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INVESTIGATIONS INTO THE PROPOSED MECHANISMS OF HIV-ASSOCIATED PERIPHERAL LIPODYSTROPHY, HYPERLIPIDAEMIA AND INSULIN RESISTANCE

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The precise mechanism(s) or causative agent for the metabolic changes observed in HIV patients are not known; however, a recent hypothesis suggests PIs are responsible. Preclinical investigations were initiated to investigate several aspects of the mechanisms that have been proposed. The first study compared the three-dimensional crystal structure of the cellular retinoic acid binding protein (CRABP1) and the HIV-1 protease enzyme. No structural similarity between the two proteins was found; the root mean square distance between the alpha-carbon atoms of a homologous 12 amino acid sequence was greater than 4 Å. In addition, the expression of CRABP1 in adipocytes was assessed by western blot analysis. CRABP1 was not detected, suggesting this protein may not be constitutively expressed in adipocytes. The second study investigated the role of cytochrome P450 3A4 (CYP3A4) in the isomerization of retinoic acid. Reactions performed with and without the addition of the CYP3A4 inhibitor, troleandomycin, showed that the isomerization of retinoic acid was not catalysed by this P450 isoform. These data confirm previous reports that the isomerization of retinoic acid is not catalysed by an enzymatic reaction. Additional studies were also performed to assess the effect of therapeutic concentrations of PIs on adipocyte differentiation. Saquinavir and indinavir were found to be the most potent inhibitors followed by ritonavir, nelfinavir and amprenavir. The relevance of this *in vitro* inhibition of adipocyte differentiation is currently unknown. The lack of significant homology between CRABP1 and HIV-1 protease together with the lack of CYP3A4 involvement in retinoic acid isomerization demonstrate that mechanisms other than those previously proposed may be involved in the metabolic effects. Recent studies have also implicated reverse transcriptase inhibitors

as possible causative agents. Studies to investigate the effects of RTIs on adipocyte differentiation and lipolytic activity are in progress.

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29

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