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LEPTIN REPLACEMENT THERAPY BUT NOT DIETARY POLYUNSATURATED FATTY ACID AMELIORATES HIV PROTEASE INHIBITOR-INDUCED HYPERLIPIDEMIA AND LIPODYSTROPHY IN MICE

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Hyperlipidemia and lipodystrophy are major complications associated with protease inhibitor (PI) therapy in patients with HIV. Previous studies have shown that ritonavir treatment results in lipid abnormalities due to constitutive induction of lipid biosynthetic pathways regulated by sterol regulatory element binding proteins (SREBPs). Dietary polyunsaturated fatty acid (PUFA) or leptin replacement have been shown to be effective in reducing metabolic abnormalities associated with increased SREBP activities. Therefore, we examined whether leptin replacement and/or dietary PUFA treatment suppresses protease inhibitor-induced lipid abnormalities. Male C57BL/6 mice were placed on four diets: standard chow, 4% PUFA, 21% PUFA and 21% milk fat and gavaged with either 2 mg/day ritonavir or a corresponding vehicle control for 21 days. Weekly plasma lipid levels were determined. Half the animals were sacrificed and white adipose, scapular fat and livers were excised for weight, morphology and histochemistry analysis. Ritonavir treatment resulted in a 1.5- to twofold increase in triglycerides, regardless of diet. Total cholesterol levels showed a similar trend. In addition, the scapular mass increased with ritonavir treatment 1.5- to fourfold with little or no change in white adipose mass. Mice on the two high fat diets without ritonavir treatment also displayed increased plasma lipid levels and body fat mass. The effect of dietary fat and ritonavir on plasma lipid and body fat mass appears to be additive, and PUFA did not suppress the effect of ritonavir on hyperlipidemia and lipodystrophy. In contrast, when the ritonavir-treated mice were placed on leptin replacement therapy, by daily i.p. injection of 5 μ g leptin, a twofold decrease in both plasma triglyceride levels and scapular fat mass was observed after 7 days. The ritonavir-induced liver steatosis was improved by 25% after leptin replacement therapy. These data suggest that PI-induced lipid abnormalities may be reduced with leptin replacement therapy.

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