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RITONAVIR AND INDINAVIR PROMOTE LIPID-INDUCED ATHEROSCLEROSIS BUT INHIBIT ENDOTHELIAL DENUDATION-INDUCED NEOINTIMAL HYPERPLASIA IN MICE

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The use of protease inhibitors (PIs) for treatment of HIV infection is associated with increased risk of peripheral and coronary artery disease (CAD). The pathogenesis of CAD is a complex process involving macrophage infiltration and lipid accumulation in the vessel wall, endothelial dysfunction and the migration of medial smooth muscle cells (SMC) to the intima, followed by their proliferation and matrix deposition to form an occlusive plaque. Although PI therapy has been shown to induce hyperlipidaemia and insulin resistance, thereby increasing the risk of lipid-laden foam cell formation and deposition at the vessel wall, whether PI therapy also contributes to the pathogenesis of CAD by modulating vascular cell activation has not been explored. This study used the mouse model to evaluate the effects of two different PIs, ritonavir and indinavir, on early (lipid-laden foam cell deposition) and late (SMC hyperplasia after endothelial injury) events of CAD. Administration of ritonavir 1.25 $\mu\text{g}/\text{kg}/\text{day}$ or indinavir 1.875 $\mu\text{g}/\text{kg}/\text{day}$ exacerbated foam cell-enriched atherosclerotic lesions in LDL receptor-deficient C57BL/6 mice fed an atherogenic diet for 16 weeks. To evaluate the effects of PI on SMC activation in response to endothelial injury, fat-fed wild-type FVB/N mice were treated with or without PI for 16 weeks. Endothelial denudation in the carotid arteries was accomplished with a resin-modified catheter probe. The carotid arteries were dissected and examined histologically after 14 days. Despite a similar increase in plasma lipid levels in the PI-treated mice, neointimal hyperplasia – as characterized by SMC migration and proliferation – in the injured carotid arteries was dramatically reduced in PI-treated mice as compared with vehicle-treated controls. *In vitro* cell culture experiments also showed ritonavir and indinavir inhibition of SMC migration and proliferation in response to PDGF. These results indicated that PI therapy promotes CAD mainly through its effects on metabolic parameters that lead to lipid-laden foam cell

formation instead of vascular SMC activation, thus suggesting that lowering plasma lipid and glucose levels may alleviate the accelerated CAD events associated with PI therapy in HIV-infected patients.

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