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Nitric oxide-independent regulation of the vascular injury response

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A plethora of cellular and molecular signaling pathways are elicited in response to vascular trauma that eventuates in formation of an invasive neointima and adaptive remodeling of the vessel wall. The pivotal role of nitric oxide (NO) and downstream soluble guanylate cyclase (sGC)/cyclic guanosine monophosphate (cGMP) in mediating vasoprotection under both homeostatic and inimical conditions has been extensively studied in clinical medicine and basic science research. Recently, the parallel system of sGC-activating heme oxygenase (HO) and the diatomic gas carbon monoxide (CO) has emerged as a viable alternate pathway in mediating vascular protection following injury. Potential candidate factors involved in this regulation include inducible HO (HO-1) and CO and the novel exogenous sGC/cGMP-sensitizing agents YC-1 and BAY 41-2272. The overall goal of these studies is to elucidate potential protective influence of these NO-independent systems in regulating the neointimal and vascular remodeling responses to experimental carotid artery balloon injury in laboratory rats. Results show that HO-1 and CO independently attenuate neointima development 2 weeks following injury through inhibition of acute vascular smooth muscle cell (SMC) DNA synthesis and proliferation, decreased acute expression of growth-promoting TGF-β_1 and the G_1 cyclins E and A, and enhanced SMC apoptosis. Similar experiments utilizing the sGC-sensitizing benzyl indazole compound YC-1 found vessel wall cGMP to correlate with reduced vascular SMC growth and platelet function and diminished neointima formation. Promising early results suggest the NO-independent sGC activator BAY 41-2272 reduces the neointimal response to injury through anti-proliferative and anti-migratory actions on vascular SMCs. In addition, the anti-proliferative effects of BAY 41-2272 were significantly potentiated in the presence of the HO-1 inducer and substrate hemin. These cumulative results strongly suggest that the HO-1/CO system and novel NO-independent routes of sGC/cGMP activation exert salutary influence upon compromised blood vessels via regulation of various cellular growth-promoting functions and may represent attractive therapeutic strategies aimed at reducing vascular lesion formation.