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DIRECT EFFECTS OF PROTEASE INHIBITORS ON LIPID METABOLISM IN CULTURED MAMMALIAN CELLS

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BACKGROUND: Lipodystrophy with associated hyperlipidaemia is commonly observed with HAART. The direct or indirect contribution of the protease inhibitor component of HAART to this syndrome is a current focus of investigation.

OBJECTIVES: To investigate the direct contribution of the protease inhibitors ritonavir and saquinavir to lipid metabolism utilizing *in vitro* microsomal assays and cell culture systems.

DESIGN: Ritonavir and saquinavir were applied to a human carcinoma cell line (HepG2) and to rat and human microsomal preparations *in vitro* to investigate effects on lipid metabolism. Cholesterol ester (CE) and triglyceride (TG) biosynthesis were measured by metabolic incorporation of labelled precursors. In addition, we assessed lipoprotein uptake by HepG2 cells utilizing artificially prepared, apolipoprotein E-associated, core-labelled triglyceride-rich emulsion particles (TGRP).

RESULTS: Ritonavir, and to a lesser extent saquinavir, markedly inhibited the incorporation of (¹⁴C)acetate, (³H)oleate, (³H)cholesterol, or (³H)mevalonate into CE. Only moderate effects on TG synthesis were observed. Both ritonavir and saquinavir (IC₅₀ approximately 15 and 60 µM, respectively) inhibited sterol esterification by the acyl-coenzymeA:cholesterol O-acyltransferase (ACAT) reaction in an *in vitro* microsomal assay, suggesting that these compounds act as ACAT inhibitors. No effect on TG synthesis was observed in an *in vitro* diacylglycerol-acyltransferase (DGAT) assay. Ritonavir was also associated with a twofold decrease in TGRP uptake.

CONCLUSIONS: We propose that hypertriglyceridaemia associated with ritonavir treatment may in part result from a defect in clearance of particles. The inhibition of the ACAT reaction may alter multiple aspects of lipid metabolism, including lipoprotein assembly, lipoprotein composition and transcriptional control of cholesterol homeostasis, all of which could contribute to the complications seen with current anti- HIV therapies.

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