Thyroid hormones are transport substrates and transcriptional regulators of Organic Anion Transporting Polypeptide 2B1

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Levothyroxine replacement therapy forms the cornerstone of hypothyroidism management. Variability in levothyroxine oral absorption may contribute to the well-recognized large interpatient differences in required dose. Moreover, levothyroxine-drug pharmacokinetic interactions are thought to be caused by altered oral bioavailability. Interestingly, little is known regarding the mechanisms contributing to levothyroxine absorption in the gastrointestinal tract. Here, we aimed to determine whether the intestinal drug uptake transporter Organic Anion Transporting Polypeptide 2B1 (OATP2B1) may be involved in facilitating intestinal absorption of thyroid hormones. We also explored whether thyroid hormones regulate OATP2B1 gene expression. In cultured MDCKII-OATP2B1 cells and in OATP2B1-transfected Caco-2 cells, thyroid hormones were found to inhibit OATP2B1-mediated uptake of estrone 3-sulfate. Competitive counter-flow experiments evaluating the influence on the cellular accumulation of estrone 3-sulfate in the steady-state, indicated that thyroid hormones were substrates of OATP2B1. Additional evidence that thyroid hormones were OATP2B1 substrates was provided by OATP2B1-dependent stimulation of thyroid hormone receptor activation in cell-based reporter assays. Bidirectional transport studies in intestinal Caco-2 cells showed net absorptive flux of thyroid hormones, which was attenuated by the presence of the OATP2B1 inhibitor, atorvastatin. In intestinal Caco-2 and LS180 cells, but not in liver Huh-7 or HepG2 cells, OATP2B1 expression was induced by treatment with thyroid hormones. Reporter genes assays revealed thyroid hormone receptor α-mediated transactivation of the SLCO2B1 1b and the SLCO2B1 1e promoters. We conclude that thyroid hormones are substrates and transcriptional regulators of OATP2B1. These insights provide a potential mechanistic basis for oral levothyroxine dose variability and drug interactions.

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