl-resistant DR rats can be made mildly hypertensive if they are fed the high NaCl diet and have the DOCA implantation for 6 weeks and then allowed to recover from the NaCl and hormone for a subsequent 4 weeks. According to our results, rats with this degree of mild hypertension will develop a lethal amount of vascular disease if fed a high NaCl diet and will suffer almost no premature death if fed a low NaCl diet. Moreover, because the DR rat was used for this study, we could document that the high NaCl diet caused no increase in average blood pressure. Nevertheless, the high NaCl intake was associated with an increase in vascular disease sufficient to cause the deaths of all 49 rats within 15 weeks of starting the high NaCl diet. Based on these findings, salt’s infamy seems to go beyond blood pressure.

Because some hypertensive patients get a big increase in blood pressure if they switch from a low NaCl diet to a high NaCl diet and other hypertensive patients have virtually no change in blood pressure with the change of salt intake, many physicians advise their NaCl-resistant patients to eat as much salt as they want. These current studies cast some doubt on this therapeutic decision. Our rats with mild hypertension had the ultimate degree of NaCl resistance, yet they had a pronounced increase in incidence of vascular disease as a result of a high NaCl diet. The same might be true of hypertensive patients who are NaCl-resistant. It is possible that such patients might be spared some vascular injury if they eat a moderately low NaCl diet, and they might show aggravated vascular lesions if they eat a high NaCl diet. It is certainly true that the northern Japanese, who in the past have almost uniformly consumed a high NaCl diet, show a very high incidence of death from stroke.14 In fact, in past years, stroke was the leading cause of death in Japan.

References


Key Words • sodium chloride • cerebral artery diseases • cardiovascular disease • deoxycorticosterone • salt intake
High sodium chloride diets injure arteries and raise mortality without changing blood pressure.
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