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Analysis of mice with genetic modifications of PKG I

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The signaling molecule nitric oxide (NO) exerts both beneficial and deleterious effects on the vasculature; however, the molecular signaling pathways are incompletely understood. In smooth muscle cells (SMCs), the second messenger cyclic guanosine monophosphate (cGMP) mediates many effects of NO via the activation of cGMP-dependent protein kinase type I (cGKI). The cGKI gene, *prkg1*, encodes two isoforms, cGKIα and cGKIβ, both of which are expressed in SMCs. The isoforms differ only in their individual amino-terminal ends, which mediate the interaction with partner proteins and target the kinases to different subcellular compartments. Conventional knockouts carrying a cGKI null mutation (cGKI$^{-/-}$) show multiple phenotypes. These animals are difficult to analyse, since most die before adulthood. Recently, two mouse lines were generated that express either the cGKIα or cGKIβ isoform exclusively in SMCs of cGKI$^{-/-}$ mice. These mouse lines allow an isoform specific of individual smooth muscle functions in adult "healthy" animals. 8-Br-cGMP treatment of aortic SMCs from rescued mice reduced norepinephrine- and depolarization-induced Ca^{2+}-increases to wild type levels. In addition, the 8-Br-cGMP-induced relaxation of hormone contracted aorta and jejunum was intact in the rescued animals. Finally, telemetric blood pressure recordings in awake, freely moving mice revealed no differences between rescued and control (wild type) mice. Taken together, these results suggest that both isoforms can rescue a major part of the cGMP/cGKI signaling in SMCs and either isoform can compensate for the other in the modulation of vascular tone. Irrespective of the reconstituting isozyme, 50% of the rescued cGKIα and cGKIβ mice die within 52 weeks. Abnormalities found in the mouse lines that possibly cause premature death will be discussed.