Abstract

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Title of diploma thesis: Role of selected ABC and SLC transporters in transmembrane permeability of maraviroc: effect on transport in placenta

Antiretroviral drug maraviroc is an inhibitor of CCR5-trophic HIV virus and belongs to the group of entry inhibitors. Nowadays, maraviroc is administered as part of combination antiretroviral therapy (cART) primarily in adults, children over the age of two and pregnant women to reduce the risk of transmission of HIV to the fetus. The knowledge of interactions of maraviroc with drug transporters in placenta is crucial for optimizing the therapy during pregnancy, both in terms of efficacy and potential adverse effects. Maraviroc is known substrate of ABCB1 transporter, which plays a protective role to the fetus by its efflux activity in the apical membrane of trophoblast. However, the results of recent study employing dually perfused human placenta suggest involvement of other transport mechanisms in the maraviroc transplacental pharmaocokinetics, especially those operating in the opposite direction to ABCB1.

The aim of this study was to evaluate *in vitro* studies whether, besides ABCB1, maraviroc interacts with other transplacentar transporters. First, an accumulation study and bidirectional transport of maraviroc across the monolayer of placental BeWo b30 cells was performed. Significant reduction in maraviroc accumulation in the presence of verapamil (100 μM), ritonavir (10 μM) and elacridar (2 μM) suggests, that some influx transporters might be involved. On the other hand, an increase of accumulation in the presence of inhibitor MK-571 (50 μM) suggests also involvement of some ABCCs efflux transporter(s). After the following evaluation of the transport study a significant transfer of maraviroc in B-A direction was observed sensitive to the presence of ritonavir and MK-571. In order to identify the interacting transport mechanisms *in vitro* studies were performed using MDCKII cells overexpressing human ABCC1 transporter and A431 cells overexpressing human OATP2B1, - 1A2 or -1B3 transporter. We revealed substrate affinity of maraviroc to ABCC1, OATP1A2 and OATP1B3, but not to OATP2B1.

Based on the obtained data we can suggest, that maraviroc interacts with several drug transporters in placenta that could partly reverse the effect of apically localized ABCB1. Considering the fact that antiretroviral therapy is always administered as combination of drugs in developed countries, it can be assumed that maraviroc will be susceptible to drug-drug interactions and this newly obtained data could contribute to better understanding of the transplacental pharmacokinetics of maraviroc and optimization of the therapy.