

Hyperforin Mediated PXR Activation is Influenced by the Uptake Transporter OATP2B1

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Introduction: St. John's wort (SJW) is an herbal remedy commonly used to treat moderate depressive symptoms. Beside its pharmacological effects, SJW is known for its drug-drug interaction potential, where enhanced expression of CYP3A4 modifies the clearance of concomitantly applied substrates. One constituent of SJW known for its alteration in CYP3A4 expression is hyperforin [1]. This phloroglucinol is a potent activator of the nuclear receptor Pregnane X Receptor (PXR), which functions as transcriptional regulator of a gene network summarizing multiple genes involved in drug metabolism and elimination. Little is known about the transmembrane transport of the lipophilic hyperforin. One membrane protein which is involved in cellular entry of drugs is the uptake transporter, organic anion transporting polypeptide (OATP) 2B1 [2].

Aims: It was aim of this study to test whether hyperforin interacts with OATP2B1, and whether interaction with the transporter influences hyperforin-mediated PXR activation.

Methods: Transport inhibition studies and competitive counterflow (CCF) experiments were conducted using the MDCKII-OATP2B1 cell line. CCF was performed as previously reported by Harper et al. [3]. CCF results were supplemented by cell based-reporter genes assays testing the influence of heterologously expressed OATP2B1 on hyperforin-mediated transactivation of CYP3A4 in HepG2 and HeLa cells. Caco-2 Transwell[®] experiments using the known OATP2B1-substrate atorvastatin were applied to test the influence of the phloroglucinol on transcellular fluxes. Hyperforin content was determined by HPLC.

Results: Transport inhibition and CCF experiments suggested that hyperforin is an inhibitor and substrate of OATP2B1. The latter was validated showing that presence of OATP2B1 significantly enhanced the hyperforin-induced PXR activation in cell based luciferase assays, whereby supporting the notion that this transporter may be a determinant of hyperforin-drug interactions as the transporter is known to be expressed in hepatocytes. The role of OATP2B1 inhibition in intestinal absorption was investigated in Transwell[®] experiments revealing a significant increase in the efflux-ratio of atorvastatin. Testing the influence of the 11 SJW formulations currently marketed in Switzerland on OATP2B1-mediated estrone 3-sulfate accumulation revealed significant inhibition for most of the tested formulations, but Rebalance[™], Remotiv[™], Hyperimed[™] and Hyperiforce[™]. Importantly, assessing the content of hyperforin in all formulations suggested a direct correlation between amount and PXR activation as determined in subsequent luciferase assays.

Conclusions: Taken together, our results show that hyperforin is a substrate of OATP2B1, which is not only known to contribute to hepatocellular uptake, but also to intestinal absorption of its substrates. Our findings extend the complexity of drug-hyperforin interactions that have to be considered, when evaluating the interaction potential of the herbal remedy.

Keywords: Transmembrane transport, OATP2B1, St. John's wort, pregnane X receptor, hyperforin

References:

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