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Regulation of cardiovascular physiology by cyclic GMP-dependent protein kinase Iα

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The nitric oxide (NO)/cyclic GMP signaling system regulates both vascular and cardiac function in fundamental ways. Vascular tone is dynamically regulated by vascular smooth muscle cell contractile state. The main effector of NO/cGMP action in cardiovascular target tissues is cyclic GMP-dependent protein kinase I (PKG), a cGMP-activated serine-threonine kinase with multiple targets in vascular and cardiac cells. In the vasculature, the NO/cGMP/PKG signaling system is the most important endogenous vasodilator system known. Vascular contraction by many agonists is mediated by G_q-coupled receptor activation, calcium mobilization and myosin light chain (MLC) phosphorylation. Nitric oxide (NO) inhibits vascular contraction by activating PKGIα, which both attenuates calcium mobilization by GPCR and activates myosin phosphatase (PP1M), causing dephosphorylation of myosin light chain and VSMC relaxation. We have shown that PKGIα binds directly to the MBS subunit of the PP1M phosphatase. PKGIα also attenuates signaling by G_q-coupled receptors via a direct interaction with the regulator of G-protein signaling, RGS2, which PKGI phosphorylates and activates to terminate G_q-coupled receptor-mediated signaling. The N-terminal leucine zipper (LZ) of PKGIα mediates its interaction with PP1M and RGS2. To explore the role of PKGIα in blood vessels and heart, we used gene targeting several years ago to create mice that express a LZ mutant (LZM) form of PKGIα in which critical amino acids in the leucine zipper motif have been substituted to disrupt LZ binding. Newer studies of these mice will be described. VSMC from PKGIα mutant mice display multiple phenotypic abnormalities in culture. In addition, PKGIα-mediated regulation of Rho/Rho kinase signaling is disrupted in intact VSMC from LZM mice. Blood vessels from PKG1α mutant mice relax abnormally and intact PKG1α mutant mice have systemic hypertension, without detectable abnormalities of renal function. New data regarding PKGIα and myocardial function in wild type and LZM mice will also be discussed. These data demonstrate the central importance of PKGIα signaling in maintenance of normal vascular physiology and blood pressure, and in the regulation of myocardial hypertrophy.

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