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Phenotype of Knockout of Kidney-Specific Prostaglandin Transporter OAT-PG and Salt-Responsive Blood Pressure Changes

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Summary

In renal cortex, prostaglandin E_2 (PGE_2) is released from macula densa of distal convoluted tubules and regulates constriction and dilation of afferent and efferent arterioles as well as renin release from juxtaglomerular apparatus. After transmitting signals, PGE_2 needs to be removed to terminate the signals, which is essential to ensure the rapid regulation by means of PGE_2 signaling. The PGE_2 transporter in proximal tubules is supposed to be responsible for the PGE_2 clearance in renal cortex because PGE_2 metabolizing enzyme 15-PGDH is present in the proximal tubule cells. We identified a kidney-specific prostaglandin transporter OAT-PG (prostaglandin -specific organic anion transporter) which is expressed in the proximal tubules and transports PGE_2. In this study, we analyzed the phenotypes of OAT-PG knockout mice.

In this study, by means of cell fractionation and coimmunoprecipitation assays, we revealed that OAT-PG is physically coupled with 15-PGDH. This is beneficial to ensure efficient clearance of PGE_2 by coupling transport and metabolism. OAT-PG homo knockout (KO) mice exhibited reduced PGE_2 uptake by tubular suspension prepared from the renal cortex. We, thus, concluded that OAT-PG is the major PGE_2 transporter of renal proximal tubules. Furthermore, OAT-PG KO mice showed the reduced trans-epithelial metabolism of PGE_2. When PGE_2 was applied to the basolateral side of trans-well culture of the proximal tubule epithelial cells, less PGE_2 metabolites excreted form the apical side in the OAT-PG KO mice, indicating the importance of OAT-PG in the trans-epithelial metabolism of PGE_2. In the renal cortex of OAT-PG KO mice, PGE_2 accumulated more on furosemide treatment compared with wild type mice. PGE_2 metabolites were less in the renal cortex and urine of OAT-PG KO mice, consistent with the roles of OAT-PG in the PGE_2 clearance. The plasma rennin activity and angiotensin II levels were elevated in OAT-PG KO mice compared with wild type mice.

Blood pressure of OAT-PG KO mice was measured by Tail Cuff method and telemetry. However, significant changes in blood pressure responding to high-salt or low-salt diets have not been concluded at the moment. In contrast, we have obtained interesting results indicating the resistance of OAT-PG KO mice to ACE inhibitors, which should be examined in future studies.