Mechanisms of vascular dysfunction in mice with endothelium-specific deletion of the PPAR-delta gene.

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Public Summary: Peroxisome proliferator-activated receptor (PPAR)-delta is a nuclear hormone receptor that is mainly involved in lipid metabolism. Recent studies have suggested that PPAR-delta agonists exert vascular protective effects. The present study was designed to characterize vascular function in mice with genetic inactivation of PPAR-delta in the endothelium. Mice with vascular endothelial cell-specific deletion of the PPAR-delta gene (ePPAR-delta(-/-) mice) were generated using loxP/Cre technology. ePPAR-delta(-/-) mice were normotensive and did not display any sign of metabolic syndrome. Endothelium-dependent relaxations to ACh and endothelium-independent relaxations to the nitric oxide (NO) donor diethylammonium (Z)-1-(N,N-diethylamino)diazen-1-ium-1,2-diolate were both significantly impaired in the aorta and carotid arteries of ePPAR-delta(-/-) mice (P < 0.05). In ePPAR-delta(-/-) mouse aortas, phosphorylation of endothelial NO synthase at Ser1177 was significantly decreased (P < 0.05). However, basal levels of cGMP were unexpectedly increased (P < 0.05). Enzymatic activity of GTP-cyclohydrolase I and tetrahydrobiopterin levels were also enhanced in ePPAR-delta(-/-) mice (P < 0.05). Most notably, endothelium-specific deletion of the PPAR-delta gene significantly decreased protein expressions of catalase and glutathione peroxidase 1 and resulted in increased levels of H2O2 in the aorta (P < 0.05). In contrast, superoxide anion production was unaltered. Moreover, treatment with catalase prevented the endothelial dysfunction and elevation of cGMP detected in aortas of ePPAR-delta(-/-) mice. The findings suggest that increased levels of cGMP caused by H2O2 impair vasodilator reactivity to endogenous and exogenous NO. We speculate that chronic elevation of H2O2 predisposes PPAR-delta-deficient arteries to oxidative stress and vascular dysfunction.

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