ABSTRACT

Charles University
Faculty of Pharmacy in Hradec Králové
Department of Pharmacology & Toxicology
Student: Patrícia Čečková
Supervisor: PharmDr. Ivan Vokřál, Ph.D.
Title of diploma thesis: Study of drug interactions with OATP family transporters using intestinal tissue slices

An essential role in the action of orally administered drugs is their absorption through the intestinal barrier. It expresses a variety of transporters, including the OATP2B1 and OATP1A2 influx transporters, belonging to the SLC family. They are located on the apical membrane of enterocytes and allow the flow of endogenous and exogenous substances from the lumen of the intestines to the enterocyte. They affect not only the pharmacokinetics of drugs, but also their safety and efficacy. They represent sites of drug interactions with other drugs/food components that may altered drug efficacy or toxicity. Since FDA (The Food and Drug Administration) and EMA (European Medicines Agency) do not have intestinal OATP transporters included in their guidelines for preclinical studies, there is no single model of interaction study. The limitations of cell models and genetically modified organisms lead to the development of new methods such as the *ex vivo* method of precision cut intestinal slices (PCIS), which represents a tissue model reflecting the true 3D structure of the intestinal barrier.

The aim of this diploma thesis was to optimize the PCIS method to study drug interactions of intestinal OATP transporters (OATP1A2 and OATP2B1). We chose estrone-3-sulfate as a model substrate. Using rat intestinal slices, we analyzed the accumulation of estrone-3-sulfate in the individual intestinal segments and also attempted to create its saturation curve. We studied the interactions of selected OATP1A2, OATP2B1 inhibitors (cyclosporine A, verapamil, chrysine, rosuvastatin, quercetin, naringin) and ABC inhibitors (Ko, Ly, CP) in rat jejunum. Moreover, we analyzed the interactions of some inhibitors (cyclosporin A, naringin) in human jejunum.

We were unable to optimize the PCIS method for intestinal OATP transporters. However, if we want to understand more about the complex functioning of the intestinal barrier and the role of the OATP transporters, its optimization should continue.