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Elucidation of Mechanism of AKI Prevention by Salt Loading - Participation of (Pro)Renin Receptor

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Summary

(Background) (Pro)renin receptor [(P)RR], a trans-membrane receptor for renin and prorenin, is involved in the local activation of renin-angiotensin system (RAS) in the kidney. However, it remains to be determined whether (P)RR plays a role in the development of ischemic acute kidney injury (AKI)**.**

(Methods) We examined the abundance of (P)RR, renin/prorenin, angiotensinogen (AGT), AT_1 receptor (AT_1R), phosphorylation of extracellular signal-regulated protein kinase 1/2 (ERK 1/2) and nuclear factor-κB (NF-κB) by Western blots at 6, 24 and 48 h, and at 7 days after 45-min ischemic injury in rats. Intrarenal angiotensin II (Ang II) levels were determined by radioimmunoassay. We then tested whether the beneficial effects of oral loading of saline solution (1.0% NaCl) for 7 days prior to ischemic injury were associated with changes in RAS components and ERK 1/2 and NF-κB phosphorylation in the kidney. We also examined the effect of AT_1R blocker ~~(ARB)~~, olmesartan, on ischemia-induced changes of (P)RR downstream such as AGT and phosphorylation of ERK 1/2.

(Results) Renal ischemia increased the abundance of (P)RR protein at 24 h, and peaked at 48 h. (P)RR was mainly stained in the connecting tubules and collecting ducts in control rats, while ischemia increased its immunointensity in the damaged proximal tubules. Renal ischemia increased phosphorylation of ERK 1/2 and NF-κB proteins as early as at 6 h. There was a significant increase in AGT and Ang II levels at 24 and 48 h. Prior saline loading prevented the increase in serum creatinine at 48 h (5.36 ± 1.26 vs. 3.38 ± 1.74 mg/dL, $p < 0.05$), and suppressed the increases in renal (P)RR, AGT and Ang II contents. Saline drinking also significantly blocked the ischemia-induced increases in phosphorylation of ERK 1/2 and NF-κB. In contrast, although treatment with olmesartan (10 mg/kg/day) for 14 d suppressed an increase of intrarenal **AGT**, olmesartan did not alleviate ischemic AKI, along with no change of (P)RR and phosphorylated ERK 1/2.

(Conclusions) These findings suggest that increased (P)RR is associated with activation of RAS-independent downstream such as ERK 1/2 and NF-κB phosphorylation in the ischemic kidney.