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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 the function of renal tubular angiotensin II type 1 receptor (AT1R)-signaling using an immortalized cell line of mouse distal convoluted tubule (mDCT) cells. AT1R and its associated protein (ATRAP) were expressed endogenously in mDCT cells. Stimulation of mDCT cells with ANG II increased the production of transforming growth factor-β (TGF-β), with increases in mRNA expression of NADPH oxidase 4 (NOX4) and the epithelial sodium channel α-subunit (αENaC) in mDCT cells. These activating effects of ANG II were completely inhibited by an AT1R-specific blocker ARB). Furthermore, overexpression of ATRAP by adenoviral gene transfer suppressed the ANG II-mediated pathologica responses. These results demonstrate the functional significance of renal distal tubular AT1R signaling and the antagonistic effect of tubular ATRAP on this signaling.

To examine further whether the regulation of renal ATRAP expression is related to the development of hypertension and renal injury and therapeutic effects of ARB, we investigated regulatory effects of transient ARB treatment on renal ATRAP expression in salt-sensitive hypertension. Dahl salt-sensitive hypertensive rats (DS rats, 3 wks of age) were divided into three groups for oral administration of vehicle (vehicle group) or ARB either continuously from 6 to 16 wks of age (continuous ARB group) or transiently from 3 to 10 wks of age (transient ARB group) and fed high salt diet from 6 to 16 wks of age. DS rats fed a normal salt diet were used as controls (control group). Not only continuous ARB treatment (SBP 149 ± 9 mmHg) but also transient ARB treatment (SBP 142 ± 7 mmHg) significantly improved hypertension at 16 wks of age with reduction of urinary protein excretion, as compared to vehicle group (SBP 199 ± 15 mmHg). With respect to the regulation of ATRAP expression in the kidney, the renal ATRAP expression was significantly suppressed in vehicle group compared with control group. However, transient ARB treatment as well as continuous ARB treatment significantly recovered the suppressed renal ATRAP expression. These results indicate that the transiently administrated ARB-mediated sustained activation of renal ATRAP expression may play a role in the long-term therapeutic effects of ARB even after withdrawal on hypertension and renal injury in salt-induced hypertension.