Publication

Identification of centrally active drugs and herbal constituents as substrates of OATP2B1 and OATP1A2 applying the method of competitive counterflow

Thesis (Dissertationen, Habilitationen)

ID 4627478
Author Schäfer, Anima
Author at UniBasel Schäfer, Anima Magdalena ;
Year 2021
Title Identification of centrally active drugs and herbal constituents as substrates of OATP2B1 and OATP1A2 applying the method of competitive counterflow
Type of Thesis Dissertation;
Start of thesis 01.04.2017
End of thesis 31.03.2021
Name of University University Basel
Name of Faculty Philosophisch-Naturwissenschaftliche Fakultät;
Supervisor(s) / **Fachvertreter/in** Meyer zu Schwabedissen, Henriette ;
For a large number of compounds in clinical use we know that membrane transporter proteins modulate their pharmacokinetic properties. The family of organic anion transporting polypeptides (OATP) facilitates the cellular entry of such compounds. In my thesis I will focus on two members of this phylogenetically conserved protein family, namely OATP2B1 and OATP1A2. While OATP2B1 is relatively unique in its ubiquitous expression throughout the body, particularly in key organs contributing to drug absorption, metabolism and elimination, the tissue localization of OATP1A2 is more restricted to few organs such as the brain. Currently, various exogenous substrates of OATP2B1 and OATP1A2 have been identified, many of which are shared among other members of the OATP family. Important tools to better understand the physiological and pharmacological functions of each OATP are the use of transporter-specific substrates. Consequently, experimental approaches for fast and easy transporter substrate identification are desired. The competitive counterflow technique is one such method enabling the screening of compounds with reasonable throughput and cost. In this work, I demonstrated that the method could be successfully applied to identify substrates of OATP2B1 and OATP1A2. Competitive counterflow experiments were performed with both transporters to test centrally active drugs belonging to the class of dopamine receptor agonists and antagonists. Bromocriptine, cabergoline, and domperidone were identified as novel substrates of OATP2B1 while OATP1A2 was additionally identified to transport metoclopramide. Confirmation of the transporter expression in cellular structures of the brain suggests their involvement in the uptake of the drugs from the blood-stream into the central nervous system. Beside synthetic drugs, there are also herbal remedies with therapeutic indications to manage diseases of the central nervous system. In this regard, constituents of *Passiflora incarnata* and *Valeriana officinalis* were investigated for interaction with OATP2B1 and OATP1A2. Whereas no transporter interactions were shown for constituents of *Valeriana officinalis*, the flavonoids orientin and vitexin present in *Passiflora incarnata* were identified as substrates of OATP2B1. Vitexin was also identified as a substrate of OATP1A2 as well as the aglycon apigenin. Mass spectrometric analysis of *Passiflora incarnata* formulations identified vitexin and orientin, but not apigenin. Consequently, these two constituents could be involved in possible interactions between the formulations and the transporters. Importantly, there is still limited knowledge about systemic availability of flavonoids and to what extent they reach the central nervous system. However, OATP2B1 is widely considered to be important in intestinal drug absorption,

and it follows that constituents of herbal remedies may interact with co-administered oral drugs which are OATP2B1 substrates. Another herbal constituent that we found to interact with OATP2B1 is the St. John's wort constituent hyperforin. It is a potent inhibitor of OATP2B1 function with an IC50 of 0.32 μM and indeed, competitive counterflow experiments identified it as an OATP2B1 substrate. This phloroglucinol is known for drug-herb interactions involving induction of enzymes which mediate drug metabolism. Our finding of OATP2B1 playing a role in cellular uptake of hyperforin suggests that the transporter is a determinant influencing the intracellular effect of the herbal constituent. Furthermore, the identification of hyperforin as an OATP2B1 substrate would imply by extension the plant's interaction potential with OATP2B1 substrates.

Full Text on edoc ;