ABSTRACT

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Title of doctoral thesis: Interactions of selected antiretroviral drugs and methylmercury with placental membrane transporters.

Pregnant women are especially in developed countries exposed to high amount of various xenobiotic including environmental pollutants and drugs. Antiretroviral therapy (ART) is administered to HIV positive pregnant women for the purpose of prevention of HIV mother-to-child-transmission. Pharmacokinetics of many antiretrovirals is limited or enhanced by activity of ATP-binding cassette (ABC) or Solute carrier's transporters, of which many are expressed also in placental tissue. ART therapy usually consists of combination of 3 – 4 antiretroviral drugs, thereby leading to higher risk for development of drug-drug interactions on ABC and SLC transporters. In this study we described influence of non-nucleoside reverse transcriptase inhibitors etravirin and rilpivirin on BCRP- and MDR1-mediated transport of tenofovir disoproxil fumarate (TDF) and/or abacavir. Etravirin showed potent inhibition of BCRP transporter significantly changing transport of both, TDF and abacavir, across monolayers of MDCKII-BCRP cells. However, in placental tissue, the relevance of this interaction was confirmed only for TDF, but not abacavir. Besides etravirin, rilpivirin inhibits also MDR1 transporter, suggesting this interaction as responsible causative mechanism for increased oral bioavailability of abacavir after oral administration in rat. Further, detailed transfer of chemokine receptor 5 antagonist maraviroc across placenta was described in this study which revealed involvement of four placental transporters: MDR1, MRP1, OATP1A2 and OATP1B3.

Consumption of certain type of sea fish is the main way of exposure of methylmercury in pregnant women. Methylmercury enters placenta and permeates through the tissue to the fetus, causing neurotoxic effects. The toxic activity of methylmercury directly in placental tissue is still uncertain. Performing *in vitro* transport assay in MDCKII-MRP1 cells, we brought for the first time the direct proof that methylmercury interacts with human MRP1. This transporter thereby seems to be responsible for driving of methylmercury from syncytiotrophoblast deeper into the placental tissue. MRP1 knockout in placental cell line HTR-8/SVneo induced by siRNA further caused increase of intracellular methylmercury concentration resulting in higher

oxidative stress and earlier cellular apoptosis. This data proves that MRP1 play an important role in placental protection against toxic effects of methylmercury.