Uricosuric agents and renal tubular transporters

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Membrane transporters play important roles in various cellular functions. Renal tubular transporters function not only as pathways for nutrients uptake and metabolites efflux across cellular membranes but also as one of the specialized tissue functions such as transepithelial transport in the kidneys. Recent molecular cloning approaches successfully enable us to identify the molecular nature of various membrane transporters so that numerous inborn human diseases such as idiopathic renal hypouricemia are caused by the mutation of the transporter genes. In addition, several tubular transporters are clarified as drug targets such as NKCC2 (SLC12A1) for loop diuretics and NCC (SLC4A3) for thiazide diuretics. In this lecture, I will present following topics obtained from our laboratory to understand molecular physiology and pharmacology. Urate is present at much higher levels in human blood (200-400 uM) than in other mammals (20 uM), because humans have acquired an effective renal urate reabsorption system in spite of the loss of hepatic uricase by mutational silencing during the course of their evolution. We successively identified renal urate transporters such as apical urate/anion exchanger URAT1 (SLC22A12) (Enomoto et al. Nature 417: 447, 2002) and basolateral voltage-driven urate efflux transporter URATv1/GLUT9 (SLC2A9) (Anzai et al. J Biol Chem, 283: 26834, 2008). Uricosuric agents such as benzbromarone inhibited URAT1- and URATv1-mediated urate uptake in a dose-dependent manner. In addition, we and others provide evidence that the defects both in URAT1 and URATv1 were found in patients with idiopathic renal hypouricemia. Thus, clarification of transcellular pathways for urate in human kidney should provide important insights into the nature of urate homeostasis, as well as lead to the development of better agents against hyperuricemia targeting renal tubular transporters (Anzai and Endou, Semin Nephrol, 2010, in press).

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