Abstract:
Signalling via cGMP-dependent protein kinase I (cGKI) is the major pathway in vascular smooth muscle (SM), by which endothelial NO regulates vascular tone. Recent evidence suggests that canonical transient receptor potential (Trpc) channels are targets of cGKI in SM and mediate the relaxant effects of cGMP signalling. We tested this concept by investigating the role of cGMP/cGKI signalling on vascular tone and peripheral resistance using Trpc6(-/-), Trpc3(-/-), Trpc3(-/-)/6(-/-), Trpc1(-/-)/3(-/-)/6(-/-), and SM-specific cGKI(-/-) (sm-cGKI(-/-)) mice. ?-Adrenergic stimulation induced similar contractions in L-NG-nitroarginine methyl ester (l-NAME)-treated aorta and comparably increased peripheral pressure in hind limbs from all mouse lines investigated. After ?-adrenergic stimulation, 8-Br-cGMP diminished similarly aortic tone and peripheral pressure in control, Trpc6(-/-), Trpc3(-/-), Trpc3(-/-)/6(-/-), and Trpc1(-/-)/3(-/-)/6(-/-) mice but not in sm-cGKI(-/-) mice. In untreated aorta, ?-adrenergic stimulation induced similar contractions in the aorta from control and Trpc3(-/-) mice but larger contractions in sm-cGKI(-/-), Trpc6(-/-), Trpc3(-/-)/6(-/-), and Trpc1(-/-)/3(-/-)/6(-/-) mice, indicating a functional link between cGKI and Trpc6 channels. Trpc3 channels were detected by immunocytochemistry in both isolated aortic smooth muscle
cells (SMCs) and aortic endothelial cells (ECs), whereas Trpc6 channels were detected only in ECs. Phenylephrine-stimulated Ca\(^{2+}\) levels were similar in SMCs from control (Ctr) and Trpc6(-/-) mice. Carbachol-stimulated Ca\(^{2+}\) levels were reduced in ECs from Trpc6(-/-) mice. Stimulated Ca\(^{2+}\) levels were lowered by 8-Br-cGMP in Ctr but not in Trpc6(-/-) ECs. The results suggest that cGKI and Trpc1,3,6 channels are not functionally coupled in vascular SM. Deletion of Trpc6 channels impaired endothelial cGKI signalling and vasodilator tone in the aorta.

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