

CO Provides Antioxidant Protection by Reducing Carbonylated MnSOD During Remote Inflammatory Stress

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Although the anti-inflammatory benefits of exogenous CO are well recognized, its antioxidant potential remains unknown. We examined the role of CO in regulating hepatic oxidant generation using bilateral hindlimb ischemia/reperfusion (I/R) as a model of systemic inflammation. Immediately following the onset of I/R, mice were treated with exogenous CO (methylene chloride or gaseous CO). Bilateral hindlimb I/R caused significant liver damage and lipid peroxidation. In vivo digital microscopy with the oxidant-sensitive probe dihydrorhodamine confirmed the generation of hepatic oxidants. Treatment with CO significantly reduced all aspects of liver damage and oxidant formation. Due to its chemistry, CO is not likely a direct oxidant scavenger. Thus we investigated whether the antioxidant benefit of exogenous CO occurred via regulation of manganese superoxide dismutase (MnSOD) activity. As with direct I/R, MnSOD protein expression was unchanged yet its activity was diminished. Concomitant to this functional MnSOD demise was an increase in its carbonylation - an inactivating oxidative protein modification. Treatment with CO reduced the carbonylation of MnSOD and restored its activity. These results suggest that exogenous CO indirectly reduces the hepatic oxidant stress that accompanies a remote inflammatory insult by diminishing MnSOD carbonylation, and thereby restoring MnSOD activity.