Countervailing vascular effects of rosiglitazone in high cardiovascular risk mice: role of oxidative stress and PRMT-1.

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Abstract

In the present study, we tested the hypothesis that the PPARgamma (peroxisome-proliferator-activated receptor gamma) activator rosiglitazone improves vascular structure and function in aged hyperhomocysteinaemic MTHFR (methylene tetrahydrofolate reductase) gene heterozygous knockout (mthfr+/-) mice fed a HCD (high-cholesterol diet), a model of high cardiovascular risk. One-year-old mthfr+/- mice were fed or not HCD (6 mg x kg-1 of body weight x day-1) and treated or not with rosiglitazone (20 mg x kg-1 of body weight x day-1) for 90 days and compared with wild-type mice. Endothelium-dependent relaxation of carotid arteries was significantly impaired (-40%) only in rosiglitazone-treated HCD-fed mthfr+/- mice. Carotid M/L (media-to-lumen ratio) and CSA (cross-sectional area) were increased (2-fold) in mthfr+/- mice fed or not HCD compared with wild-type mice ($P<0.05$). Rosiglitazone reduced M/L and CSA only in mthfr+/- mice fed a normal diet. Superoxide production was increased in mthfr+/- mice fed HCD treated or not with rosiglitazone, whereas plasma nitrite was decreased by rosiglitazone in mice fed or not HCD. PRMT-1 (protein arginine methyltransferase-1), involved in synthesis of the NO (nitric oxide) synthase inhibitor ADMA (asymmetric omega-NG,NG-dimethylarginine), and ADMA were increased only in rosiglitazone-treated HCD-fed mthfr+/- mice. Rosiglitazone had both beneficial and deleterious vascular effects in this animal model of high cardiovascular risk: it prevented carotid remodelling, but impaired endothelial function in part through enhanced oxidative stress and increased ADMA production in mice at high cardiovascular risk.