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EFFECTS OF NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS ON DIFFERENTIATION, RESPONSE TO INSULIN AND APOPTOSIS IN CULTURED ADIPOCYTES

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BACKGROUND: Antiretroviral therapy can induce severe adverse effects including fat tissue redistribution and metabolic abnormalities. Though HIV protease inhibitors (PIs) have been causally associated with adipocyte and metabolic alterations both *in vivo* and *in vitro*, the effects produced by nucleoside reverse transcriptase inhibitors (NRTIs) are less clear. We studied *in vitro* the effects of five NRTIs on adipose cell differentiation, insulin sensitivity and survival. Stavudine (d4T), didanosine (ddI), zidovudine (ZDV), lamivudine (3TC) and abacavir (ABC) were tested alone or in association.

METHODS: Drugs were used at C_{max} concentration, that is, a concentration higher than the mean human exposure, for at least 11 days. 3T3-F442A differentiation was assessed by adipocyte counting and protein expression of the transcription factors SREBP-1, PPAR γ and C/EBP α . Insulin action was tested by the phosphorylation of the insulin receptor β subunit (IR β) and its substrate IRS-1, and the activation of ERK 1/2 and Akt/PKB. Lipid accumulation was estimated by oil red O staining and by the incorporation of [¹⁴C]glucose into lipids. Cell viability, apoptosis and necrosis were assessed by MTT hydrolysis and flow cytometry.

RESULTS: Chronic exposure (day -4 to +8) of adipocytes to d4T, ddI, 3TC (each 10 μ M) or ABC (4 μ M) did not alter adipose cell differentiation. Also, treatment with d4T, ddI, 3TC or ABC but not ZDV (1 μ M) did not alter cell response to insulin. However, ZDV or d4T decreased the lipid accumulation into adipocytes as shown by red oil staining (-43 and -23%) and insulin stimulation of lipogenesis (-38 and -40%). Whereas ddI, ABC and 3TC did not alter cell viability or apoptosis, d4T and ZDV mildly

increased cell apoptosis (6.0 ± 1.9 and $7.6 \pm 2.5\%$ as compared to $2.2 \pm 0.2\%$ in control cells). When the drugs were tested in association, the combination of ABC/3TC did not alter adipose cell functions, while the combination of 3TC/ZDV and 3TC/ABC/ZDV partly decreased lipid accumulation, cell viability and response to insulin.

CONCLUSIONS: Three of the NRTIs (ABC, ddI and 3TC) did not modify adipose cell functions, while d4T and ZDV decreased cell lipid content and mildly increased apoptosis. ZDV also induced insulin resistance. These results indicated that the thymidine analogues d4T and ZDV, but not the other NRTIs, presented some adverse effects in cultured adipocytes.

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