ABSTRACT

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Title of diploma thesis: Study of the effect of novel antiretroviral drugs on carnitine transport in the placenta

Nowadays, the antiretroviral treatment of HIV-positive pregnant women is the standard approach for restriction of transmission of HIV infection from mother to the fetus. In spite of necessity of this pharmacotherapy, it is important to know its safety and risks. For the correct fetal development and function of placenta it is (besides others) essential to ensure the optimal supply of L-carnitine, the key factor for oxidation of fatty acids from mother´s blood to the placenta and fetal blood circulation.

The deficiency of L-carnitine generally leads to significant metabolic changes in the cells and in it usually demonstrated with cardiomyopathies and myopaties. Published studies indicate higher incidence of cardiovascular diseases and cardiomyopathies in children born to mothers treated with antiretroviral therapy during pregnancy. Optimal transport of carnitine into the placental cells, is ensured due to the presence of functional transport protein OCTN2 in the apical membrane of trophoblast. The aim of this study was to evaluate, if antiretrovirals from groups of non-nucleoside reverse transcriptase inhibitors (rilpivirne and efavirenz), protease inhibitors (ritonavir, saquinavir, tipranavir, lopinavir and atazanavir) and integrase inhibitors (dolutegravir and elvitegravir) are able to inhibit OCTN2 transporter and thereby restrict the active transfer of carnitine into the cells. *In vitro* model of BeWo cell line derived from choriocarcinoma of the placenta and *ex vivo* model of microvillous plasma membrane vesicles isolated from human placenta obtained after the delivery were employed.

Our results demonstrate significant inhibitory effect of protease inhibitors ritonavir and saquinavir on the uptake of L-carnitine in both used models. The inhibitory effect of elvitegravir and rilpivirine on the OCTN2 was demonstrated only in BeWo cells but was not confirmed on isolated microvillous membranes. Our study indicates that possible carnitine defficit should be considered therapeutic regimens involving protease inhibitors (mainly ritonavir and

saquinavir). On the other hand, the tested antiretroviral drugs seem to be safe from the perspective of L-carnitine availability for placenta.