TREATMENT WITH SIMVASTATIN MODIFIES AT_1R EXPRESSION AND FUNCTION IN POLYMORPHONUCLEAR LEUKOCYTE OF HIGH CARDIOVASCULAR RISK SUBJECTS: A LONGITUDINAL STUDY

Maio Ramona Consuelo, Marino F., Guasti L., Cosentino M., Rasini E., Ferrari M., Cimpanelli M.G., Loraschi A., Legnaro M., Cereda E., Crespi C., Venco A., Lecchini S.

Department of Clinical Medicine, Section of Experimental and Clinical Pharmacology, University of Insubria, Varese

Background and Aim: Polymorphonuclear leukocytes (PMNs) play an important role in pathological processes related to atherosclerosis (ATH) and are the major source of reactive oxyigen species (ROS) and of the proinflammatory cytokine interleukin [IL]-8). Angiotensin (Ang) II exerts pro-atherogenic effects through Ang II type-1 receptor (AT_1R); Rac-1 plays a key role in Ang II-operated signalling pathways involved in leukocyte activation. Statins administration reduces cardiovascular morbidity and mortality in high-risk subjects (hRS). Subjects and Methods: We investigated AT_1R mRNA expression, IL-8, ROS production in hRS PMNs (ATP III criteria) before (visit-1), at 30 days (visit-2) and 1 year (visit-3) of simvastatin treatment (20 mg/day). Healthy subjects age and sex-matched were enrolled. We investigated the direct effects of Ang II on ROS generation, the effects of 24 h-incubation with Ang II and simvastatin on AT_1R expression in untreated hRS PMNs. In PMNs obtained from venous blood of healthy subjects we investigated the ability of simvastatin to interfere with Ang II-dependent Rac-1 activation. Results: Simvastatin treatment significantly reduced total cholesterol, LDL-c, Apo-B while triglycerides, hs-CRP and CK were unaffected. AT_1R mRNA levels in PMNs from hRS at visit-1 was higher *vs* control and was significantly reduced after 1 month of simvastatin treatment (visit-2 *vs* visit-1: $P<0.01$) and further decreased at visit-3 (visit 3 *vs* visit-1: $P<0.001$). PMNs at visit-1 showed higher resting and N-formyl-Met-Leu-Phe (fMLP) stimulated IL-8 production ($P<0.01$, $P<0.01$; respectively) and ROS generation (resting, $P<0.01$; fMLP-stimulated, $P<0.05$) *vs* controls. IL-8 resting and stimulated production was significantly affected by simvastatin treatment at visit 2 ($P<0.01$ and $P<0.05$, respectively) and further reduced at visit-3 ($P<0.001$ and P<0.001, respectively) while fMLP-induced ROS production was affected only at visit-3 ($P<0.001$). Ang-II increased membrane associated Rac-1 ($P<0.01$ *vs* control); this effect was prevented by coincubation with simvastatin ($P<0.01$ *vs* Ang II alone), which alone had no effect on Rac-1 (n.s.). In untreated hRS PMNs, Ang-II increased ROS generation (visit-1; $P<0.05$ *vs* resting ROS production) while during statin treatment a significant reduction was observed at visit-2 ($P<0.05$ *vs* visit-1). *In vitro* incubation with simvastatin significantly reduced AT_1R mRNA expression ($P<0.05$ *vs* control). Conclusion: In PMNs of hRS simvastatin induces down-regulation of AT_1R expression, reduces proinflammatory mediators production, interferes with Ang II activity and contributes to the anti-inflammatory profile of statins that can explain the therapeutic effects of these drugs.