How does potassium supplementation lower blood pressure?

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TO THE EDITOR: Hypertension is one of the most common diseases in the United States, not easily controlled with medication, and its sequela are among the most common causes of mortality. Interestingly, hypertension is found mainly in industrialized societies, with very low prevalence in isolated societies. Anthropological and epidemiological studies suggest the decrease in the dietary K:Na ratio that occurs as people move from isolated to industrialized societies is a key culprit. The dietary intake of K:Na is 150 mmol K:30 mmol Na (K:Na = 5) in isolated people and 50 mmol K:250 mmol Na (K:Na = 0.2) in Western societies that consume prepared foods high in Na and drastically less fruits and vegetables high in K (1, 9). Two interventional studies have varied dietary Na and K in humans and found remarkable beneficial effects of increasing the K:Na ratio on blood pressure (BP) and cardiovascular disease endpoints. The “DASH diet” study (2) challenged groups of nonhypertensive adults with varied Na intake (from 65 to 142 mmol/day) and then evaluated the effects of adding a diet rich in fruits and vegetables and low-fat dairy (K~120 mmol/day). The study found that the rise in BP for a given increase in Na intake was significantly blunted by the DASH diet after just a couple of weeks. In another study, conducted in Taiwanese Veterans retirement homes (men 75 ± 7 yr old) (4), 50% of the NaCl was replaced with KCl in half of the kitchens. After 31 mo, cardiovascular disease mortality was reduced 41% in the elderly veterans receiving the K supplemented salt. Based on these limited studies, the American Heart Association (AHA) and Institute of Medicine (IOM) recommend lowering dietary Na to no more than 100 mmol/day and while the AHA states that “the dearth of dose-response trials precludes a firm recommendation for a specific level of K to lower BP” (2), the IOM recommends raising K to 120 mmol/day based on what was consumed in the DASH diet study.

There are also classic basic research studies in rodents that complement the DASH and Taiwanese studies: Dahl (6) reported that feeding hypertension-prone rats with 4.5% NaCl and an increasing amount of KCl from 0.57 to 5.74% decreased systolic BP from 169.9 to 137.4 mmHg, and Ganguli and Tobian (7, 10) reported that mortality of spontaneously hypertensive rats fed 8% NaCl diet was reduced from 90 to 5% when dietary K was raised from 0.5 to 2.1%. Many beneficial properties of high K intake have been reported (reviewed in Refs. 1 and 5), including vasodilation, increased GFR, and decreased renin, renal Na reabsorption, reactive oxygen species production, and platelet aggregation. Nonetheless, the molecular mechanisms responsible for the significant effects of raising the dietary K:Na ratio on BP and cardiovascular disease mortality remain to be clearly elucidated.

In 2007, Carlstrom and colleagues (3) developed a very useful model of salt-sensitive hypertension in which young rats are uninephrectomized (uNx) then subsequently fed a 3% NaCl diet (HS) for 3 wk. This protocol raises mean arterial pressure to 145 ± 8 mmHg. In a recent paper published in the American Journal of Physiology-Renal Physiology, Jung et al. (8) used this model (uNx+HS) to explore the molecular mechanisms responsible for the BP-lowering effects of potassium supplementation. In their hands, systolic BP rose to 208 ± 6 mmHg in uNx+HS and was reduced to 180 ± 2 mmHg in uNx+HS rats that are provided with 1% KCl in the drinking water (uNx+HS+KCl) for 3 wk. Their study aimed to evaluate the underlying mechanisms of the antihypertensive effect of K supplementation by determining the effects on renal ion transporter abundance. The purpose of this Letter to the Editor is to addresses a number of unexpected findings in the Jung et al. study (8) that warrant clarification, correction or further scrutiny.

1) The key variable in this study was potassium intake, yet the intake of KCl is not provided. Rats were given 1% KCl in the drinking water. The amount consumed can be estimated from FεK (Table 1 in Ref. 8), which is increased five- to sixfold over that measured in rats fed 0.82% K chow. Thus the reader can infer that the rats with 1% KCl in the water consume the equivalent of 5% K, the equivalent of 10% KCl chow, along with the 3% NaCl in the diet. Providing a measure of actual intake would have been preferable. Along the same lines, providing kidney weight in the two groups would provide a measure of the impact of K supplementation on the renal hypertrophy occurring after uNx.

2) The study uses immunoblots to estimate Na-K-ATPase α-subunit expression and concludes that when rats are K supplemented (uNx+HS+KCl), α abundance decreases to ~10% of the levels measured in the uNx+HS. In addition to the near disappearance of Na-K-ATPase, α (a 100-kDa protein) is indicated to run between 50 and 60 kDa. The reader is left to ponder how a kidney can still effect transepithelial transport with only 10% of its sodium pumps, and if they are looking at α between 50 and 60 kDa.

3) The changes in apical Na transporter proteins in uNx+HS+KCl, detected by immunoblot, are also unexpectedly large compared with that routinely reported in response to altered dietary electrolytes: apical NHE3 decreases >75% and NCC decreases >90%, while NKCC increases to 400% of that observed in the uNx+HS group. In comparison, Vallon et al. (11) have reported that a 5% K diet suppresses the Na+-2Cl− cotransporter (NCC) in normal mice with two kidneys by ~40%.

4) By immunohistochemical (IHC) analysis in this study, Na+/H+ exchanger 3 labels long stretches of tubule rather than round lumens with tall microvilli typically observed in proximal tubules; these are quite unlikely to be proximal tubules. The IHC of NCC is not particularly informative, and IHC of the Na+-K+-2Cl− cotransporter is not provided.

5) Jung et al. (8) conclude that “the downregulation of NHE3 and NCC may contribute to the blood pressure attenuating effect of dietary potassium associated with increased...
sodium excretion.” However, despite the >75% suppression of Na-K-ATPase, NHE3, and NCC, there was no “increase in sodium excretion” as urine volume and FENa were not significantly increased by K supplementation at 3 wk.

6) Wade et al. (12) recently reported that feeding normal mice with two kidneys a 10% KCl diet, equivalent to the calculated K intake in this study, increased ROMK abundance threefold (at 1 wk) to ninefold (at 3 wk) in the uNx+HS+KCl group.

It is evident that the Carlstrom model of salt-sensitive hypertension generated by uninephrectomy plus a high-salt diet may be appropriate to investigate the BP-lowering effects of K supplementation. While it may turn out that uninephrectomy amplifies the magnitude of changes provoked by a high K intake, this study fails to provide a clear and quantitative explanation for how K loading reduces BP in the uNx model of salt-sensitive hypertension. A more compelling case for these large changes in Na transporter abundance could be made by analyzing a full sample volume alongside a half-sample volume on the same blot to validate that the amount of protein analyzed is in the linear range of the detection system (e.g., renal Na-K-ATPase α-subunit is linear at <1 μg/lane). Similarly, actin is not a useful loading control in the kidney because it is in the linear range at <1 μg/lane. A measure of ouabain-sensitive Na-K-ATPase activity would have been an excellent complement to validate that the amount of protein analyzed is in the linear range of the detection system (e.g., renal Na-K-ATPase α-subunit is linear at <1 μg/lane). Similarly, actin is not a useful loading control in the kidney because it is in the linear range at <1 μg/lane. A measure of ouabain-sensitive Na-K-ATPase activity would have been an excellent complement to validate that the amount of protein analyzed is in the linear range of the detection system (e.g., renal Na-K-ATPase α-subunit is linear at <1 μg/lane).

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