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Protease inhibitor atazanavir induces leukocyte-endothelial cell interactions in the microvasculature

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Purpose of the study

Combined antiretroviral therapy is associated with atherosclerosis and cardiovascular complications. Since patients receive various drugs simultaneously, it has been difficult to determine the role of each particular antiretroviral group or specific agent in these side-effects. Although clinical studies suggested protease inhibitors (PIs) as the agents responsible for these complications, this issue remains unclear. The present study was designed to analyze the acute effects of PIs on one of the first steps in the pathogenesis of atherosclerosis, i.e. leukocyte recruitment.

Methods

Leukocyte rolling, adhesion and emigration were monitored in the mesenteric post-capillary venules of anaesthetized rats by using intravital video microscopy. We compared the effects of the protease inhibitor atazanavir, lopinavir and indinavir (the two last boosted with ritonavir) administered orally 5 hr before the measurements. Doses were chosen according to the literature in order to generate plasma levels in animals similar to those clinically present in humans. Data were compared using a one-way analysis of variance followed by a Newman-Keuls post hoc test. All experiments were performed in groups of $n \geq 5$ animals.

Summary of results

Acute administration of the proteases inhibitors lopinavir (53, 106 mg/kg), boosted with ritonavir (13, 26 mg/kg, respectively) or indinavir (20, 40 mg/kg), boosted with ritonavir (20, 40 mg/kg, respectively) did not cause any effect on leukocyte parameters. Acute administration of the protease inhibitor atazanavir (100 mg/kg) promoted a significant increase in leukocyte rolling flux (59.8 ± 16.6 vs. 32.5 ± 2.7 cells/min), adhesion (16.1 ± 4.3 vs. 3.77 ± 0.7 cells/100 μm, $p < 0.001$) and emigration (7.5 ± 1.7 vs. 3.63 ± 0.8 cells/field, $p < 0.05$) compared with animals treated with vehicule. All values are mean ± SEM.

Conclusion

These studies indicate that acute exposure to atazanavir induces leukocyte recruitment and suggest that atazanavir could be responsible of precipitating the cardiovascular diseases observed in HIV-infected patients treated with protease inhibitors as part of combined antiretroviral therapy.

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