Abstract

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Title of diploma thesis: *In vitro* and *ex vivo* study of drug-drug interactions of antiretrovirals on intestinal ATP-binding drug transporters

The absorption of orally administered drugs takes place especially in the intestine, where it can affect by the activity of drug´s ABC transporters located on the apical membrane of the intestinal epithelium. Study of drug interactions in intestinal ABC transporters is essential to ensure effective and safe pharmacotherapy. Testing of bi-directional transport on Caco-2 cells is generally the preferred method for *in vitro* evaluation of substrates and inhibitors of ABC transporters. Drawbacks of the Caco-2 model increase the need and necessity to introduce new models. A great potential is the involvement of *ex vivo* methodologies in the human or rat intestine. The aim of the work was to introduce an *in vitro* methodology using the Caco-2 cell monolayer and the *ex vivo* methodology of precision-cut rat intestinal slices. By the bi-directional transport method, we analyzed drug interactions of the model substrate P-gp and BCRP Rhodamine 123 (RHD123) and clinically-used tenofovir disoproxil fumarate (TDF) antiretroviral agents (ARV) with selected P-gp/BCRP inhibitors of the antiretroviral group. Lopinavir, ritonavir and abacavir decreased the efflux ratio of RHD123 and the *ex vivo* accumulation study with RHD123 demonstrated the concentration-dependent inhibitory effect of lopinavir and ritonavir. In addition, Lopinavir significantly affected transport of TDF through the monolayer of Caco-2 cells. In conclusion, we have been able to introduce *in vitro* and *ex vivo* methods for drug interaction analysis on intestinal P-gp and BCRP, and we have confirmed that some ARV (i.e. the protease inhibitor group) can inhibit intestinal P-gp and BCRP and to modify the TDF transmembrane transport.