Potassium Reduces Cerebral Hemorrhage and Death Rate in Hypertensive Rats, Even When Blood Pressure Is Not Lowered

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SUMMARY In a study of the effects of K+ in stroke prone spontaneously hypertensive rats, adding K+ to normal chow was found to reduce the mortality from 83% to 2%, a 98% reduction. An 86% reduction in mortality occurred even when blood pressure was virtually equal in the two stroke prone spontaneously hypertensive groups being compared. Dietary K+ supplements also reduced mortality in hypertensive Dahl salt-sensitive rats from 55% to 4%, a 93% reduction. There was an 87% reduction in mortality even when blood pressure was equal in the Dahl salt-sensitive groups being compared. The added dietary K+ decreased blood pressure moderately in stroke prone spontaneously hypertensive rats and modestly in Dahl salt-sensitive rats, which probably contributed to the reduced death rate. More importantly, however, the added K+ seemed to prevent severe lesions in cerebral arteries and deaths even when blood pressure lowering was eliminated as a protective factor. In another group of stroke prone spontaneously hypertensive rats, there was a 40% incidence of cerebral hemorrhage in surviving rats not receiving K+ supplements and no incidence of cerebral hemorrhage in similar surviving rats receiving K+ supplements, which suggests that K+ supplements confer protection against brain hemorrhage. (Hypertension 7 [Suppl I]: I-110–I-114, 1985)

KEY WORDS • strokes • cerebral infarct • cerebrovascular disease

The natural foods that primitive hunter-gatherers in remote corners of the world eat contain very high levels of K+. The men in these hunter-gatherer groups eat between 150 and 270 mEq of K+ per day, whereas whites in the United States average 70 mEq per day and blacks in the southeastern United States average 35 mEq per day. Archaeological evidence indicates that men and women ate mainly natural foods until about 10,000 years ago and that such a diet would have provided a high level of K+. Evolutionary forces generally cause surviving species to adapt exceedingly well to their environments, including the foodstuffs in those environments. Thus, during the long prehistoric period of primates, hominoids, and humans, evolutionary forces literally would have molded humankind to function well on this high K+ intake. The same general principles would apply to other mammals living in the wild and presumably eating the large amount of K+ in natural foods.

In a recent study we explored the possibility that adding K+ supplements to the diet would reduce the renal lesions in hypertensive, salt-fed Dahl salt-sensitive rats (DS). They were fed a standard Purina chow with 4% added NaCl for 24 weeks. This diet produced the expected hypertension and the expected lesions in the tubules and arterioles of the kidney. Several rats also had 1.36% K+ added to the diet over the entire 24 weeks of the study. The addition of K+ did not lower the blood pressure; however, renal tubular lesions in the renal cortex were reduced by 50%, in the outer medulla by 30%, and in the inner medulla by 44%. Thus, the addition of K+ provided a protective effect of major proportions against renal tubular lesions without lowering the blood pressure. Furthermore, the hypertension had produced the expected 38% thickening of the walls of the renal arterioles, but when K+ supplements were added to the diet (1.36% added K), the thickness of the arteriolar walls was reduced by 20 to 30% even though the blood pressure was not lowered.

If renal arteriolar lesions could be greatly reduced with K+ supplements, then other hypertensive arterial lesions also might be favorably affected by extra dietary K+. Stroke prone spontaneously hypertensive

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rats (SHRSP) acquire cerebral arterial lesions quite readily, along with their severe hypertension, and these lesions frequently lead to strokes from cerebral hemorrhage or from cerebral infarction. Strokes develop more readily in SHRSP if there is extra NaCl in the diet and if they are fed a Japanese type of rat chow rather than an American type of rat chow. Strokes also develop quite readily in DS fed this diet. These studies were done to determine whether dietary supplements of K+ would protect SHRSP and DS against death from strokes.

Methods

Study I

Male, 6-week-old SHRSP from our breeding colony were fed a Japanese type of chow (designed by Dr. J. Knappka of the National Institutes of Health) for 17 weeks. This basic diet contains 0.75% K+, and up to 4% NaCl was added to the basic diet to increase the likelihood of strokes. This basic diet containing 4% NaCl was fed to 74 SHRSP. 24 of these rats received only this basic diet with no added K+, while 26 SHRSP received this same diet plus 1.36% K+ in the form of KCl (final K+ concentration, 2.11%). The remaining 24 SHRSP received the basic diet plus 1.36% K+ in the form of K+ citrate (final K+ concentration, 2.11%). The K+ citrate was used in one of the diets because K+ in ordinary foodstuffs is rarely present as KCl. Systolic blood pressures were taken on all rats after 6 weeks on the diets, with the microphonic meth-

Study II

The same type of feeding experiment was carried out in three groups of DS. All the rats received the Japanese type of chow supplemented with 4% NaCl between 3 and 5 weeks of age and with 8% NaCl thereafter. The 33 Dahl S rats of Group I (n = 33) received the basic diet without any added K+. The 22 rats of Group II received this same diet plus 1.36% K+ in the form of KCl. The 23 rats of Group III received the basic diet plus 1.36% K+ in the form of K+ citrate. The three diets were continued for 9 weeks. Blood pressures were taken on all rats after 6 weeks on the diets.

Study III

A second batch of SHRSP was fed the three diets described in Study I for 5 months. The K+ supplements were withheld from 28 and administered to 36 SHRSP. At the end of this feeding period, the brain was examined in every surviving rat for evidence of spots of cerebral hemorrhage.

Statistics

Statistics were performed with Hill's method of statistical evaluation of the differences between proportions. Briefly, the standard error of the difference between two proportions is divided by this standard error, the resulting quotient (similar to a t value) provides an estimate of the likelihood that the difference is or is not due to chance. A quotient of 2 indicates a p value of approximately 0.05. In Studies I, II, and III, the main t values were all greater than 5.0. The standard error of the difference between means was used for comparisons of blood pressure in various groups.

Results

Study I

After 17 weeks on the three Japanese diets with each diet containing 4% NaCl, 20 of the 24 SHRSP rats in the group with no added K+ had died, an 83% mortality. During this same period, 49 of the 50 rats on the same diet plus 1.36% K+, were still alive and showed no evidence of a nonfatal stroke. One rat died in the final week, which gave a 2% mortality for the K+-supplemented groups. Because the two diets with K+ supplements had comparable effects on weight, blood pressure, and mortality, the rats receiving these types of K+ salts were combined into one group for comparison purposes. The results are striking: 83% of the rats on the diet with no added K+ died, while only 2% of the rats with the 1.36% added K+ died. This 98% reduction in mortality was highly significant (p < 2 x 10^-1; Figure 1). After 6 weeks on the diets, the blood pressure of the 20 surviving SHRSP on the diet with no added K+ averaged 233 mm Hg, while the average blood pressure of the 50 rats on diets with 1.36% added K+ was 187 mm Hg, a 46 mm Hg decrease (p < 0.0001). Thus, the K+ supplements significantly reduced blood pressure in the SHRSP. The K+ supplements also appeared to reduce the death rate for a given level of hypertension. For example, the 11 SHRSP with the highest blood pressure among the 50 rats in the K+-supplemented groups and the 11 SHRSP with the lowest blood pressure among the 20 rats with no added dietary K+ had the same average systolic blood pressure (212 mm Hg). Thus, although these two groups had virtually equal average blood pressures of 212 mm Hg, the group of 11 K+-supplemented rats had only one death (9% mortality) while the group of 11 rats without K+ supplements had seven deaths (64% mortality). In these two groups, very closely matched for blood pressure, the 86% decrease in mortality, 64% versus 9%, was significant (p < 0.003; see Figure 1). This difference indicates that K+ supplementation in SHRSP was very effective in preventing death even though blood pressure was almost identical in the two groups being compared.
Figure 1. Mortality of hypertensive SHRSP on either normal or high dietary NaCl intake (A, B). The actual final concentration of NaCl in each diet is listed. BP = blood pressure.

Muscle Urea Studies

Postmortem urea concentrations in dried skeletal muscle were measured to determine whether uremia was the cause of death in the SHRSP of Study I. The average muscle urea concentration in 12 "normal" dead rats was 91 mg per decagram dry weight. Twenty-eight hours after bilateral nephrectomy in 12 other rats, the highest muscle urea level was 91 mg per decagram dry weight. All of these rats were very lively 2½ days before their expected demise from bilateral nephrectomy. Among the 24 SHRSP that did not receive NaCl supplements and eventually died, only 22 had a muscle urea level above 91; 1 rat had a level of 120 mg per decagram dry weight and 1 had a level of 99 mg per decagram dry weight. These two levels were not high enough to signify a fatal uremia. As the other 22 SHRSP had average muscle urea levels of 54 mg per decagram dry weight, uremia apparently was not the cause of death.

Study II

After 9 weeks on the high NaCl diets, 18 of 33 DS with no NaCl supplement had died (55% mortality), while only 2 of 45 DS with 1.36% NaCl supplements had died (4% mortality; Figure 2). This 93% reduction in mortality rate, 55% versus 4%, was significant (p < 10^-6). Although a previous study found that K+ supplementation did not reduce the blood pressure of DS on a 4% NaCl diet, we found that it did effect a modest reduction in blood pressure in the DS on an 8% NaCl diet. In the 33 rats of Group I (no added K+) the systolic blood pressure averaged 214.5 ± 4.1 mm Hg (mean ± SEM). In the 22 rats of Group II (1.36% added K+, as KCl), the blood pressure averaged 198.5 ± 3.3 mm Hg. In the 23 rats of Group III (1.36% added K+, as K+ citrate), the blood pressure averaged 202.7 ± 4.5 mm Hg. The average blood pressure in Group II rats supplemented with KCl was 16 mm Hg lower than that of Group I rats (p < 0.005), while the average blood pressure in Group III rats supplemented with K+ citrate was 12 mm Hg lower than that of Group I (p < 0.06).

This modest reduction of blood pressure in the K+-supplemented groups could explain some of the lowering of mortality in these groups. Again, however, it is possible to remove the effect of this reduction of blood pressure and still be able to analyze the influence of K+ supplements on mortality. For example, among the 33 DS not receiving K+ supplements, the average blood pressure of the 21 with the lowest blood pressures was 205 mm Hg. Among the 45 DS that did receive K+ supplements, the 39 Dahl rats with the highest blood pressure also had an average blood pressure of 205 mm...
Hg. In these two groups of DS with very closely matched blood pressures, the mortality was 38% (8 of 21) in the group with no K⁺ supplement and 5% (2 of 39) in the group with K⁺ supplementation (see Figure 2). This 87% reduction in mortality rate was significant ($p < 0.001$). ¹⁰

**Study III**

In the second batch of SHRSP, after 22 weeks of the diets, 18 of 28 rats had died in the group with no added K⁺, a 64% mortality. In contrast, only 2 of 36 SHRSP receiving K⁺ supplements had died, a 5.6% mortality. This finding represents a 91% reduction in mortality ($p < 10^{-6}$; Figure 3). ¹⁰

Spots of brain hemorrhage were sought among the survivors in this group of SHRSP. In the group of 10 survivors not receiving K⁺ supplements, 4 of 10 had spots of cerebral hemorrhage, a 40% incidence. Among the 34 survivors in the SHRSP that received K⁺ supplements, none had spots of cerebral hemorrhage. Thus, K⁺ supplementation was associated with a striking reduction in the incidence of cerebral hemorrhage ($p < 0.0001$). ¹⁰

**Discussion**

In both SHRSP and DS, the addition of either KCl or K⁺ citrate strikingly reduced the death rate (see Figure 3). This marked reduction occurred even when blood pressure was virtually equal in the two groups being compared. These K⁺ supplements reduced blood pressure considerably in SHRSP and modestly in DS, and these reductions undoubtedly contributed to the lower death rate. The reduction in pressure would lessen the tension in the walls of the cerebral arteries and would therefore be expected to reduce the tendency to arterial lesions and strokes. This is undoubtedly a partial explanation for the remarkable protective effect of the K⁺ supplements. The SHRSP did not die of uremia and did not exhibit the ascites and edema of congestive heart failure. They often suffered a hemiplegia during the 14 days before death. It is likely that the majority of these deaths were due to a stroke, either a rupture or a closure of a cerebral artery, caused by hypertensive lesions in the artery. Extra K⁺ in the diet appeared to greatly reduce the incidence of these lesions, even when blood pressure was quite similar in the groups being compared. This finding could explain the total absence of cerebral hemorrhage spots in the survivors of the second batch of K⁺-supplemented SHRSP (Study III) and the 40% incidence of cerebral hemorrhage spots in the surviving SHRSP that received no added K⁺. Moreover, if the 10 survivors had a 40% incidence of brain hemorrhage, it is quite likely that the 18 dead rats had an even higher incidence. The extra K⁺ in the diet appears to allow the cerebral arteries to carry a high arterial pressure without sustaining

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**Figure 3.** Cumulative percent survival of the rats on either normal or high K⁺ diets in Studies I, II, and III.
much damage. These results strongly imply that K+ supplements in SHRSP reduce the incidence of cerebral hemorrhage.

The mortality in the DS receiving 8% NaCl was quite high in this study. Werber et al. observed a similarly high mortality in DS: 50% were dead after 74 days of feeding a Japanese-style chow containing 8% NaCl, and 78% had sustained a stroke, either a cerebral hemorrhage or a cerebral infarct. Meneely and Ball also reported a significantly reduced death rate in Sprague-Dawley rats fed 5.6% NaCl, which occurred when 1.2% K+ was added to the 5.6% NaCl diet. This study was a 2½-year feeding experiment, and the 50% survival rate was 7.4 months longer in the K+-supplemented rats — 26.9 months versus 19.5 months in the control rats. The mortality was much lower in these control rats than in ours, which suggests that the added K+ prolonged life mainly by reducing renal lesions.

In another study, Gordon and Drury produced renal hypertension in rabbits, which caused a mesenteric vascular disease with many tiny hemorrhages in the mesentery. Supplements of K+ in these rabbits did not reduce the blood pressure but greatly reduced the small hemorrhages in the mesentery, which suggests a partial prevention of some of the mesenteric vascular lesions.

The precise mechanism by which extra dietary K+ reduces deaths is as yet elusive. Moderately severe hypertension can cause rents and irregularities in a stretched, tense arterial endothelial layer, which increase the permeability of the endothelial lining. Such endothelial irregularities in cerebral arteries can ultimately produce strokes. The high K+ diet may preserve the integrity of endothelial cells even when they are under great tension from high blood pressure. Studies are under way to confirm or deny this possibility.

The percentage of K+ in the K+-supplemented rat diets was similar to that in a human hunter-gatherer diet and most likely similar to that of prehistoric humans and mammals. The type of food processing that we take for granted results in a K+ intake among U.S. whites only a third that of a hunter-gatherer. Scots and southeastern U.S. blacks have one-sixth the daily K+ intake of a hunter-gatherer. Thus, civilization has greatly lowered our dietary K+. In addition, U.S. blacks have 18 times more hypertensive renal failure than U.S. whites, and they also have a substantially lower K+ intake. People in Mississippi, Alabama, and Georgia have the highest death rate from strokes and the lowest K+ intake in the United States. Moreover, virtually no evolutionary adaptation to the modern low K+ diet would occur because its bad effects on health mainly show up after the procreative years have ended. A return toward the high K+ levels of prehistoric cuisine might well diminish these high rates of stroke and hypertensive renal failure. As this study indicates, the added dietary K+ appears to retard the development of lesions in cerebral arteries exposed to high arterial pressure.

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References

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