Abstract

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Title of doctoral thesis: Interactions of antiretrovirals with drug transporters; role in pharmacokinetics

Current pharmacotherapy of HIV positive patients consists of co-administration of three or more antiretrovirals from different pharmacotherapeutic groups, so called combination antiretroviral therapy (cART). Using this approach, a significant reduction in viral load, delayed viral resistance progression and prolonged efficacy of therapy is achieved. However, the use of cART often bears the risk of drug-drug interactions, which may result in subtherapeutic or supratherapeutic concentrations of drugs in organism with subsequent failure of therapy, or manifestation of toxic effects. Drug transporters expressed in many tissues of human body are widely responsible for occurrence of drug-drug interactions. Therefore, detailed knowledge on antiretrovirals pharmacokinetics and their interactions with drug transporters is important to ensure safe and effective therapy of HIV infection.

The aim of this thesis was to study interactions of drugs used in combination antiretroviral therapy with selected ABC and SLC drug transporters. We further focused on the role of several drug transporters in pharmacokinetics of various antiretroviral drugs and on potential risk to develop drug-drug interactions. Several established experimental models such as *in vitro* accumulation and transport assays on cell lines expressing ABC or SLC transporters, *in situ* method of dually perfused rat placenta and *in vivo* pharmacokinetic experiments on Wistar male rats were used in this project.

Using *in vitro* assays, we revealed emtricitabine, a nucleoside reverse transcriptase inhibitor (NRTI), as a substrate of MATE1, but with no affinity to OCT1, OCT2, P-gp, BCRP or MRP2 transport proteins. In contrast, transport of NRTI lamivudine is ensured by both OCT

and MATE1 transporters. This interaction probably does not influence transplacental passage of lamivudine, however, it is responsible for active tubular excretion of this compound into urine. In another part of our study, a non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz, was described as a strong inhibitor of OCT1, OCT2, MATE1 and MRP2; correspondingly, the drug was able to significantly decrease renal clearance of lamivudine *in vivo* in rats and increase accumulation of this antiretroviral in renal tissue.

In addition, we proved that a novel NNRTI, etravirine, is able to increase transport of tenofovir disoproxil fumarate (TDF) across the rat placenta from mother to foetus by inhibition of placental BCRP. We also found, that another drug from this group, rilpivirine, is a strong inhibitor of P-gp and BCRP but not MRP2, OCT1, OCT2 or MATE1. Subsequently, rilpivirine was able to increase the bioavailability of co-administered abacavir by inhibition of intestinal P-gp and BCRP.

Our results significantly enlarge the current knowledge on interactions of antiretrovirals with drug transporters and clarify the mechanisms that influence absorption, elimination and distribution of co-administered drugs within cART. These results may contribute to composing more efficient and safer therapy of HIV positive patients.