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Signaling through NO and cGMP-dependent Protein Kinase

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Many but not all NO effects are mediated by activation of soluble guanylyl cyclase and cGMP. Important cellular effectors of cGMP are cGMP Kinase I (cGKI) and II (cGKII). Analysis of the functional significance of these kinases has been carried out by targeted inactivation of the genes for cGKI and cGKII in the mouse. The major phenotypes observed in conventional cGKI knockout mice are decreased life span (1), impaired relaxation of vascular (1), visceral (1-3), and penile (4) smooth muscle, disturbed platelet function (5) and defects in the guidance and connectivity of sensory axons (6). The phenotype of cGKII knockout mice includes normal life span (7), decreased longitudinal bone growth (7,8), decreased intestinal chloride secretion (7,9), altered renin secretion (10) and shift in circadian clock adaptation (11). Tissue specific deletion of the cGKI gene showed decreased negative cardiac inotropy (12), impaired hippocampal LTP in older mice (13), decreased cerebellar LTD (14) and increased atherosclerosis (15). Activation of cGKI promotes smooth muscle cell growth (15,16). The spectrum of phenotypes revealed by gene targeting is in line with the tissue distribution of each cGK isozyme and points to an important role for cGKI in the cardiovascular (17) and nervous system (6). It is possible that cGKII influences hemodynamic parameters by regulating renin release and ion transport in the kidney. cGKII affects also the perception of ethanol (18) and other brain functions (11).

Murine aortic smooth muscle cells express both the Iα and the Iβ isozymes of cGKI and IRAG. In Cos cells, IRAG is phosphorylated specifically by cGKIβ and regulates the release of calcium from IP_3 sensitive stores (19,20). However, reconstitution of the cGKI isoenzymes into cGKI-negative aortic smooth muscle cells suggested that the calcium decreasing effects of cGMP were mediated by the Iα isozyme (21). The target for this isozyme has not been identified unequivocally (22). Inactivation of the IRAG-gene results in disturbed intestinal function and a decreased expression of the cGKIβ isozyme. In addition, cGKI-/- mice have in most smooth muscle cells a decreased expression of IRAG. This finding may be the cause of the unresponsiveness of reconstituted cGKI-/- smooth muscle cells to the cGKIβ isoenzyme. In general, the use of targeted inactivation of the cGMP kinase genes and its substrate IRAG shows that these proteins are important regulators in many tissues.

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