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Role of Na^+-dependent lactate transport in renal urate reabsorption

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Summary

Urate is the major inert end product of purine degradation in higher primates because of the genetic silencing of hepatic oxidative enzyme uricase. The kidney plays a dominant role in urate elimination. Therefore, it is important to understand renal urate handling mechanism because the underexcretion of urate has been implicated in the development of hyperuricemia that leads to gout. Recently, we have identified the urate-anion exchanger URAT1 (SLC22A12) in the human kidney and found that defects in SLC22A12 lead to idiopathic renal hypouricemia. URAT1 is targeted by uricosuric and antiuricosuric agents that affect urate excretion. Using yeast two-hybrid approach, we identified the multivalent PDZ domain-containing protein PDZK1 as an apparent partner of URAT1 in the kidney. Co-expression experiments demonstrated that URAT1 transport activities are increased by PDZK1/URAT1 interactions. Recently, Ganapathy and his colleagues identified that SLC5A8 is a Na^+-coupled transporter for monocarboxylates such as lactate and nicotinate. SLC5A8 is a candidate tumor suppressor gene, recently cloned from human intestine and demonstrated its functional identity as a sodium-coupled monocarboxylate transporter (SMCT). Through the Na^+-coupled reabsorption of lactate, the counterion for URAT1, the modulation of SMCT function may affect the URAT1-mediated urate transport. We have preliminary observed that SMCT C-terminal that has PDZ motif (-T-R-L) binds to PDZK1. Physical coupling between URAT1 and SMCT via PDZK1 forms a single functional complex and it seems appropriate for the effective reabsorption of urate through the monocarboxylate handling in the renal proximal tubules. Deletion of the SMCT1 C-terminal PDZ motif abolished the interaction with PDZK1 in the yeast two-hybrid system. In addition, the first and third PDZ domains of NHERF3 associate strongly with the SMCT1 C-terminus. Localization of SMCT1 was detected at the apical side of the proximal tubules in human kidney. The association of hSMCT1 with PDZK1 enhanced [^{3}H]nicotinate transport activites in HRPE cells (1.7-folds).