K^+–Mediated Regulation of Distal Convoluted Tubule Na/Cl Cotransporter Phosphorylation During Angiotensin II–Induced Hypertension

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The thiazide-sensitive Na/Cl cotransporter NCC mediates NaCl reabsorption by the distal convoluted tubule (DCT) playing an important role in Na homeostasis and blood pressure regulation. In addition, the DCT is involved in maintaining K^+ homeostasis by controlling the amount of K^+ secreted into the lumen through the apical channel ROMK (renal outer medulla K^+ channel).[1]

NH_2-terminal NCC phosphorylation by SPAK (STE20-related proline–alanine rich kinase) kinases is known to stimulate NCC activity. It is well established that chronically elevated angiotensin II (Ang II) increases NCC phosphorylation, and this thought to be mediated in part by activation of SPAK kinases. Several lines of evidence indicate that WNK (with-no-lysine kinase) kinases are upstream of SPAK and involved in Ang II–induced stimulation of NCC phosphorylation. However, recent data point to an important role of plasma potassium in the regulation of NCC phosphorylation that may override NCC regulation by hormones and dietary salt. For example, acutely increasing plasma K^+ in rats decreased NCC phosphorylation.[2] Terker et al[3] later showed that feeding mice with low dietary K^+ increased NCC phosphorylation and overrides the inhibition caused by high dietary salt. More recently, the same group showed that increasing dietary K^+ from 0.05% to 5% in mice, increased plasma K^+ from 2.8 to 4 mmol/L, and decreased NCC phosphorylation and expression.[4] SPAK phosphorylation seems to be required for this process because low-K^+ diet-induced NCC phosphorylation is severely diminished in SPAK-knockout mice.[5] Together, these data suggest that dietary K^+ plays an essential role in modulating NCC phosphorylation through changes in plasma K^+.

The stimulation of NCC phosphorylation by Ang II was shown to be dependent on WNK4 kinase because it was absent in WNK4 knockout mice.[6] However, the mechanism by which Ang II acts in the DCT is not clear, and the relationship between Ang II–mediated NCC phosphorylation and dietary K^+ has not been studied in detail. For example, it is unclear whether a meal containing high-K^+ content is sufficient to affect NCC phosphorylation and to which extent an increase in plasma K^+ is required to decrease NCC phosphorylation. In this issue, Veiras et al[8] studied whether a single meal containing 2% K^+ induced kaliuresis in control or Ang II–induced hypertensive rats. They report that in Ang II–infused rats, fasted overnight, plasma K^+ was lower and urinary K^+ was higher. Interestingly, the high-K^+ meal did not induced kaliuresis despite normalizing plasma K^+. NCC phosphorylation was elevated by Ang II–induced hypertension, but was not decreased by the high-K^+ meal. These data point to a kaliuretic effect of Ang II infusion with potential depletion of overall K^+ stores, which is evident after fasting rats and restored by high-K^+ diet. These data also suggest that it is the kaliuresis not an increase in plasma K^+ that affects NCC phosphorylation. To understand the effect of a chronic high-K^+ diet, rats were fed 1% or 2% K^+ diets and infused with Ang II. The authors describe that Ang II infusion induces kaliuresis in rats fed 1% K^+ diet, and this is tripled in rats fed 2% K^+ diet without any significant changes on plasma K^+. They also found that chronic Ang II infusion increased NCC and SPAK phosphorylation in rats fed 1% K^+; however, doubling K^+ intake (2% K^+ diet) in Ang II–infused rats decreased NCC and SPAK phosphorylation. These effects occurred despite enhanced plasma aldosterone. Different from the effects on NCC, the epithelial Na channel subunits were enhanced by Ang II and not decreased by high-K^+ diet. These data indicate that stimulation of NCC by Ang II during normal K^+ intake could be secondary to a K^+-deficient state induced by Ang II–induced hypertension. Although the mechanisms for this K^+-deficient state induced by Ang II are unclear, these new data suggest that the stimulation of epithelial Na channel in by Ang II induces urinary K^+ secretion, secondary to increased Na reabsorption, and this mechanism stimulates NCC phosphorylation. Recent data[7] show that DCT signaling is sensitive to changes in extracellular K^+ through the actions of the basolateral Kir4.1 (KcnJ10) K^+ channel, such that higher extracellular K^+ inhibits NCC expression and phosphorylation. Thus, together with these studies, these new data by Veiras et al[8] suggest that K^+ provided by rodent diets and urinary K^+ excretion must be carefully assessed in studies of chronic Ang II–induced hypertension. Taken together, this and other recent studies point to an essential role in dietary K^+ as a master regulator of NCC phosphorylation that can override the direct stimulation of the DCT by aldosterone or Ang II.

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Disclosures

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