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Poster presentation

Negative feedback regulation within NO/cGMP pathway attenuates vasodilatory response in renovascular hypertension

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Background

Hypertension, the leading risk factor for cardiovascular mortality has been associated with alterations in endothelium- and smooth muscle-dependent vascular relaxation. The NO/cGMP signaling cascade is one of the major pathways that mediate vascular relaxation. In this pathway, the NO receptor guanylyl cyclase (NO-GC) holds a key position by converting the NO signal into cGMP increases. Two isoforms of the heterodimeric NO receptor GC exist; both isoforms share an identical β subunit but differ in their respective α subunit (α_1 or α_2) and are referred to as NO-GC1 (so far $\alpha_1\beta_1$heterodimer) and NO-GC2 (so far $\alpha_2\beta_1$heterodimer), respectively. Knockout (KO) mice deficient in either one of the NO-GCs, NO-GC1 or NO-GC2, revealed that both NO-GCs are capable to mediate vascular relaxation. The NO-GC1 appears to be the major isoform, particularly in the aorta, where NO-GC1 represents approximately 90% of total NO-GC content. Deletion of the NO-GC1 resulted in reduced endothelium-dependent relaxation and reduced vasodilatory response to exogenous NO, which is mediated by the NO receptor GC2 in NO-GC1-deficient mice. Despite the low NO-GC2 content, NO-GC1 KO mice exhibit only a minute blood pressure increase.

Results

In the present study, we used the Goldblatt model of renovascular hypertension (2 kidney 1 clip [2K1C] operation) to induce hypertension in the NO-GC1 KO mice and investigated the impact of renovascular hypertension in aorta and renal vasculature of 2K1C-operated NO-GC1-deficient mice. Much to our surprise, blood pressure increases induced by the 2K1C operation did not differ between NO-GC1 KO and WT mice. Moreover, unlike as in WT mice, the 2K1C operation did not cause a reduction of endothelium-dependent relaxation in the NO-GC1-deficient mice. The reduced endothelium-dependent relaxation observed in WT vessels was paralleled by a reduced response to exogenous NO indicating an alteration of smooth muscle relaxation induced by the 2K1C operation. An increase of phosphorylated PDE5 indicates activation of PDE5 as the underlying mechanism for the attenuated vasodilatory response.