Reinterpreting Sodium-Potassium Data in Salt-Sensitivity Hypertension: A Prospective Debate

To the Editor:

The relationship between sodium and potassium (K) ions in hypertension has attracted the interest of the scientific community for almost a century, and sodium-sensitivity hypertension has been an outstanding part of this investigation.

In a recent review article of Hypertension, Aviv et al. present a model suggesting that a major cause of sodium sensitivity in African-Americans is an augmented activity of Na-K-2Cl cotransport in the thick ascending limb of Henle’s loop. Since irrefutable evidence for this hypothesis does not exist, the authors proposed that racial differences in urinary excretion of K and response to diuretics are critical points. However, there are 2 major points that deserve consideration. First, the Na-K-2Cl cotransport is an obligatory, coupled transport for all 3 co-ions on the side of the membrane from which the flux originates (termed the cis-side), where any of the cotransported ions, for example, Cl, rapidly increase the net and unidirectional fluxes of Na and K. Thus, if such hypothesis involves an increased reabsorption of Na-K-Cl ions, how could it explain that a greater K delivery to the thick ascending limb of Henle’s loop? Since there is not a physiological mechanism for renal K transport in humans increases potassium delivery to the thick ascending limb of Henle’s loop, since irrefutable evidence for this hypothesis does not exist, the authors find it difficult to reconcile such observations with a sodium sensitivity hypertension?3

Second, it is clear that the lower urinary excretion of K in blacks has been universally related to a relative deficient K diet, basically because there is not a physiological mechanism for renal K conservation in the presence of normal K balance.4 In this way, any different hypothesis should first explain how the phosphorylation of a tyrosine molecule that inactivates the secretory K channel in a low K-diet5 would do the same in the presence of normal K intake, peritubular K concentration, and normal cell K. However, the authors find it difficult to reconcile such observations with a systemic K deficit in African Americans on the basis that their total body K (TBK) is higher (Table 1, Reference 41 of Aviv et al.). Unfortunately, the data of He et al have probably confused most readers as well as Aviv et al, since it included unmatched height-weight ethnic groups. In fact, TBK is almost identical in black and white males (3889 ± 684 versus 3867 ± 621 mmol), the former being heavier (80.7 ± 14 versus 78.9 ± 13 kg); and higher in black females (2506 ± 446 versus 2426 ± 372 mmol) solely in the basis of more body weight (75.3 ± 7.2 versus 63.9 ± 6.9 kg). Such differences in weight, if expressed as body cell mass (BCM kg TBK mmol/108.6, =30% to 42% of males weight) certainly explain the differences in TBK. Indeed, predictive TBK is based on age, height, and weight (a = H ^ 15 \cdot V ^ 1).6

Although this relationship between TBK in sodium-sensitivity hypertension has never been analyzed, it is interesting to note that blacks have the greater decline in TBK with age after 30 years (in Reference 41) and exhibit a decreased tolerance to an intravenous K load, despite no differences in serum K, urinary K excretion, and plasma renin activity, compared with their white peers.7 These studies and our findings of a decreased TBK, RBC K content, and transtubular K gradient in hypertensives compared with their normotensive control, regardless of sex, age, or race,8 support a new search on the mechanisms for TBK declining with age (0.23 to 0.26 mmol/kg per year),9 and those affecting TBK in hypertension. In conclusion, this is a very interesting article by Aviv et al, albeit the hypothesis of sodium sensitivity of blood pressure might be better addressed as the genetic differences in potassium and sodium handling at different tubular sites, cellular electrolyte transports, and body K-Na content.

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Urinary Potassium Excretion and Sodium Sensitivity in Blacks (Response: Reinterpreting Sodium-Potassium Data in Salt Sensitivity Hypertension: A Prospective Debate)

Dr Delgado-Almeida1 raises a number of important issues, which we wish we had given greater emphasis in our article. Here are our responses.

Delgado-Almeida’s first major concern is that the Na-K-2Cl cotransport is “an obligatory, coupled transport for all 3 co-ions.” Thus, he questions whether potassium supplementation may enhance the activity of the Na-K-2Cl cotransport by increasing potassium delivery to the thick ascending limb of Henle’s loop, the locale of the transporter. This, in turn, would result in sodium and chloride retention. The ultimate regulation of potassium excretion rests in the distal tubules/collection ducts. It is this region where the extrusion of K into the tubular lumen would increase to maintain potassium balance in the face of “excess” potassium intake. Even if it turned out that potassium supplementation in humans increases potassium delivery to the thick ascending limb of Henle’s loop, sodium and chloride transport systems situated distally are likely be downregulated as an adaptive response.

Delgado-Almeida queries why drugs such as furosemide and bethanidine—potent inhibitors of the Na-K-2Cl cotransport—
have not been recommended to treat the sodium-sensitive type of essential hypertension by the Seventh Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure? We suspect that not recommending these agents has to do with the limited information derived from large-scale clinical trials about their chronic use to treat hypertension.

Delgado-Almeida indicates that the black-white differences in urinary excretion of K have been “universally” attributed to the consumption of a potassium-deficient diet by blacks. In our article and its predecessor, we underscored that neither salt sensitivity nor potassium homeostasis fits neatly into black-and-white boxes. We really do not know the cause of the lower urinary potassium in blacks versus whites, though unfortunately, without the stringency of evidence, this phenomenon has been attributed to lower potassium intake in blacks than whites. On carefully reviewing what had been known about this subject, we concluded that the jury was still out on this matter. In our view, it may well be that in some geographic regions and, perhaps, depending on socio-economic status, blacks consume less potassium than do whites. But it is highly unlikely that this holds for blacks everywhere and across socio-economic strata, because multiple investigators throughout the world have documented the lower urinary potassium excretion in blacks than whites.

We propose that under steady state and assuming equivalent potassium losses in blacks and whites via sweat and respiration, if on similar diets blacks excrete less urinary potassium, they must excrete more gastrointestinal (GI) potassium than do whites. In further support of the idea that it is unlikely that as a group, all blacks consume less potassium than whites, we have stated in our article: “It is difficult to reconcile such observations with the idea that the lower urinary potassium excretion in blacks is caused by a chronic systemic deficit in potassium, particularly in light of a recent study showing that the total body potassium, primarily reflects muscle mass, is actually higher in blacks than in whites until the ninth decade of life.” Delgado-Almeida argues that in the study that we cited blacks were heavier than whites, thereby explaining why blacks exhibited higher total body potassium than whites. We note, however, that the data (Table 2 in the cited article) were adjusted for both weight and height.

Delgado-Almeida proceeds to cite an article published after the publication of our model. In this article Suh et al examined the effect of acute intravenous (IV) infusions of KCl on serum potassium levels and urinary potassium excretion over a 3.5-hour period. These IV infusions were performed twice: once while subjects were on their habitual diets and once after 10 days on an equivalent diet.

On their habitual diet, blacks excreted less of the IV potassium load than whites within the 3.5-hour period. After 10 days of the same dietary intake for both racial groups, when the acute IV loadings were repeated, there were no statistical differences between blacks and whites in the 3.5-hour excretion of the potassium IV load. Thus, it appears that indeed, the lower urinary potassium excretion in blacks during baseline potassium load stunningly reflected a lower habitual potassium intake in blacks than whites. Yet the story does not end here, as the serum potassium levels in response to the potassium IV infusion provide compelling evidence in support of black-white differences in potassium handling.

What Suh et al observed was that both on their habitual and after 10 days of equivalent diets, the rise in the serum potassium during and post KCl infusion was consistently higher in blacks than in whites. The authors suggest that these findings are indicative of a slower rate of potassium “disposal” in blacks than whites—a phenomenon which “does not appear to be secondary to racial differences in the antecedent diet.” (Delgado-Almeida characterizes these findings as decreased “tolerance” of blacks to an IV potassium load.) The authors are not certain as to the underlying reason for their findings, but suggest that the slower potassium “disposal” in blacks than whites was not “solely a consequence of racial differences in renal excretion of K.” They ascribe their findings primarily to retarded skeletal muscle uptake of potassium because of perhaps a lower activity of the Na-K-ATPase in skeletal muscle of blacks. They also suggest the possibility of a higher potassium sequestration in the colon of blacks than whites, though they attribute less importance to this route of potassium “disposal.”

The urine collected in this study was through spontaneous voiding, so unfortunately, the authors could not determine whether blacks lagged behind whites in the rate of urinary potassium excretion, even though the overall potassium excretion during the course of the 3.5-hour period after 10 days of an equal diet did not differ statistically between the 2 racial groups. Diminished skeletal muscle Na-K-ATPase activity, as proposed by the authors, might provide a viable explanation for the finding. However, potassium excretion in the distal tubules/collection ducts is mediated in large measure via potassium uptake through the Na-K-ATPase on the baso-lateral side and its extrusion down its electrochemical gradient on the apical side. Reduced Na-K-ATPase activity in the baso-lateral side may hence retard the renal excretion of potassium load, if Na-K-ATPase is uniformly reduced in all tissues of blacks than in whites, as speculated by Suh et al.

Regardless of the etiology for the findings reported by Suh et al, the fact remains that to excrete an equivalent urinary excretion of an IV potassium load, blacks resort to a greater rise in the extracellular potassium than whites. Given that food is consumed episodically, it is rather unlikely that an oral potassium load absorbed during a meal and post-perennially will raise the serum potassium as swiftly as that of the same load administered via a rapid IV infusion. In principle, however, blacks would lag behind in the urinary potassium excretion, so that an increase in potassium disposal via the GI tract may keep them in balance. At bottom, the racial differences in potassium excretion and the expression of salt sensitivity are not facile issues to parse. In crafting our model we resorted both to clinical observations and evolutionary arguments, neither of which is grounded in indisputable evidence. Thus, our model simply provides the framework for dialogue and scientific inquiry. In this spirit, we thank Delgado-Almeida for his interest and the contribution to keeping the discussion active.

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