Endothelin-1 potentiates TRPV1-mediated vasoconstriction of human adipose arterioles in a protein kinase C-dependent manner

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Abstract

Background: Vascular TRPV channels have emerged as important regulators of vascular tone. TRPV1 and endothelin-1 (ET-1) are independently associated with the pathophysiology of coronary vasospasm but the relationship between their vasomotor functions remains unclear. We characterized the vasomotor function of TRPV1 channels in human arterioles and investigated regulation of their vasomotor function by ET-1. Approach: Arterioles were threaded on two metal wires, equilibrated in a physiological buffer at 37 oC and exposed to increasing concentrations of capsaicin in the absence or presence of SB366791 (TRPV1-selective inhibitor) or GF109203X (PKC-selective inhibitor). Some arterioles were preconstricted with ET-1 or phenylephrine or high K+ buffer. TRPV1 mRNA and protein expression in human arteries were assessed. Results: TRPV1 transcripts and proteins were detected in human resistance arteries. Capsaicin (1 μM) induced concentration-dependent constriction of endothelium-intact (35 ± 8 %) and endothelium-denuded (43 ± 11 %) human adipose arterioles (HAA), which was significantly inhibited by SB366791 (0.2 ± 0.1 %). Preconstriction of HAA with ET-1, but not high potassium buffer or phenylephrine, significantly potentiated capsaicin-induced constriction (33 ± 7 % vs 12 ± 8 %). GF109203X significantly inhibited potentiation of capsaicin-induced constriction by ET-1. Conclusion: TRPV1 channels are expressed in the human vasculature and can influence vascular tone of human arterioles upon activation. Their vasomotor function is modulated by ET-1, mediated in part by PKC.. These findings reveal a novel interplay between ET-1 signaling and TRPV1 channels in human VSMC, adding to our understanding of the ion channel mechanisms that regulate human arteriolar tone and may also contribute to the pathophysiology of coronary vasospasm.

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