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THE DEVELOPMENTAL STAGE DETERMINES THE EFFECT OF NRTIS ON ADIPOCYTE MTDNA DEPLETION AND ADIPONECTIN PRODUCTION

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OBJECTIVE: To evaluate the *in vitro* contribution of nucleoside-analogue reverse transcriptase inhibitor (NRTI) therapy to lipoatrophy as a result of mitochondrial DNA toxicity in adipose tissue.

METHODS: Relationships between adipocyte mitochondrial DNA (mtDNA) content, adiponectin production and the incubation with three different NRTI in 3T3 L1 cell line were investigated. Longitudinal effects (21 days) of NRTIs on different stages of adipocyte development and differentiation were studied. Adipocyte mitochondrial DNA depletion was also assessed according to the particular drug and developmental stage using real-time PCR. Fat content was measured with Oil Red O staining and adiponectin production by real-time PCR and ELISA.

RESULTS: Stavudine (d4T) incubation was associated with more severe adipocyte mtDNA depletion, but heavily depended on adipocyte proliferation. Stavudine also directly leads to decreased adiponectin production. Zidovudine (AZT) incubation was associated with impaired differentiation and decrease in adiponectin production. Effects of zalcitabine (ddC) on adipocytes mtDNA were stronger in preadipocytes with almost no effect on differentiating cells and adiponectin production.

CONCLUSIONS: Different NRTIs affect mtDNA content of adipose tissue and its function through different mechanisms depending on the developmental stage. We provide evidence at the cellular level that d4T-induces mitochondrial DNA depletion and that this depletion is associated with decrease in adiponectin production.

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