The following is the abstract of the article discussed in the subsequent letter:

Choi, Cheol S, Curtis B. Thompson, Patrick K. K. Leong, Alicia A. McDonough, and Jang H. Youn. Short-term K⁺ deprivation provokes insulin resistance of cellular K⁺ uptake revealed with the K⁺ clamp. Am J Physiol Renal Physiol 280: F95–F102, 2001; 10.1152/ajprenal.00174.2001.—We aimed to test the feasibility of quantifying insulin action on cellular K⁺ uptake in vivo in the conscious rat by measuring the exogenous K⁺ infusion rate needed to maintain constant plasma K⁺ concentration ([K⁺]) during insulin infusion. In this “K⁺ clamp” the K⁺ infusion rate required to clamp plasma [K⁺] is a measure of insulin action to increase net plasma K⁺ disappearance. K⁺ infusion rate required to clamp plasma [K⁺] was insulin dose dependent. Renal K⁺ excretion was not significantly affected by insulin at a physiological concentration (~90 μU/ml, P > 0.05), indicating that most of insulin-mediated plasma K⁺ disappearance was due to K⁺ uptake by extrarenal tissues. In rats deprived of K⁺ for 2 days, plasma [K⁺] fell from 4.2 to 3.8 mM, insulin-mediated plasma glucose clearance was normal, but insulin-mediated plasma K⁺ disappearance decreased to 20% of control, even though there was no change in muscle Na-K-ATPase activity or expression, which is believed to be the main K⁺ uptake route. After 10 days K⁺ deprivation, plasma [K⁺] fell to 2.9 mM, insulin-mediated K⁺ disappearance decreased to 6% of control (glucose clearance normal), and there were 50% decreases in Na-K-ATPase activity and α2-subunit levels. In conclusion, the present study proves the feasibility of the K⁺ clamp technique and demonstrates that short-term K⁺ deprivation leads to a near complete insulin resistance of cellular K⁺ uptake that precedes changes in muscle sodium.

Extrarenal Potassium Transport

To the Editor: The paper by Choi et al. entitled “Short-term K⁺ deprivation provokes insulin resistance of cellular K⁺ uptake revealed with the K⁺ clamp” (Am J Physiol Renal Physiol 280: F95–F102, 2001) suggests that quantifying the potassium given to maintain the plasma potassium stable is a useful new technique for evaluating extrarenal potassium transfer into muscle during hypokalemic conditions. I think there may be a significant problem with this approach.

During saline loading alone, plasma potassium remains stable but K⁺ excretion is approximately 500 μeq (Fig. 2), thereby suggesting that the potassium that enters the urine has derived from potassium efflux from muscle. Similarly, during insulin infusion in normal rats undergoing the potassium clamp, excretion is about 600 μeq (Fig. 2), and this potassium presumably derives from potassium efflux from muscle in the face of potassium influx into muscle from the administered insulin. Consistent with this interpretation is my calculation that the administered potassium during this period is about 600 μeq. In potassium-depleted rats, potassium excretion must be quite low (data not shown). Thus the decrease in administered potassium in the potassium-depleted rats receiving insulin and the potassium clamp may be consequent to the fact that potassium excretion is low. A fall in plasma potassium with modest potassium depletion (2 days) may reflect a decreased efflux of potassium from muscle, which in turn signals the kidney not to excrete potassium.

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REPLY

To the Editor: We are pleased to have the opportunity to clear up misconceptions about our new technique for the quantification of insulin’s action on cellular K⁺ uptake in vivo (the K⁺ clamp). Dr. Thomas Kahn proposes that the decrease in K⁺ infusion rate during insulin infusion in K⁺-depleted rats is consequent to the low K⁺ excretion in this condition, rather than reduced action of insulin to stimulate cellular K⁺ influx. Dr. Kahn is correct that during saline infusion (in the postabsorptive state) urinary K⁺ excretion rate is derived from and equivalent to K⁺ efflux rate from intracellular fluid, which is mainly muscle. However, this simple equilibrium is disrupted during the hyperinsulinemic K⁺ clamp, in which exogenous K⁺ infusion is used to maintain constant plasma K⁺ concentration ([K⁺]) to balance insulin-stimulated cellular K⁺ uptake. We do not think there is any support for the notion that urinary K⁺ excretion determines or restricts muscle K⁺ efflux or insulin’s action to stimulate cellular K⁺ uptake during K⁺ restriction.

During the K⁺ clamp in control animals, K⁺ infusion was 490 μeq over 150 min, and urinary K⁺ excretion increased 130 μeq (from 510 to 640 μeq, P > 0.05). Thus a small fraction of K⁺ infusion might be due to insulin’s action to increase urinary K⁺ excretion. As we reported, K⁺ excretion during the K⁺ clamp is near zero in K⁺-deprived rats. Therefore, a component of the reduction in K⁺ infusion during the K⁺ clamp in K⁺-deprived rats indeed can be attributed to the decrease in renal K⁺ excretion. However, this would account for only 20–25% of the 85–95% drop in K⁺ infusion during the hyperinsulinemic K⁺ clamp.

Dr. Kahn proposes that the fall in plasma K⁺ early in K⁺ restriction reflects a decrease in K⁺ efflux from muscle, which signals the kidney to retain K⁺. We do not think it is easy to predict whether K⁺ efflux ini-
creases (due to reduced plasma [K\(^+\)]) or decreases (due to reduced cell [K\(^+\)]) early in K\(^+\) restriction. Regarding this point, our recent experiments (unpublished observations) demonstrate that modest K\(^+\) restriction (to 1/3 normal K\(^+\) in diet) reduces the action of insulin on both cellular K\(^+\) uptake and urinary K\(^+\) excretion, without any change in postabsorptive plasma [K\(^+\)]. Thus there seems to be a mechanism to sense K\(^+\) intake independently of postabsorptive plasma [K\(^+\)] that leads to a concerted regulation of renal and extrarenal mechanisms to maintain extracellular [K\(^+\)]. The K\(^+\) clamp method continues to be a great tool to dissect renal vs. extrarenal components of regulation of K\(^+\) homeostasis.

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