Young Scientist Award

OCT1 of mice and men: Differences in metformin and thiamine uptake – Structural causes and potential clinical consequences for hepatic metformin concentrations

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Metformin, the most commonly used oral antidiabetic drug, is a substrate of the hepatic uptake transporter OCT1 (gene name SLC22A1). OCT1 deficiency was shown to lead to more pronounced reductions of metformin concentrations in the mouse than in the human liver. Similarly, the effects of OCT1 deficiency on the pharmacokinetics of thiamine were reported to differ between human and mouse.

The aim of this study was to compare the uptake characteristics of metformin and thiamine between human and mouse OCT1 *in vitro* to explore underlying structural mechanisms causing differences in hepatic concentrations between humans and mice. Furthermore, we used the differences in uptake between human and mouse OCT1 as a tool to improve our understanding of the transport mechanism of OCT1.

To this end, we used HEK293 cells stably transfected to overexpress human or mouse OCT1 and targeted proteomics to scale up the results for human and mouse liver. The affinity for metformin of human OCT1 was 4.9-fold lower than that of mouse OCT1, resulting in a 6.5-fold lower intrinsic clearance. Using *in vitro* to *in vivo* extrapolation, the estimated liver-to-blood partition coefficient for metformin was only 3.34 in human compared with 14.4 in mouse and may contribute to higher hepatic concentrations in mice. Similarly, the affinity for thiamine of human OCT1 was 9.5-fold lower than that of mouse OCT1. Using HEK293 cells overexpressing human-mouse chimeric OCT1, we showed that simultaneous substitution of transmembrane helices TMH2 and TMH3 resulted in reversal of affinity for metformin. Using homology modeling, we suggested several structural explanations, of which a different interaction of leucine$_{155}$ in human TMH2 compared with the corresponding valine$_{156}$ in mouse TMH2 with residues in TMH3 had the strongest experimental support.

In conclusion, the contribution of human OCT1 to the cellular uptake of thiamine and especially to that of metformin may be much lower than the contribution of mouse OCT1. This may lead to an overestimation of the effects of OCT1 on hepatic metformin concentrations in humans when using the mouse as model organism. Nevertheless, comparative analyses of human and mouse orthologs may help to reveal mechanisms of OCT1 transport.