S52-6 Regulation of vascular tone by the phosphorylation of TRPC channels

◯Motohiro NISHIDA[1], Kinue NISHIOKA[1], Marina ARIYOSHI[1], Michio NAKAYA[1], Hitoshi KUROSE[1]
[1]Kyushu Univ., Grad. Sch. of Pharm. Sci.

Sustained increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) via Ca^{2+} influx across the plasma membrane plays a critical role in agonist-induced contraction of vascular smooth muscle cells. Canonical transient receptor potential (TRPC) proteins are non-selective cation channels activated by stimulation of phospholipase C-linked receptors, and are thought to directly or indirectly mediate agonist-induced Ca^{2+} influx. Although TRPC channel activity is negatively regulated by Ser/Thr phosphorylation of TRPC proteins, its physiological significance has not been elucidated. Here, we demonstrated that activation of PKA by PDE3 inhibition suppresses activities of diacylglycerol (DAG)-activated TRPC channels (TRPC3, TRPC6, and TRPC7). Pretreatment with a selective PDE3 inhibitor for 30 min induced phosphorylation of TRPC6 at Thr^{69}, and significantly attenuated TRPC6-mediated inward current and increase in $[Ca^{2+}]_i$ induced by agonist stimulation. Inhibition of PDE3 attenuated the contraction of rat thoracic aorta and rat aortic smooth muscle cells induced by angiotensin (Ang) II, which was abolished by the expression of dominant negative (DN) mutant of TRPC6 (TRPC6-DN). These results suggest that DAG-activated TRPC channels are critical targets of vasodilating effects of PDE3 inhibition elicited via PKA-dependent pathway, and suggest that blockade of DAG-activated TRPC channels could be an effective therapeutic strategy for preventing hypertension.