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Hypothesis

Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance

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Summary

HIV-1 protease-inhibitor treatments are associated with a syndrome of peripheral lipodystrophy, central adiposity, breast hypertrophy in women, hyperlipidaemia, and insulin resistance. The catalytic region of HIV-1 protease, to which protease inhibitors bind, has approximately 60% homology to regions within two proteins that regulate lipid metabolism: cytoplasmic retinoic-acid binding protein type 1 (CRABP-1) and low density lipoprotein-receptor-related protein (LRP). We hypothesise that protease inhibitors inhibit CRABP-1-modified, and cytochrome P450 3A-mediated synthesis of cis-9-retinoic acid, a key activator of the retinoid X receptor; and peroxisome proliferator activated receptor type gamma (PPAR-Î³) heterodimer, an adipocyte receptor that regulates peripheral adipocyte differentiation and apoptosis. Protease-inhibitor binding to LRP

would impair hepatic chylomicron uptake and triglyceride clearance by the endothelial LRP-lipoprotein lipase complex. The resulting hyperlipidaemia contributes to central fat deposition (and in the breasts in the presence of oestrogen), insulin resistance, and, in susceptible individuals, type 2 diabetes. Understanding the syndrome's pathogenesis should lead to treatment strategies and to the design of protease inhibitors that do not cause this syndrome.

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