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GMP-mediated regulation of cardiovascular Ca^{2+} entry channel TRPC6 and its pathophysiological implications

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TRPC6 is a ubiquitous and predominant isoform expressed in vascular smooth muscle cells (VSMCs) and has been implicated in the regulation of vascular tone and remodelling via neurohormonal and mechanosensitive mechanisms. Although these two mechanisms are generally thought to work independently, our recent investigation has revealed that TRPC6 channel is synergistically activated by receptor and mechanical stimulations via the phospholipase C/G_q-protein/diacylglycerol and phospholipase A_2/ω-hydroxylase/20-hydroxyeicosatetraenoic acid pathways. Experiments with pressurized mesenteric artery have suggested that this synergism likely contributes to enhanced myogenic responsiveness under near-threshold receptor stimulation. Different lines of evidence also suggest that TRPC6 channel is subject to both positive and negative regulation via activation of Ca^{2+}/ calmodulin-dependent kinase (CAMKII), and protein kinases C (PKC) and G (PKG); while CAMKII- and PKC-mediated phosphorylation accelerates the time courses of TRPC6 activation and inactivation during receptor stimulation respectively, activation of PKG via stimulation of the nitric oxide or atrial natriuretic peptide/guanylate cyclase/cGMP pathway tonically suppresses TRPC6 channel activity through its phosphorylation on T69, regardless of receptor or mechanical stimulation[1]. Interestingly, prolonged activation of PKG (10–20 min) reactivated TRPC6 channel rendering it spontaneously active with loss of receptor- and mechano-sensitivities. Disruption of actin cytoskeleton by cytochalasin D treatment induced similar consequences. It can be speculated that phosphorylation of TRPC6 channel by PKG may not only cause an acute tonic inhibition of the channel activation by neurohormonal and mechanical stimuli, but also induce a slow transition between differential activation modes, presumably altering the VSMC phenotype from 'contractile' to 'proliferative' ones.

References

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