Pharmacological induction of vascular extracellular superoxide dismutase expression in vivo.

Abstract:

Pentaerythritol tetranitrate (PETN) treatment reduces progression of atherosclerosis and endothelial dysfunction and decreases oxidation of low-density lipoprotein (LDL) in rabbits. These effects are associated with decreased vascular superoxide production, but the underlying molecular mechanisms remain unknown. Previous studies demonstrated that endogenous nitric oxide could regulate the expression of extracellular superoxide dismutase (ecSOD) in conductance vessels in vivo. We investigated the effect of PETN and overexpression of endothelial nitric oxide synthase (eNOS(++) on the expression and activity of ecSOD. C57BL/6 mice were randomized to receive placebo or increasing doses of PETN for 4 weeks and eNOS(++) mice with a several fold higher endothelial-specific eNOS expression were generated. The expression of ecSOD was determined in the lung and aortic tissue by real-time PCR and Western blot. The ecSOD activity was measured using inhibition of cytochrome C reduction. There was no effect of PETN treatment or eNOS overexpression on ecSOD mRNA in the lung tissue, whereas ecSOD protein expression increased from 2.5-fold to 3.6-fold (P<0.05) by 6 mg PETN/kg body weight (BW)/day and 60 mg PETN/kg BW/day, respectively. A similar increase was found in aortic homogenates. eNOS(++) lung cytosols showed an increase of
ecSOD protein level of 142 +/- 10.5% as compared with transgene-negative littermates (P < 0.05), which was abolished by N(omega)-nitro-L-arginine treatment. In each animal group, the increase of ecSOD expression was paralleled by an increase of ecSOD activity. Increased expression and activity of microvascular ecSOD are likely induced by increased bioavailability of vascular nitric oxide. Up-regulation of vascular ecSOD may contribute to the reported antioxidative and anti-atherosclerotic effects of PETN.