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NEVIRAPINE DID NOT ALTER CELL DIFFERENTIATION, LIPID METABOLISM, INSULIN RESPONSE AND SURVIVAL IN CULTURED ADIPOCYTES

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OBJECTIVES: Drug-associated adipocyte dysfunction plays a role in the aetiology of adverse symptoms that occur in HIV-infected patients treated with antiretrovirals. Protease inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs) and more recently the non-NRTI efavirenz were shown to affect adipocyte functions *in vitro*. Thus nevirapine (NVP), the other NNRTI used with success in switching studies, was evaluated *in vitro* for its potential to alter adipocyte functions.

METHODS: 3T3-F442A cells were treated with nevirapine (4.50 μ M) all along the differentiation process. Differentiation was estimated at day 7 by the percentage of cells with lipid droplets and the protein expression of adipocyte differentiation markers: SREBP-1, PPAR gamma and C/EBP alpha. Lipid metabolism was evaluated by lipid staining, mRNA expression of fatty acid synthase (FAS) and adipocyte lipid binding protein 2 (aP2), and insulin activation of lipogenesis. Insulin response was evaluated by the insulin-induced tyrosine phosphorylation of the insulin receptor β -subunit and IRS-1, and the activation of ERK 1/2 and Akt/PKB. Apoptosis was estimated by flow cytometry and cytotoxicity by MTT lysis.

RESULTS: In the therapeutic range (4.10 μ M), NVP did not alter adipose cell proliferation and differentiation. Indeed the number of cells with lipid droplets (92.95% of total cells), lipid staining, protein expression of SREBP-1, PPAR gamma and C/EBP alpha, and expression of FAS, PPAR gamma and aP2 were unchanged. At higher concentrations (50–100 μ M), NVP decreased lipid staining and expression of adipogenic markers. Cell response to insulin was not altered by NVP up to 50 μ M: insulin (100 nM) almost normally increased the insulin receptor β -subunit and IRS-1 tyrosine

phosphorylation and promoted ERK 1/2 and Akt/PKB activation. Insulin-induced lipogenesis was not affected by NVP up to 10 μ M. Up to 50 μ M, NVP did not promote cell toxicity and apoptosis (1–3% of cells in sub-G1). At higher concentrations (50–100 μ M), NVP induced toxicity and apoptosis.

CONCLUSIONS: Thus, in the therapeutic range (4–10 μ M), NVP had no effect on the main adipose cell functions measured *in vitro*. These data are of interest since NVP-containing regimens are often used as a switching option in patients treated with PI-containing regimens.

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