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INTRACELLULAR DISPOSITION OF ZIDOVUDINE, STAVUDINE AND PROTEASE INHIBITORS AND THEIR METABOLIC EFFECTS IN CULTURED ADIPOCYTES

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The development of a metabolic syndrome known as lipodystrophy characterized by dysregulated fat metabolism has offset the benefits of highly active antiretroviral therapy. Both protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) have been implicated in the pathogenesis, but it is unclear what cellular and biochemical mechanisms are affected by the drugs. We used both 3T3-L1 and 3T3-F442A murine cell lines to investigate: (1) the ability of the cells to phosphorylate stavudine and zidovudine to their phosphate metabolites; and (2) the effects of these NRTIs and the protease inhibitors (PIs), nelfinavir, ritonavir, saquinavir and indinavir on adipogenesis. Phosphorylation and intracellular PI concentrations were determined by fully validated HPLC and HPLCMS/MS methodologies, respectively. The effects of the antiretrovirals on lipolysis, adipocyte differentiation, glucose uptake, protein synthesis and toxicity were determined by glycerol, triglyceride estimations, radio-labelled glucose and methionine incorporation and MTT cytotoxicity studies, respectively. We present the first *in vitro* evidence that cultured adipocytes rapidly accumulate and phosphorylate [³H]-zidovudine and stavudine to their phosphate metabolites. Concentrations of zidovudine and stavudine up to 20 μ M were not cytotoxic, and did not markedly inhibit adipogenesis or induce lipolysis, and had no effects on pre-adipocyte protein synthesis. We demonstrate that PIs associate extensively with adipocytes, with nelfinavir and saquinavir accumulating more extensively than ritonavir and indinavir. The drugs, except indinavir, are cytotoxic, decreased cellular triglyceride accumulation, increased lipolysis and markedly impaired preadipocyte protein synthesis and glucose uptake. In the presence of insulin, however, cellular concentrations of the PIs were reduced with a consequent increase in protein synthesis and glucose uptake. PIs inhibited glucose uptake in the presence or absence of insulin according to the following rank order: indinavir > saquinavir > ritonavir > nelfinavir. These data suggest that PIs play a role in the insulin resistance observed in

lipodystrophy by affecting adipogenesis and lipolysis. NRTIs alone do not seem to have any effect on adipocyte metabolism despite undergoing phosphorylation, although their effects in combination with PIs needs further investigation.

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