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Molecular Studies on Clinical Significance of Renal Vasoactive Substances in the Regulation of Salt Metabolism and Renal Microcirculation
—Roles of the Prostanoid System—

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Summary

Prostanoids are arachidonic acid metabolites, and there are 5 main prostanoids acting on 8 distinct receptors. Of them, prostaglandin (PG) E_2 and prostacyclin (PGI_2) are major vasoactive prostanoids in the kidney, and are thought to be involved as autocrine/paracrine regulators in the control of renal blood flow, glomerular filtration, sodium and water reabsorption, and possibly of renin release. Recent advances have revealed the primary structure of all the prostanoid receptors, and mice deficient in each of the receptors have been established. In this study, to elucidate the physiological and pathophysiological significance of prostanoids in salt metabolism and renal microcirculation, we investigated the roles of PGE (EP_{1-4}) and PGI receptors (IP) in the kidney *in vitro* and *in vivo* using animal models.

In rat kidney, PGE receptor EP_3 subtype is expressed in the tubules and EP_4 in the glomeruli, while EP_1 is present in the glomeruli as well as in the collecting ducts. Cultured rat mesangial cells expressed EP_1 and EP_4. PGE_2 stimulated mesangial cell growth via EP_1, but inhibited via EP_4. Mesangial cells prepared from stroke-prone spontaneously hypertensive rats (SHRSP) were more proliferative than those from control Wistar-Kyoto rats (WKY), and EP_1-mediated cell proliferation was more enhanced in the cells from SHRSP than from WKY. High glucose stimulated growth of WKY mesangial cells, and the blockade of EP_1 by antagonists completely abolished this enhancement, suggesting that augmentation of autocrine PGE_2/EP_1 system could contribute to the proliferative nature of mesangial cells under high glucose states. We also found that attenuated PGE_2/EP_4 signaling has a critical role in this EP_1 augmentation.

Renal function, urinary Na excretion, and renal histology were normal in EP_1-knockout ($EP_1^{-/-}$) mice and IP-knockout ($IP^{-/-}$) mice. When mice were fed with 2% NaCl diet for 2 weeks, wild-type (WT) mice exhibited increase in urine volume and urinary Na excretion without significant blood pressure changes. Interestingly, urine volume increase was significantly attenuated in $EP_1^{-/-}$ mice. In $IP^{-/-}$ mice, 2% NaCl loading for 2 weeks resulted in significant blood pressure increase. Water deprivation for 48 h resulted in marked increase in plasma renin activity, and the increment tended to be higher in $IP^{-/-}$ mice than in WT.

These results indicate that renal prostanoid receptors are expressed with region specificity, and suggest that an imbalance between PGE receptor subtypes might be involved in disease states such as hypertension and diabetes. Furthermore, although not essential for maintaining renal function under physiological condition, the PGE_2/EP_1 system may be involved in the regulation of water diuresis under high salt loading, and the PGI_2/IP system may be implicated in the regulation of blood pressure and renin release in excessively salt-loaded or dehydrated states.