Nitric oxide (NO) and other reactive oxygen species (ROS) are involved in angiogenesis. Recently, we demonstrated that NO enhances VEGF synthesis in vascular smooth muscle cells (VSMC) [Dulak et al., ATVB 20 (2000) 659, Józkowicz et al., Cardiovasc Res. 51 (2001) 773] and we showed that HO-1 activity modulates NO-induced VEGF synthesis, with CO being an activator and iron an inhibitor of VEGF production [Dulak et al., Antioxid Redox Signal 4 (2002) 229]. Here, we further elaborate on the potential pathways of HO-1 mediated modulation of VEGF synthesis. NO-donors or over-expression of NO synthases (NOS II or NOS III) induce VEGF generation in VSMC through the activation of hypoxia responsive element (HRE) in VEGF promoter. Similarly, gene transfer of HO-1 activates the human VEGF promoter and augments the expression of VEGF mRNA and protein in VSMC and a microvascular endothelial cell line (HMEC-1) 2-4 fold. Iron, a by-product of HO, inhibits VEGF synthesis, potently reducing the activity of HRE. Interestingly, the effect of NO and HO appears to be independent of cGMP, as methylene blue and ODQ, the inhibitors of soluble guanylate cyclase, did not influence NO- or HO-dependent VEGF synthesis. VEGF synthesis in VSMC and 3T3 fibroblasts is potentiated by exogenous H$_2$O$_2$ (50-400 µM; up to a 3-fold increase). Accordingly, the gene transfer of human Cu, Zn superoxide dismutase (SOD), an enzyme generating H$_2$O$_2$, strongly enhances VEGF transcription, influencing the HRE activity. The increase in VEGF production is inhibited by exogenous catalase or by transfection of cells with expression plasmid containing catalase cDNA. The induction of VEGF by H$_2$O$_2$ appears to correlate with HO-1 expression. In conclusion, ROS potently increase VEGF production. ROS also induce HO-1, which can modulate VEGF synthesis.