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HIV DRUGS ENTER HUMAN ADIPOCYTES AND INHIBIT DIFFERENTIATION OF PRECURSOR CELLS

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Lipodystrophy is a major side effect of antiretroviral therapy. This therapy can be composed of three classes of drugs: protease inhibitors (PIs), non-nucleosidic reverse transcriptase inhibitors (NNRTIs) and nucleosidic reverse transcriptase inhibitors (NRTIs).

PIs alter the adipocyte differentiation of mouse clonal preadipocytes. However, no study has been performed on human cell lines because of the lack of appropriate cellular models. Our laboratory has isolated human multipotent cells (human multipotent adipose-derived stem; hMADS), which differentiate into adipocytes. We have thus investigated the effect of PIs and NNRTIs on the differentiation process and the ability of these drugs to enter and accumulate in differentiated cells.

The effect of six different PIs (indinavir, saquinavir, ritonavir, amprenavir, nelfinavir and lopinavir) and two NNRTIs (nevirapine and efavirenz) was analysed by Oil-Red O staining for triglycerides and glycerophosphate dehydrogenase activity as indicator of adipocytes differentiation. The ability of ritonavir and nevirapine to accumulate in preadipocytes and adipocytes was estimated using two ELISA in the presence of various activators and inhibitors of drug transporters (verapamil, reserpine, sulfapyrazone, probenecid).

Saquinavir, ritonavir and lopinavir inhibit adipocyte differentiation but amprenavir, indinavir and nevirapine are ineffective. We show that ritonavir accumulates in preadipocytes and adipocytes as a function of its external concentration. Concentration of

5-6 nmol ritonavir/ 10^6 cells and 1-2 nmol of nevirapine/ 10^6 cells are present intracellularly throughout a adipocyte differentiation.

In conclusion, ritonavir and nevirapine accumulate in human preadipocytes and adipocytes, but only a direct effect of ritonavir is observed. As adipose tissue contains both preadipocytes and adipocytes, our results are consistent with a direct effect of PIs, which could lead to the development of a lipodystrophic syndrome.

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32

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