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URIDINE ABROGATES THE ADVERSE EFFECTS OF STAVUDINE AND ZALCITABINE ON ADIPOSE CELL FUNCTIONS

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UA Walker¹, M Auclair², D Lebrecht¹, M Kornprobst², J Capeau^{2,3} and M Caron²

¹Medizinische Universitätsklinik, Department of Rheumatology and Clinical Immunology, Freiburg, Germany; ²INSERM U402, Faculty of Medicine Saint-Antoine, Paris, France; and ³Hôpital Tenon, Paris, France

OBJECTIVES: The adverse effects of nucleoside analogue reverse transcriptase inhibitors (NRTIs) have been attributed to their mitochondrial toxicity. Beneficial effects of the pyrimidine precursor uridine on NRTI-induced mitochondrial damage have recently been described in hepatic cells. In the present study, we assessed whether uridine can prevent the adverse effect of stavudine and zalcitabine on adipocyte functions *in vitro*.

METHODS: 3T3-F442A preadipocytes were exposed to stavudine (10 μ M) or zalcitabine (0.2 μ M) in the absence or presence of uridine (200 μ M) for 21 days before, and 7 days after induction of differentiation. Lipid accumulation (oil red staining), apoptosis (flow cytometry), mitochondrial DNA (mtDNA) levels and mitochondrial membrane potential (JC-1) were evaluated at day 7 of differentiation.

RESULTS: Prolonged treatment with stavudine or zalcitabine markedly altered adipocyte morphology. Adipocytes were enlarged and contained lipid droplets of reduced size and number. Stavudine and zalcitabine significantly decreased lipid accumulation (by 36 and 20%, respectively) and increased apoptosis (by 5.6- and 2.2-fold, respectively). Stavudine and zalcitabine markedly decreased adipocyte mtDNA to residual amounts of 36% ($P=0.006$) and 45% ($P=0.01$), respectively. Both NRTIs also induced mitochondrial depolarization, as shown by the 40–45% decrease of the JC-1 aggregate/monomer ratio. Uridine had no intrinsic effect, but abrogated the adverse effects of both NRTIs on adipocyte morphology and lipid staining. Uridine normalized apoptotic indices (1.1-fold for both NRTIs). Uridine prevented mtDNA depletion by stavudine and zalcitabine (mtDNA-levels 101% and 78% of control adipocytes, respectively) and normalized mitochondrial respiration (JC-1 aggregate/monomer ratio).

CONCLUSIONS: Uridine supplementation protects cultured adipocytes from the adverse effects of stavudine and zalcitabine on lipid accumulation, cell survival and mitochondrial functions. The beneficial effect of uridine is seen whatever the parameter tested, suggesting that the toxic effects of these NRTIs could be linked to depletion of uridine or its metabolites inside the cells. Elevating the intracellular uridine level could allow competition of uridine metabolites with NRTIs at polymerase- γ and thus prevent the decreased mtDNA synthesis. Uridine is an interesting candidate in the prevention of the NRTI-induced lipotrophy *in vivo*.

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