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VASCULAR PEROXIDE 1 IS INVOLVED IN VASCULAR REMODELLING IN SPONTANEOUSLY HYPERTENSIVE RATS VIA MATRIX METALLOPROTEINASE-2 ACTIVATION

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Objectives Vascular peroxide 1 (VPO1) is a newly identified heme-containing peroxidase, which can utilise hydrogen peroxide (H₂O₂) generated from NAD (P) H oxidase to produce hypochlorous acid (HOCl) and catalyse peroxidative reactions. Considering the well-defined effects of matrix metalloproteinase (MMP) on the vascular remodelling during hypertension, and HOCl has a potential regulator role in the activation of MMP via oxidative modifications, the aims of this study was to determine whether VPO1 is a regulator of MMP activity via HOCl formation and play an important role in vascular remodelling in spontaneously hypertensive rats (SHRs).

Methods Morphometry of structural changes in the aortic wall from SHRs and Wistar Kyoto rats were studied in haematoxylin/eosin, orcein and picrosirius red sections. The expressions of VPO1, MMP-2 and tissue inhibitor of MMP-2 TIMP-2 in arterial tissues were measured with immunohistochemical staining, western blot or gelatine zymography. Cultured rat aortic smooth muscle cells (rVSMCs) were treated with angiotensin II, the expression of VPO1, MMP-2 and gelatinolytic activity of pro-MMP-2 were examined while the concentration of HOCl were measured. The effect of VPO1 RNA interference on HOCl generation, pro-MMP-2 activity and MMP-2 expression were observed. Moreover, the direct effects of HOCl on pro-MMP-2 activity and MMP-2 expression were also examined.

Results We found increased aortic collagen and elastin content in SHRs, which were associated with vascular hypertrophy. Increased vascular MMP-2 (but not TIMP-2) levels, and increased gelatinolytic activity, possibly as a result of increased VPO1 expression. In cultured rVSMCs, treatment with angiotensin II significantly increased the gelatinolytic activity of pro-MMP-2 and MMP-2 expression while unregulated VPO1 expression and generation of HOCl. Using VPO1 RNA interference rVSMCs, effects of angiotensin II on HOCl generation, pro-MMP-2 release and MMP-2 expression were significantly inhibited. Furthermore, treatment with HOCl also markedly increased the gelatinolytic activity of pro-MMP-2 and MMP-2 expression.

Conclusions These results indicate that VPO1 is involved in vascular remodelling in arterial hypertension by play a key role in the activation of MMP-2 via HOCl formation.