Abstract

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Title of diploma thesis: Effect of abacavir on the expression of nucleoside transporters, adenosine receptors, and enzymes involved in adenosine synthesis and biodegradation in trophoblasts

The nucleoside reverse transcriptase inhibitor (NRTI) abacavir (ABC) is now the mainstay of combination antiretroviral therapy (cART) for HIV in pregnant women. The introduction of cART, along with several other measures, has reduced mother-to-fetus transmission of HIV to less than 1% in recent years. The placenta is a key organ for the health of both the fetus and the mother. Imbalances in placental development can result in adaptive changes and fetal programming errors. cART recommended in pregnancy is known for its good safety profile, but some epidemiological studies suggest a higher risk of reduced fetal weight, preterm birth, etc. The placenta is a rapidly growing organ dependent on the supply of building materials that resembles tumor growth in certain aspects. Nucleosides are promoters of tumor proliferation and are involved in the development of immunotolerance. The placenta is complexly equipped for nucleoside synthesis, uptake, metabolism and interaction with the physiologically most important nucleoside adenosine (Ado). In other organ systems, NRTIs have been shown to have the potential to influence adenosine production and metabolism. Therefore, the aim of this thesis is to test the effect of ABC on gene expression of nucleoside transporters, adenosine receptors and enzymes involved in Ado synthesis and biodegradation in the trophoblast. Analyses were performed on the BeWo cell line and placental explants. Gene expression of selected genes was then measured by RT-PCR. These findings could lead to a significant improvement in the safety profile of cART. We found that ABC had a minimal regulatory effect; at a non-therapeutic concentration of 100 μM, it only increased gene expression for the adenosine receptor A2B in the BeWo cell line. In contrast, Ado showed a regulatory effect even at physiological concentrations on the adenosine deaminase enzyme and CD73 ectonucleotidase and at a supraphysiological concentration of 100 μM on the adenosine receptor A2A. The Ado effect was only observed in placental explants prepared from placentas at the end of gestation, which represent a more complex model compared to BeWo cells. Thus, ABC does not affect gene expression of molecules involved in homeostasis and regulatory mechanisms of Ado. Our findings increase the knowledge of the safety profile of ABC in HIV therapy in pregnant women.