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Emodin dissipates tonic tension through suppressing PKCδ-mediated calcium sensitization in blood vessel

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Dysregulated tonic tension and calcium sensitization in blood vessels has been frequently observed in many cardiovascular diseases. Despite a huge therapeutic potential, little is known about natural products targeting tonic tension and calcium sensitization. Here we found that emodin, an anthraquinone derivative in herbal medicines, can dissipate tonic tension by inhibiting protein kinase C δ-mediated calcium sensitization. Emodin was identified as an active ingredient of Polygonum multiflorum extract for the inhibition of phenylephrine (PE)-induced vasoconstriction in rat isolated thoracic aorta. Emodin also inhibited vasoconstriction induced by serotonin and endothelin-1. Of note, emodin generally suppressed vasoconstrictions mediated by voltage-operated, store-operated calcium channels and intracellular calcium store. However, emodin did not affect agonist-induced calcium increases in primary smooth muscle cells. In contrast, post-treatment of emodin following PE stimulation significantly and potently dissipated tonic tension in rat aortic ring. Western blot analysis revealed that emodin attenuated PE-increased phospho-MLC (pMLC) along with phosphorylation of MYPT and CPI-17. This was mediated by the selective inhibition of PKCδ while PKCα was not involved. Taken together, we demonstrated that emodin dissipates tonic tension through the blockade of PKCδ and CPI-17 mediated MLC-phosphatase inhibition. This new mode of action for anti-hypertensive agents and a structural insight for PKCδ inhibition given by emodin may provide a new insight for the development of modulators of tonic tension and hypertensive diseases.

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