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Oral presentation

Creation and characterization of mice with selective mutation of the cyclic GMP-dependent protein kinase I interaction domain

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Vascular tone is dynamically regulated by vascular smooth muscle cell contractile state. 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 cGMP-dependent protein kinase I α (PKGI-α), which causes MLC dephosphorylation and vascular smooth muscle relaxation. Cyclic GMP-dependent protein kinase I (PKGI) is the principle effector of nitric oxide (NO) signaling in vascular smooth muscle cells (VSMC). Activation of PKGI? by NO signaling has several effects in VSMC, including activation of myosin phosphatase (PP1M), which dephosphorylates the myosin light chain, causing relaxation. We have shown that PKGIα binds directly to the MBS subunit of the PP1M phosphatase via leucine zipper (LZ) motifs in each protein, providing a molecular basis for the effects of NO and cGMP on vascular relaxation. In recent studies, we found that PKGI-α also attenuates signaling by the G_q-coupled thrombin receptor PAR-1 by directly activating the regulator of G-protein signaling, RGS2. The same PKGI-α LZ domain that interacts with PP1M also mediates binding of PKGIα to RGS2. PKGI phosphorylates RGS2 and thereby activates the GTPase activity of G_q, inhibiting PAR-1 signaling. In addition, $Rgs2^{-/-}$ mouse blood vessels have enhanced contraction and decreased cGMP-mediated relaxation, and these mice have marked hypertension. The presence of vasomotor dysfunction and hypertension in the RGS-2 knockout mice raises the possibility that intrinsic abnormalities of VSMC relaxation alone are sufficient to cause hypertension. To explore this hypothesis and the role pf PKGIα in regulation of vascular tone and blood pressure, we have used gene targeting to generate 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. The generation and characterization of the LZM mice will be described and data from LZM mouse studies will be presented. The studies support an essential role for PKGIα in maintenance of normal vascular tone and blood pressure and are consistent with the hypothesis that intrinsic abnormalities of VSMC regulation can be a primary, non-renal cause of high blood pressure.

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