Mechanisms involved in the inhibition of neointimal hyperplasia by abciximab in a rat model of balloon angioplasty

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摘要

Abstract

Monoclonal antibodies raised against β3 integrin are able to inhibit the binding of ligands to certain β3 integrins such as αIIbβ3 (glycoprotein IIb/IIIa complex) and αvβ3 (vitronectin receptor) and as such are inhibitors of platelet aggregation and smooth muscle cell (SMC) migration, both of which are involved in neointimal hyperplasia. The present study was designed to explore the detailed mechanisms of abciximab (Reopro), a monoclonal antibody (mAb) raised against αIIbβ3 integrin in neointimal hyperplasia. In this study, carotid arteries of Wistar rats were damaged, and neointimal hyperplasia and lumen occlusion was determined at different time points. Abciximab was administered intravenously by an implanted osmotic pump. Abciximab (0.25 mg/kg/day) time-dependently inhibited both neointimal hyperplasia and lumen occlusion after angioplasty in carotid arteries of rats. Furthermore, the electromicrographs highlighted that SMCs were phenotypically different from the typical contractile, spindle-shaped SMCs normally seen in uninjured vessel walls. Platelet-derived growth factor (PDGF)-BB was strongly produced in thrombus formation and neointimal SMCs after angioplasty, while abciximab significantly reduced PDGF-BB expression in vessel lumens and neointimal SMCs after angioplasty. Balloon angioplasty caused a significant increase of nitrate and cyclic GMP as compared with sham-operated rats. Infusion of abciximab (0.25 mg/ kg/day) did not significantly change. Furthermore, the plasma level of thromboxane B2 (T×B2) obviously increased after angioplasty, while abciximab markedly suppressed the elevation of plasma T×B2 concentration. The results indicate that abciximab effectively prevents neointimal hyperplasia, possibly through the following 2 mechanisms: (1) Abciximab binds to αIIbβ3 integrin on platelet membranes resulting in inhibition of platelet adhesion, secretion, and aggregation in injured arteries, followed by inhibition of

thromboxane A2 formation and PDGF-BB release from platelets. (2) Abciximab may also bind to $\alpha v \beta 3$ integrin on SMCs, thus, subsequently inhibiting cell migration and proliferation.