

Publication

OATP2B1 and Thyroid Hormone Interplay in Intestinal Drug Absorption

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Background: Oral levothyroxine (T4) absorption is variable between individuals and can be affected by pharmacokinetic drug-drug interactions. Furthermore, it is known that hypothyroidism affects oral drug absorption. The uptake drug transporter, organic anion transporting polypeptide (OATP) 2B1, is considered to play a central role in the intestinal absorption of drugs. Previously we characterized the expression and function of intestinal and hepatic variants of OATP2B1. We hypothesize that thyroid hormone is absorbed by OATP2B1 in the intestine and that thyroid hormone regulates the expression of OATP2B1.

Methods: Transport studies were performed in cultured HeLa cells using a heterologous gene expression system. After transducing cells with OATP2B1 adenovirus and LacZ adenovirus as a control, triiodothyronine (T3), T4 as well as rosuvastatin, [³H]rosuvastatin and [³H]E1S (positive controls) uptake was measured using LC-MS/MS or liquid scintillation spectroscopy. An indirect transport study using a thyroid hormone sensitive luciferase reporter assay was also used to assess OATP2B1-mediated cellular entry. Cultured intestinal Caco-2 and hepatic Huh-7 cell lines were exposed to T3 and T4 for examination of OATP2B1 gene expression by quantitative real-time polymerase chain reaction.

Results: Overexpression of OATP2B1 was not associated with increased T3 or T4 uptake while unlabeled, [³H]rosuvastatin and [³H]E1S cellular accumulation was increased by 55% (p<0.0001), 47% (p<0.0001) and 65% (p<0.0001), respectively. T3 and T4 treatment increased the mRNA expression of the liver specific variant of OATP2B1 by 5.4-fold (p=0.0007) and 2.6-fold (p=0.0237), respectively, in Caco-2 cells but not in Huh-7 cells. Similarly, intestinal OATP2B1 variant mRNA expression was induced by 9.7-fold (p=0.0008) by T3 and 4.6-fold (p=0.0123) by T4 only in Caco-2 cells.

Conclusions: Thyroid hormones are not transported by OATP2B1 suggesting that OATP2B1 is not involved in the intestinal absorption of T4. OATP2B1 expression is positively regulated by thyroid hormones in a cell type-dependent manner indicating that thyroid hormone status may influence the intestinal absorption of OATP2B1 substrates.

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