Response to ‘Reemergence of the maxi K\(^+\) as a K\(^+\) secretory channel’


We certainly appreciate the positive comments by Sansom regarding the value of our study in demonstrating a clear role for maxi-K channels in renal K transport in the distal convoluted tubule. We obviously agree with Sansom that our study leaves little doubt that maxi-K channels can contribute to distal K secretion and renal K excretion, especially following adaptation to a high K diet.

K excretion and hypokalemia in individuals with Type II Bartter’s syndrome associated with ROMK mutations is much less severe than in other types of hyperprostaglandin E syndrome where both ROMK and maxi-K channels can contribute to K wasting. The FE\(_K\) of 158% stated by Sansom was from the original ROMK null mouse that exhibited marked hydronephrosis. The Romk\(^{-/-}\) mouse used in our study reported in Kidney International was developed from intercrossing null males for >5 generations to select for high postnatal survival and less hydronephrosis. Clearance results in our Romk\(^{-/-}\) mice indicate that FE\(_K\) is ~50% under control diet conditions which is more in line with the less severe K wasting expected in the absence of ROMK (full details will be reported in a future publication). Thus, a highly exaggerated K secretion in the distal tubule is not a prerequisite for the K excretion observed in our Romk\(^{-/-}\) mice.

In our paper, we proposed that decreased K reabsorption by the loop of Henle as well as continued K secretion via maxi-K channels in the distal convoluted tubule (DCT) contributed to the kaluresis in the ROMK knockout animal. The former mechanism for enhanced K excretion in Romk\(^{-/-}\) mice was based on the experimental observation of an increased free-flow K concentration in early DCT fluid in ROMK knockout, compared to wild-type, mice. The primary issue raised by Sansom was our interpretation of this elevated K concentration. Our conclusion of diminished K reabsorption in the thick ascending limb (TAL) stems from previous in vivo micropuncture-microperfusion studies by us and others. In vivo studies reveal no significant K secretion in the early DCT measured under free-flow and perfusion conditions. Is it possible that the high early distal tubule fluid flow in the Romk\(^{-/-}\) mice activated maxi-K channels that were quiescent in wild-type animals? We think not because latter in vivo studies showed that K secretion in the early DCT was not clearly changed by adaptation to a high K diet or to increased tubule flow rate. In contrast, both maneuvers greatly increased K secretion in the late DCT, the region where we performed the stationary micropuncture experiments that revealed the iberiotoxin-sensitive K secretory pathway in Romk\(^{-/-}\) mice. Given the results from these in vivo studies, it is problematic to invoke K secretion via maxi-K channels as an alternative mechanism to account for the increased free-flow K concentration observed in the early DCT fluid from Romk\(^{-/-}\) mice.

In addition, as we discussed in our paper, the in vivo experiments by Walter et al. using 5 mM barium as a K channel blocker should not be used as a strong argument against the role of apical K channel activity as a requirement for TAL function including net K reabsorption. This is based on our previous study in mouse TAL where a much high concentration of barium (about 20 mM) was required to achieve a nearly complete block of the apical K conductance in the absence of luminal potassium. In addition, it is virtually impossible to eliminate K completely from the tubule fluid at the TAL in the in vivo setting and the presence of luminal K will reduce the blocking effect of barium. Thus, the ROMK KO animal provides the only model we are aware of for analyzing the effect of the absence of apical K channel activity (both 35 and 70 pS channels) on K reabsorption in the TAL.

Regarding the proposed model by Sansom for potassium transport in the absence of apical K conductance, we would like to make the following comment. Key factors required for any remaining K reabsorption by the TAL are the functional activity of apical Na-K-2Cl cotransporter, the basolateral Cl channel and the intracellular Cl\(^-\) activity. These transporters are under complex regulation and their activities cannot be deduced with certainty in the condition where there is no apical ionic conductance, basolateral membrane is depolarized and the transcellular–paracellular current circuit is disrupted. Ultimately, this issue may only be resolved by measuring tracer rubidium fluxes in the isolated perfused TAL preparation from Romk\(^{-/-}\) mice.

In conclusion, the lack of significant K secretion in the early DCT in vivo, even under circumstances that would highly activate maxi-K channels, suggests that the most likely explanation for the increased K concentration in
early distal tubule fluid is not K secretion at the early DCT, but rather a reduction in K reabsorption in the TAL.


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Parathyroid hormone synthesis suppression by 25(OH)2 vit D3
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To the Editor: The recent in vitro studies of the Slatopolsky group1 have shown that the ‘non-active’ 25-OH-vitamin D metabolite was actually efficient (even though less potent) at physiological concentration for suppressing parathyroid hormone synthesis by direct stimulation of the vitamin D receptor, and that this direct stimulation was even preponderant over that induced by 1,25(OH) vitamin D3 produced in situ. This is consistent with our earlier reports evidencing (1) in predialysis patients,2 a good long-term control of hyperparathyroid bone disease by just normocalcemic dose of 25-OH-vitamin D in association with up to 2.4 g/day of CaCO3 and (2) in dialysis patients,3 an independent inverse link between parathyroid hormone and 25-OH-vitamin D serum concentrations independently of serum concentrations of calcitriol, calcium, and phosphate.

This challenges the NKF-K/DOQI recommendation for suppressing intact parathyroid hormone >300 pg/ml in dialysis patients, to inject hypercalcemic and hyperphosphatemic dose of calcitriol and paricalcitol, instead of correcting the highly prevalent (87%) vitamin D deficiency in American patients. This correction would decrease the need of ‘active’ vitamin D derivatives for this suppression, while better preventing vascular calcification (in spite of concomitant use of calcium-phosphate binder) as suggested by the comparison of the two cohorts of young adults with childhood-onset of end-stage renal disease, as quoted in our letter to Kidney International about Kalantar-Zadeh article,4 pointing out that the survival benefit granted by paricalcitol was inversely related to its dose.


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Response to ‘PTH synthesis suppression by 25(OH)2 vit D3’

The letter from Shahapuni et al.1 cites our finding that 25-hydroxyvitamin D3 (25(OH)2D3) suppresses parathyroid hormone (PTH) synthesis in cultured parathyroid cells2 to emphasize earlier studies from their group (1) demonstrating the skeletal benefits of improving vitamin D status in chronic kidney disease patients, and (2) the inverse correlation of PTH with 25(OH)D3 but not with calcitriol in dialysis patients, relationships that have also been documented in the general population.3

In response, we feel it necessary to clarify two points in the letter. First, the authors incorrectly state that our data showed that 25(OH)D3 produced a greater decrease in PTH than calcitriol. In fact, the maximal reduction in both PTH secretion and PTH mRNA was not different. Second, the K/DOQI guidelines do not recommend injecting hypercalcemic or hyperphosphatemic doses of calcitriol or its analogs as stated in the letter. The algorithms clearly state the target ranges for plasma Ca and P and suggest modifications when they are exceeded.

The K/DOQI guidelines recommend ergocalciferol supplementation in predialysis patients with 25(OH)D3 levels less than 30 ng/ml but as Shahapuni et al. point out,