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Investigation of Pathophysiological Role of Novel Interacting Molecule with Angiotensin II Receptor in Salt Sensitive Hypertension

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Summary

We firstly examined investigate the putative functional role of renal ATRAP in the regulation of blood pressure by salt loading *in vivo*. Since C57BL/6J mice are known to be salt sensitive, we produced transgenic mice dominantly expressing ATRAP in the renal distal tubules on a C57BL/6J background. Although dietary high sodium (4%) loading for 7 days increased systolic blood pressure particularly in the dark period in wild-type mice (day 7 versus baseline, 135.8±3.7 versus 126.3±2.4 mmHg, P=0.027), this increase in blood pressure was suppressed in the renal ATRAP transgenic mice (day 7 versus baseline, 128.4±3.1 versus 127.7±2.9 mmHg, NS) with a concomitant trend of increase in urinary sodium excretion (2.17±0.09 versus 1.83±0.08 mEq/day, P=0.019). Furthermore, the mRNA level and plasma membrane level of the α-subunit of the epithelial sodium channel were significantly decreased in the renal ATRAP transgenic mice. These results demonstrate that distal tubule-dominant overexpression of ATRAP *in vivo* suppresses the salt-sensitive increase in blood pressure, thereby suggesting ATRAP to be a target of interest in the salt-mediated regulation of blood pressure.

To examine further whether the regulation of renal ATRAP expression is related to the development of hypertension and renal injury, we next investigated expression and distribution of human ATRAP in normal kidney and renal biopsy specimens from patients with IgA nephropathy. In the normal human kidney, both the ATRAP mRNA and protein were widely and abundantly distributed along the renal tubules from Bowman's capsule to the medullary collecting ducts. In all renal tubular epithelial cells, the ATRAP protein co-localized with the AT1 receptor. In renal biopsy specimens with IgA nephropathy, a significant positive correlation between ATRAP and AT1 receptor gene expression was observed. There was also a positive relationship between tubulo-interstitial ATRAP expression and the estimated glomerular filtration rate (eGFR) in patients with IgA nephropathy. Furthermore, we examined the function of the tubular AT1 receptor using an immortalized cell line of mouse distal convoluted tubule (mDCT) cells and found that overexpression of ATRAP by adenoviral gene transfer suppressed the angiotensin II-mediated increases in TGF-β production in mDCT cells. These findings suggest that ATRAP might play a role in balancing the renal renin-angiotensin system synergistically with the AT1 receptor by counter-regulatory effects in IgA nephropathy, and propose an antagonistic effect of tubular ATRAP on AT1 receptor signaling.