Abstract: P350

Deficiency in endothelial cell tetrahydrobiopterin increases resistance vascular remodelling, blood pressure, and susceptibility to aortic abdominal aneurysm in response to angiotensin II

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Topic(s):
Vascular Biology and Physiology, Other

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S90

The cofactor tetrahydrobiopterin (BH4) is a critical regulator of endothelial NOS (eNOS) function, eNOS-derived NO and reactive oxygen species (ROS) signalling in vascular physiology. We have previously shown that mice with selective loss of endothelial cell Gch1, encoding GTP cyclohydrolase 1 (GTPCH), an essential enzyme for BH4 biosynthesis, have mild vascular dysfunction. However, the consequence of endothelial cell BH4 deficiency in vascular disease pathogenesis is unknown. The aim of this study was to investigate the pathological consequence of Angiotensin II (Ang II) infusion in endothelial cell Gch1 deficient (Gch1fl/flTie2cre) mice.

Wild-type (Gch1fl/fl) and Gch1fl/flTie2cre mice were infused with a subpressor dose of Ang II (0.4 mg/kg/day, delivered by osmotic mini pump). Ang II caused a significant decrease in circulating BH4 levels in Gch1fl/flTie2cre mice and a significant increase in the L-NAME inhibitable production of H2O2 in the aorta. Chronic treatment with this subpressor dose of Ang II resulted in a significant increase in blood pressure in Gch1fl/flTie2cre mice but not in wild-type littermates. This finding was mirrored with acute administration of Ang II where increased sensitivity to Ang II was observed at both pressor and subpressor doses. Chronic Ang II infusion in Gch1fl/flTie2ce mice resulted in vascular dysfunction in resistance mesenteric arteries with an enhanced constrictor and decreased vasodilator response, and medial hypertrophy. Altered vascular remodelling was also observed in the aorta with an increase in the incidence of abdominal aortic aneurysm (AAA) formation in Gch1fl/flTie2ce mice.

Taken together, these studies demonstrate that endothelial cell BH4-dependent eNOS regulation/eNOS uncoupling is implicated in the pathogenesis of vascular remodelling, hypertension and the development of AAA. These findings suggest that Ang II has a profound effect on vascular pathology when combined with endothelial cell BH4 deficiency. Therefore, targeting vascular Gch1 and BH4 biosynthesis may provide a novel therapeutic target for the prevention and treatment of vascular dysfunction in patients with vascular disease.