Universität Basel

Research Project

Detailed analysis of expression and function of the drug transporter rat Oatp2b1

Project funded by own resources

Project title Detailed analysis of expression and function of the drug transporter rat Oatp2b1
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Drug transporters including the OATPs play a pivotal role in the cellular handling of substrate drugs. The familiy member OATP2B1 exhibits a broad tissue distrubtion with abundance in various organs of known importance in drug absorption and elimination. Thus, OATP2B1 is considered a determinant of pharmacokinetics of its substrates. In the process of drug development new molecular entities are screened for interactions with relevant drug transporters using overexpressing cellular systems. The findings of those in vitro studies mainly conducted with human transporters are supplemented by in vivo animal studies conducted to provide information on pharmacokinetics and metabolic stability. However, due to interspecies divergence in transporter expression and function extrapolation of those findings to humans in preparation of the clinical assessment is challenging. In the herein proposed study I will focus on the expression and functional comparison ofărat and humanăOatp2b1 (OATP2B1). At first, a detailed analysis on expression levels and locaclisation in various tissues will be conducted, thereby adding information to preliminary data showing a similar expression pattern of both transporters in various tissues. During the project a cell line overexpressing the transporter will be established in order to screen known substrates of OATP2B1 for interaction with the rat transporter. In addition to these in vitro experiments pharmacokinetic studies in rats will be performed to determine the contribution of Oatp2b1 to pharmacokinetics of identified substrates and inhibitors. The second part of the study will investigate structure function relation of OATP2B1. Indeed, even if preliminary data suggested a similar tissue distribution we observed pronounced differences in uptake of the known OATP2B1 substrate estrone 3-sulfate. This observation in addition to in silico data showing differences in the amino acid sequence encompassing transmembrane domain (TMD) 9, the extracellular loop (ECL) 5, and TMD10 suggests that gradual humanization of rat Oatp2b1 in this area following functional characterization may provide insights in the structure function relation of human OATP2B1. Taken together, this study will contribute to a profound understanding of rat Oatp2b1 (in comparsion to the human transporter) thereby providing information necessary for extrapolation of data obtained during the clinical assessment in drug development.

Keywords transporter, drug absorption, pharmacokinetics, rat, species differences
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