Short term serelaxin treatment reduces prostanoid-mediated endothelium-derived vasoconstriction and restores endothelial vasodilator function without concomitant changes to cardiac remodelling in spontaneously hypertensive rats

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Introduction: Endothelial dysfunction and adverse cardiac remodelling increase the risk for cardiovascular disease in hypertension. An important contributor to endothelial dysfunction involves upregulation of vasoconstrictor prostanoid action. Serelaxin is a pleiotropic peptide with vasoprotective, anti-hypertrophic and anti-fibrotic properties, however the effects of short term serelaxin infusion on prostaglandins and cardiac remodelling in spontaneously hypertensive rats (SHRs) are unclear. Therefore, the aims of the present study were to investigate the vascular and cardiac effects of a 3 day serelaxin infusion in SHRs.

Methods: Male Wistar Kyoto rats (WKYs) and SHRs were subcutaneously infused with either placebo (20mM sodium acetate) or serelaxin (13.3 μg/kg/h) using osmotic minipumps for 3 days. After 3 days of treatment, the rats were anaesthetized with 2% isoflurane in oxygen *via* inhalation followed by cardiac puncture, exsanguination and tissue collection. Reactivity of mesenteric arteries and left ventricular morphology were assessed using wire myography and histology, respectively. Pharmacological blockers were used to evaluate the relative contribution of nitric oxide (NO), prostanoids and endothelium-derived hyperpolarisation (EDH). Changes in gene expression and prostaglandins metabolites were measured by quantitative PCR and liquid chromatography mass spectrometry, respectively.

Results: In SHRs, vascular sensitivity to the endothelium-dependent vasodilator acetylcholine (ACh) was significantly reduced compared to WKYs. Endothelial dysfunction in SHRs was attributed to impairment of both NO-mediated and EDH-type relaxations. Furthermore, there was a concomitant increase in cardiomyocyte size, upregulation of hypertrophic (natriuretic peptide type B) and fibrotic (connective tissue growth factor and transforming growth factor-β) gene expression in the myocardium of SHR. These findings indicated that hypertension is associated with endothelial dysfunction and adverse cardiac remodelling. Treatment with serelaxin for 3 days selectively reversed vascular endothelial dysfunction by increasing NO-mediated relaxation but had no effect on cardiac fibrosis or hypertrophy. To investigate the contribution of vasoconstrictor prostanoids, responses to ACh were evaluated after the inhibition of NO and EDH. In resting mesenteric arteries, ACh-induced contraction was absent in WKYs but was significantly increased in SHRs. In arteries from SHR, there was increased prostacyclin (PGI2) production and downregulation of PGI2 receptor (IP) expression. Serelaxin treatment of SHRs reduced ACh-induced contraction, increased IP expression, but had no effect on PGI2 production. The contraction to ACh was abolished by the thromboxane receptor (TP) antagonist, suggesting that PGI2 targets TP to produce contraction in SHR, and this was inhibited by serelaxin treatment.

Conclusion: Short term serelaxin treatment restores mesenteric artery endothelial vasodilator function in SHRs and attenuates endothelium-dependent contraction, independent of any cardiac effects. Improvement of endothelial function involves restoring the functionality of the PGI2-IP vasodilator and NO pathway.