UREMIC TOXIN TRANSPORTER SLCO4C1 IS ENHANCED BY STATINS.
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INVOLVEMENT OF NOVEL HUMAN RIBOFLAVIN TRANSPORTERS hRFTs IN RIBOFLAVIN UPTAKE BY INTESTINAL T84 CELLS
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Purpose] The reduction of accumulated uremic toxins protects against the development of hypertension and renal damage in patients with chronic kidney disease (CKD). We have revealed that 1) human kidney-specific organic anion transporter SLCO4C1 is a responsive molecule for excreting uremic toxins (PNAS 2004), 2) the overexpression of human SLCO4C1 within rat kidney promotes renal excretion of uremic toxins and reduced hypertension, cardiomegaly and inflammation in renal failure(JASN 2009). Our purpose is to develop the new therapeutic strategy for CKD. [Methods] Analyzing the transcriptional regulation of human SLCO4C1 and exploring the drugs to enhance the expression of SLCO4C1. [Results and Discussion] Human SLCO4C1 transcription is regulated by xenobiotic responsive element (XRE)-like motifs. Various statins act as nuclear aryl hydrocarbon receptor (AhR) ligands and upregulate SLCO4C1 transcription and promote SLCO4C1 substrate uptake in kidney derived ACHN cells. Luciferase reporter assay of SLCO4C1 promoter by statins revealed transcriptional upregulation in a dose-responsive manner. In addition, co-administration of statins and corticosteroids exerted additive effects on SLCO4C1 expression. [Conclusions] These data suggest that SLCO4C1 upregulation by statins might provide a novel transporter-based therapeutic strategy for CKD patients to reduce major life-threatening events and statins could be effective drugs for CKD remedy.

INVolvement of novel human riboflavin transporters hRFTs in riboflavin uptake by intestinal T84 cells
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Purpose] An active transport process should play an important role in intestinal absorption of riboflavin. However, a mammalian riboflavin transporter has been unknown for a long time. Recently, novel human riboflavin transporters hRFT1, hRFT2 and hRFT3 were identified. Moreover, comparative functional characterization of these transporters was carried out (Yao et al., J. Nutr., in press). In this study, to reveal the involvement of hRFTs in intestinal absorption of riboflavin, we characterized the riboflavin uptake in human intestinal epithelial T84 cells.

Methods] The mRNA expression levels of hRFTs were determined by real-time PCR analysis. Transcellular transport and cellular accumulation of [3H]riboflavin by T84 cells were measured using monolayer cultures grown on Transwell chambers or 24-well plate.

Results and Discussion] hRFT2 and hRFT3 mRNA were highly expressed in T84 cells, whereas hRFT1 mRNA was hardly detected. Transcellular transport of [3H]riboflavin from the apical to basolateral side was increased in a time-dependent manner, and was greater than the opposite direction. The uptake of [3H]riboflavin from the apical side was decreased when extracellular pH was altered from 5.4 to 8.4. The dependence of extracellular Na+ on [3H]riboflavin uptake from the apical side was not observed. These functional characteristics of [3H]riboflavin transport at the apical membranes of T84 cells corresponded with those of hRFT2.

Conclusions] hRFT2 may be involved in riboflavin uptake at the apical membranes of intestinal epithelial cells.