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INHIBITION OF P300 ACTIVITY ATTENUATES INTIMAL HYPERPLASIA FOLLOWING ARTERIAL INJURY

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Background p300 has been regarded as a potential source for cell proliferation, survival, growth, and differentiation by functioning as a transcriptional bridge, scaffold, and histone acetyltransferase. It is known that p300 plays a critical role in the development of heart failure and myocardial infarction. However, the expression of p300 in the artery wall and its possible role in the development of intimal hyperplasia after vascular injury have not been determined yet.

Methods Experiments were performed with VSMCs from thoracic aorta of Sprague–Dawley rats in vitro, and a rat carotid artery balloon injury model in vivo. Levels of p300, IkBα and p65 were detected by western blot. Levels of IL-6 and MCP-1 were assayed with real-time RT-PCR. To evaluate oxidative stress, reactive oxygen species were measured using the fluorescent dye dihydroethidium and NADPH activity was examined with a commercial kit. The carotid arteries of rats were used for immunohistochemical staining and morphometric analysis at seven days and 14 days after balloon injury.

Results p300 levels were increased 24 h after stimulation of thrombin in cultured VSMCs and in balloon injury of the rat carotids at seven days on protein levels. p300 inhibitor (50 μmol/l curcumin) significantly inhibited the expression of inflammatory factors IL-6 and MCP-1 induced by thrombin. The migration of thrombin-treated VSMCs was also suppressed by curcumin (50 μmol/l). In line with these changes, p300 inhibition with curcumin reduced the IkBα degradation and nuclear translocation of NF-κB in thrombin-stimulated VSMCs. In addition, curcumin suppressed ROS production in the presence of thrombin, which was associated with reduction of NADPH activity. Furthermore, the carotid arteries from SD rats were injured by balloon catheter, followed by administration of gavage with curcumin (50 mg/kg/d) or normal saline. After seven days and 14 days treatments, the area of neointimal to media area ratio was significantly decreased by 21.2 % and 32.4 %, respectively, compared with the control group. The incidence of proliferating cells labelled with PCNA, was also down-regulated in neointimal in curcumin group at about seven days. Relative to control group, immunohistochemisty analyses found the reduction of NF-κB in the neointimal 7 days after surgery.

Conclusion Inhibition of p300 activity attenuated neointimal formation of after artery injury. Therefore, blockage of p300 might represent a novel therapeutic strategy in case of vascular injury.