Molecular mechanisms and new pharmacological approaches in experimental neointimal hyperplasia

C. Giancotta[1], V. Musolino[1], M. Gliozzi[1], C. Carresi[1], A. Scarcella[1], F. Scarano[1], F. Oppedisano[1], J. Maiuolo[1], A. Maretta[1], L.A. Giancotti[1], F. Lauro[1], S. Ilari[1], E. Palma[1], C. Muscoli[1], V. Mollace[1]

[1]Institute of Research for Food Safety & Health (IRC-FSH), University of Catanzaro

Background: Reactive oxygen species (ROS) may contribute to the development of stenosis in balloon catheter injured arteries. Moreover, inflammatory response after mechanical arterial injury correlates with the severity of neointimal hyperplasia in animal models and postangioplasty restenosis in humans.
Materials and Methods: Male wistar rats (250-300g) subjected to carotid arteries baloon injury were injected with a bacterial lipopolysaccharide (LPS) 50 μg/kg or vehicle before surgery and treated intraperitoneally for 7 days with 10mg/kg MnTBAP, a superoxide dismutase (SOD) mimetic and peroxynitrite scavenger, or placebo. At day 7 of the experimental protocol, rats were sacrified and carotid arteries harvested to determinate the MnTBAP effects on vascular smooth muscle cell proliferation, COX-2 expression, peroxynitrite formation and to measure IL-1beta and CD45 as markers of inflammation.
Results: Morphometric analysis of the injured arteries 7 days after surgery revealed significantly increased neointima-to-media ratio in injured animals compared with controls ($p<0.05$ versus sham operated animals). Injection with LPS significantly increased neointima-to-media ratio in injured animals ($p<0.05$ vs BI rats). This effect was reduced by MnTBAP administration in a dose-dependent manner. Nitrotyrosine immunoreactivity was significantly increased in correlation with the severity of intimal hyperplasia and LPS treatment. MnTBAP administration was able to reduce peroxynitrite formation. Western blot analysis showed that 7 days after balloon injury, COX-2 levels was upregulated in the neointima. COX-2 levels resulted exacerbated by injection with LPS, whereas treatment with MnTBAP reduced COX-2 levels. Markers of activated inflammatory cells were characterized by immunohistochemistry for IL-1 ß and CD45. At 7 days after injury, level of CD45+ cells and IL-1 ß production was higher in injured LPS-treated rats. The inflamatory response was reduced in the injured arteries of the animals injected with LPS and treated with 10mg/kg MnTBAP.
Conclusions: Systemic inflammation induced by lipopolysaccharide increases neointimal formation after balloon injury in rats. This event is associated with a condition of nitro-oxidative stress and with an exacerbated inflamatory response. MnTBAP decreased neointima formation, which was associated with reduced vascular smooth muscle cell proliferation and attenuated nitro-oxidative stress. MnTBAP, a superoxide dismutase (SOD) mimetic and peroxynitrite scavenger, decreased neointima formation, which was associated with reduced vascular smooth muscle cell proliferation and attenuated nitro-oxidative stress and inflammation. Hence, MnTBAP might represent a valuable strategy in the treatment of vascular diseases characterized by an exacerbated inflammatory response.