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Enhanced vascular cGMP/cGK I signaling and hypotonia in cysteine-rich-protein 2-deficient mice

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The NO/cGMP signaling pathway plays an important role in vasorelaxation and blood pressure regulation. The predominant effector of cGMP in vascular smooth muscle is cGMP kinase I (cGK I). Established substrates of cGK I in vascular smooth muscle are the large-conductance voltage- and Ca^{2+}-activated (BK) potassium channel, the IP_3-receptor-associated cGMP kinase substrate (IRAG) and the myosin phophatase 1 M. Previously, we identified the cysteine-rich protein 2 (CRP2) in blood vessels as a new substrate of cGK I which is specifically phosphorylated by cGK I *in vivo*. However, the physiological role of CRP2 and its involvement in regulation of vascular tone as an effector of cGMP/cGK I signaling was not known. To elucidate the functional role of CRP2 in vascular smooth muscle, we generated CRP2-deficient ($CRP2^{-/-}$) mice. The myogenic tone of $CRP2^{-/-}$ tibial small arteries towards stepwise pressure changes revealed no differences when compared to wild type (wt). Unexpectedly, cGMP-mediated relaxation was enhanced in $CRP2^{-/-}$ tibial small arteries and A. saphena. In contrast to cGMP, the cAMP-mediated relaxation was not affected in these vessels. Long-term radiotelemetric recordings revealed a significantly decreased mean arterial pressure (MAP) and an enhanced NO/cGMP signaling in $CRP2^{-/-}$ mice compared to wt. In-depth analysis revealed increased protein levels of cGK I, whereas the expression of cGK I targets such as BK channel and IRAG was not altered in $CRP2^{-/-}$ vessels compared to wt. Interactor screens with CRP2 as a bait revealed a specific interaction with a translation initiation factor. These findings suggest that CRP2 is a specific effector of the vascular NO/cGMP/cGK I signaling *in vivo*. CRP2 seems to be involved in the regulation of the NO/cGMP/cGK I signaling pathway by modulating cGK I expression. In addition, the $CRP2^{-/-}$ mouse line may serve as an animal model for hypotonia.