ABSTRACT

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Title of Dissertation Thesis: Study of interactions of antiviral drugs with selected placental transporters

The backbone of HIV treatment in pregnant women is the combination antiretroviral therapy which effectively suppresses the viral proliferation in maternal blood circulation. One of drugs in this therapy regimen should be a molecule with high placental transfer to assure the prophylaxis of viral transfer to fetus. There is no approved guideline for pharmacotherapy of pregnant women infected with hepatitis C (HCV), however recent evidence suggests that lowering the maternal viral load could correlate with lower likelihood of HCV transmission to the fetus. To assure and further develop the effective and safe pharmacotherapeutic approaches for treatment of HIV and HCV in pregnancy with respect to fetal safety, it is essential to understand mechanisms of placental transfer of anti(retro)viral drugs. In this Dissertation thesis we focused on molecules derived from nucleosides (anti-HIV abacavir, emtricitabine, zidovudine, tenofovir disoproxil fumarate and anti-HCV ribavirin) with reported high transplacental passage. The main theme of the proposed thesis was to investigate our hypothesis whether materno-fetal transport is mediated via nucleoside transporters. Moreover, we also studied ontogenesis of expression of placental nucleoside transporters and searched for an answer if this expression is epigenetically regulated, and thus can be related to cytotrophoblast differentiation. To address those goals, we used broad spectrum of *in vitro, ex vivo* and *in situ* experimental approaches. Our findings propose the equilibrative nucleoside transporter named ENT1 to be responsible for transport of abacavir and ribavirin across the placental barrier, while emtricitabine and zidovudine tend to cross the placenta via other mechanism(s). We described high variability of gene expression of nucleoside transporters in the first and third trimester human placenta. Results obtained in this study indicate that equilibrative nucleoside transporters are expressed constitutively, whereas concentrative nucleoside transporters are expressed asymmetrically – their expression rises with gestation age and there is also a possibility of epigenetic regulation. Apart from originally set goals, we also bring the first evidence that S-(4-Nitrobenzyl)-6-thioinosin, a supposedly selective inhibitor of equilibrative nucleoside transporters also blocks the efflux activity of one placental transporter from the ABC transporter superfamily.

In conclusion, our data presented in this dissertation thesis contribute to understanding of the transplacental kinetics of selected antivirals and their impact on the transporter expression in placenta and other maternal or fetal organs.