Differences in transport function of the human and rat orthologue of the Organic Anion Transporting Polypeptide 2B1 (OATP2B1).

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The human drug transporter Organic Anion Transporting Polypeptide (hOATP)2B1 facilitates cellular uptake of its substrates. Various studies suggest that hOATP2B1 is involved in intestinal absorption, but preclinical evaluations performed in rodents do not support this. Thus, our study aimed to compare the expression and function of hOATP2B1 with its orthologue in rats (rOatp2b1). Even if the general expression pattern was comparable, the transporters exhibited substantial differences on functional level. While bromosulfophthalein and atorvastatin were substrates of both transporters, the steroid sulfate conjugates estrone 3-sulfate (E; 1; S), progesterone sulfate and dehydroepiandrosterone sulfate were only transported by hOATP2B1. To further elucidate these functional differences, experiments searching for the E; 1; S substrate recognition site were conducted generating human-rat chimera as well as partly humanized variants of rOatp2b1. The rOatp2b1-329-hOATP2B1 chimera led to a significant increase in E; 1; S uptake suggesting the C-terminal part of the human transporter is involved. However, humanization of various regions within this part, namely of the transmembrane domain (TMD)-9, TMD-10 or the extracellular loop-5 did not significantly change E; 1; S transport function. Replacement of the intracellular loop-3, slightly enhanced cellular accumulation of sulfated steroids. Taken together, we report that OATP2B1 exhibited differences in recognition of steroid sulfate conjugates comparing the rat and human orthologues.

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