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Development of New Therapeutic Strategy by Receptor Binding Molecule-Mediated Regulation of Chronic Kidney Disease

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Summary

Angiotensin II type 1 receptor (AT1R)–associated protein (ATRAP) promotes AT1R internalization along with suppression of pathological activation of tissue AT1R signaling. However, the functional significance of ATRAP in renal sodium handling and blood pressure regulation under pathological stimuli is not fully resolved. Here we show the blood pressure of mice with a gene-targeted disruption of ATRAP was comparable to that of wild-type mice at baseline. However, in ATRAP-knockout mice, angiotensin II–induced hypertension was exacerbated and the extent of positive sodium balance was increased by angiotensin II. Renal expression of the sodium-proton antiporter 3, a major sodium transporter in the proximal tubules, urinary pH, renal angiotensinogen production, and angiotensin II content was unaffected. Stimulation of the renal expression and activity of the epithelial sodium channel (ENaC), a major sodium transporter in the distal tubules, was significantly enhanced by chronic angiotensin II infusion. The circulating and urinary aldosterone levels were comparable. The blood pressure response and renal ENaC expression by aldosterone were not affected. Thus, ATRAP deficiency exacerbated angiotensin II–mediated hypertension by pathological activation of renal tubular AT1R by angiotensin II. This directly stimulates ENaC in the distal tubules and enhances sodium retention in an aldosterone -independent manner.