Dyslipidemia due to retroviral protease inhibitors

To the editor—The biochemical basis for the development of lipodystrophy in HIV-1-infected patients treated with retroviral protease inhibitors (PIs) is unclear. Liang et al.1 demonstrate that the PIs ritonavir and saquinavir affect fat metabolism through alterations in neutral lipid synthesis and the secretion of apolipoprotein B (ApoB). The authors also propose that inhibition of proteasomal chymotryptic activity by ritonavir and saquinavir contribute to the observed intracellular accumulation of ApoB in vitro. Whereas the latter effect requires drug concentrations in the region of 50–100 µM, the former effects occur at 5–15 µM. For several reasons, we question the relevance of effects on proteasome function to the development of metabolic abnormalities associated with PI-induced lipodystrophy in vivo.

First, although we agree that ritonavir and saquinavir inhibit the chymotryptic activity of isolated 20S proteasomes in vitro, two other HIV-1 PIs, indinavir and nelfinavir, do not2,3. The use of either indinavir or nelfinavir would therefore have provided relevant controls for the experiments attributing intracellular accumulation of ApoB to inhibition of proteasomal activity. Further, although ritonavir does seem particularly likely to induce severe dyslipidemia, this metabolic complication of therapy is a feature of all retroviral PIs. Thus, it is difficult to attribute PI-associated lipodystrophy primarily to proteasome inhibition.

Second, the authors claim that the effects on ApoB metabolism attributed to inhibition of the proteasome were seen at therapeutically relevant concentrations of ritonavir and saquinavir. The in vitro IC50 (90% inhibitory concentration) of ritonavir is approximately 100 nM and that of saquinavir is less than 50 nM (ref. 4). Maximum plasma concentrations (Cmax) of these drugs in vivo are also well below the levels used by Liang et al. The Cmax of ritonavir is approximately 15 µM (ref. 4). The Cmax for saquinavir, even in ritonavir-boosted regimens, is less than 10 µM, and in non-boosted regimens is 10-fold lower.4 Although hepatocytes might be exposed to higher drug concentrations before systemic redistribution, such exposure is likely to be transient. Moreover, as both drugs are highly protein bound, any extrapolation of drug effects from in vitro to in vivo must take into account differences in protein concentrations. For any given total drug concentration, the pharmacologically active free drug levels are likely to be significantly higher in vitro, where serum concentrations are typically around 10%.

Third, we have found that concentrations greater than 10 µM of ritonavir and saquinavir compromise the viability of several B- and T-cell lines in vitro.5 The validity of drug-mediated cellular effects detected under such conditions is questionable.

The inhibition of both neutral lipid synthesis and ApoB secretion reported by Liang et al. occurs at concentrations of ritonavir and saquinavir that are feasible in vivo. Interestingly, the authors state that indinavir also causes similar alterations to neutral lipid synthesis. It may be that these in vitro drug effects provide insight into the generation of the lipid abnormalities that complicate the treatment of HIV-1 infected individuals with retroviral PIs. We would, however, caution against overemphasizing the role of proteasome inhibition in the development of lipodystrophy for the reasons outlined above.

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Sturley et al. reply—the major issue raised by Kelleher et al. regards the pharmacokinetics of HIV protease inhibitors such as...