STUDY OF DRUG-DRUG INTERACTIONS BASED ON MODULATION OF THE FUNCTION OF LIVER AND KIDNEY ACTIVE TRANSPORTERS

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ABSTRACT

The present thesis focused on closer research of drug-induced changes in the expression and function of the main hepatic and renal transporters and their effects on the pharmacokinetics of the model substrates. The subject of our particular interest were ABC efflux transporters (namely P-gp and Mrp2) localized in the apical membranes of polarized epithelium cells in the excretory organs, and also Oatp2 transporter playing an important role in the basolateral uptake of drugs. Dexamethasone and amiodarone were employed to bring about changes in the active transport. Dexamethasone is a potent corticosteroid that showed capability to increase elimination processes, i.e. to induce enzymes and transporters both *in vitro* and *in vivo*. Amiodarone, a life-saving antiarrhythmic, is a well-known inhibitor of drug metabolism. Its direct inhibitory effects on the active transport have recently been reported.
The summarized results of the included publications describe various aspects of the pharmacokinetic drug-drug interactions, where the underlying mechanism of the interaction is a modulation (either induction/activation or inhibition) of the active transport. Such modulation is produced by a simultaneous or previous administration of another drug known to affect the expression and/or function of transporting proteins. Our results also accent the importance of the usage of *in vivo* models in studies evaluating the effects of xenobiotics on transport activities in the organs of elimination.