Abstract

Predicting the disposition of drugs and new molecular entities from the bottom-up via in vitro or in silico models is highly desirable in pharmaceutical research, both from an economic and a drug safety standpoint. While compounds with low permeability, high solubility and low metabolism (BDDCS Class III) account for nearly a quarter of marketed drugs, the strategies for a bottom-up prediction of exposure for this drug class in humans have not yet proved successful. Challenges are related to the pathways BDDCS Class III drugs use for absorption and elimination i.e. specialised transport routes closely dependent on the expression and interplay of membrane transport or junctional proteins, which can differ dramatically between different models or individuals. Thus, a priori knowledge of the degree of involvement of specialised transport routes in drug disposition processes is crucial when attempting to predict the drug exposure for this drug class in living organisms.

In the present work, acamprosate was used as a model BDDCS Class III drug. Acamprosate is widely used in the prevention of alcohol relapse, however, its mechanisms of absorption and excretion have been either debated or poorly understood. In the first part of this PhD project, the absorption mechanism of acamprosate was investigated using the Caco-2 cell model. For this purpose, an in silico Caco-2 permeation model (coined Pmodelled) was built and refined with empirical permeation coefficients for a range of paracellular markers. Pmodelled could predict the relative contribution of possible passive permeation routes for acamprosate across Caco-2 monolayers and revealed a dominating contribution from the paracellular route. This argument was supported by a lack of acamprosate affinity towards a range of apical intestinal drug carriers and a low cellular acamprosate accumulation. Thus, Pmodelled can provide insight on permeation mechanisms across the intestinal epithelium.

In the second part of the PhD project, possible renal excretion mechanisms for acamprosate were investigated using cell lines overexpressing the clinically-relevant organic anion transporters (i.e., OAT1 and OAT3). The studies identify acamprosate as a novel substrate for OAT1 and suggest acamprosate does not have an affinity for OAT3. Moreover, the results show the OAT1-mediated excretion of acamprosate is inhibited by probenecid, the prototypical OAT1 and OAT3 inhibitor, and this inhibition may be clinically relevant. Thus, these studies elucidate the first step in the acamprosate excretion mechanism and reveal that in vivo drug-drug interaction (DDI) studies may be recommended to assess DDI potential if acamprosate is co-administered with other drugs that act as OAT1 inhibitors.