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Characterization of Metformin Transport by Most Prevalent Polymorphisms of hOCTs in a Korean Population

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Aim: Metformin is a substrate for organic cation transporter (OCT) and showed inter-individual difference in renal clearance. Most prevalent non-synonymous SNPs of organic cation transporter (hOCT) genes are hOCT1-P341L and hOCT2-A270S with allelic frequencies of 17 and 11%, respectively. Therefore, the purpose of this study is to characterize the transport activity of metformin in genetic variants of hOCT (hOCT1-P341L and hOCT2-A270S) and evaluate the contribution of hOCT to the transport of metformin in renal proximal tubule.

Methods: The uptake of [3H]MPP and [14C]metformin was measured in X. Laevis oocytes overexpressing hOCT1-wt, -P341L and hOCT2-wt, A270S. The uptake and transport of metformin were measured in the presence and absence of specific inhibitors for OCT, MRP, BCRP, and MDR in LLC-PK1 cell line as an in vitro model for renal proximal tubule. The kinetic parameters of the metformin transport activity were determined from the concentration dependent uptake and transport of metformin in X. Laevis oocytes and LLC-PK1 cells.

Results: The uptake of MPP was at least 40-fold increased in X. Laevis oocytes overexpressing hOCT1-wt and hOCT2-wt compared to those of control and decreased 6-fold and 15-fold decreased in hOCT1-P341L and hOCT2-A270S, respectively, compared to those in wild type. The uptake of metformin was increased only in hOCT2-wt not in hOCT1-wt and decreased 21-fold in hOCT2-A270S compared to hOCT2-wt, suggesting that metformin is a preferential substrate of hOCT2. The values of Km and Vmax for hOCT2-wt are 91.3??M and 2.95 pmole/min/oocytes, respectively. The basal to apical permeability of metformin was significantly greater than apical to basal permeability and inhibited by phenoxybenzamine, OCT inhibitor, suggesting that the active secretion of meformin is mediated OCT. Moreover, the uptake and transport of metformin was inhibited by OCT inhibitor, but no inhibition was shown by MRP, BCRP, and MDR inhibitors. Kinetic analysis revealed that the value of Vmax is 922 pmole/min; Km, 393??M; CLint, 2.35??L/min; and Kdiffusion, 0.33??L/min. These results suggested that active secretion via organic cation transporter is a major transport mechanism of metformin in LLC-PK1 cells.

Conclusion: The genetic variant in hOCT2 (hOCT2-A270S) may explain the inter-individual variations in the renal clearance of metformin although the clinical relevance of this variant remains to be evaluated.