

P58: SIGNALING PATHWAYS OF SPHINGOSINE-1-PHOSPHATE IN VASCULAR SMOOTH MUSCLE CONTRACTION

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Objectives: We aimed to examine the direct effect of sphingosine-1-phosphate (S1P) on vascular smooth muscle (VSM) contractility and to elucidate the underlying signaling pathways.

Methods: Isometric tension of endothelium-denuded thoracic aorta segments isolated from male wild type (WT) and knockout (KO) mice deficient in S1P2, S1P3 receptor or Gα12/13 was measured in myographs. Vasoactive effect of 10 μM S1P was detected at physiological (4 mM) and elevated (6-124 mM) extracellular K⁺-concentration [K⁺]_e.

Results: At physiological [K⁺]_e S1P had negligible vasoactive effect. Slightly increased [K⁺]_e (6 mM) failed to influence the vascular tone by itself, but addition of S1P induced marked vasoconstriction that was further intensified if [K⁺]_e was increased to 8 and 10 mM. At higher [K⁺]_e (20-80 mM), K⁺ increased the vascular tone progressively and attenuated the additional vasoconstriction by S1P. Further experiments on the signaling pathways were performed with 8 mM [K⁺]_e, which enhanced the action of S1P markedly without significantly influencing the resting vascular tone by itself. The vasoconstrictor effect of S1P disappeared in S1P2-KO and Gα12/13-KO vessels, whereas remained unchanged in S1P3-KO mice. S1P-induced vasoconstriction was also abolished by the Rho-kinase inhibitor Y-27632 (10 μM) in WT vessels.

Conclusion: S1P induces vasoconstriction in case of moderately increased [K⁺]_e. The effect of S1P is mediated by S1P2-receptor, Gα12/13, and Rho-kinase. This phenomenon may lead to increased vascular tone under conditions of systemic or local elevation of [K⁺]_e surrounding the VSM, like in hyperkalemia or tissue ischemia. Grant support: OTKA K-101775 and MedInProt Protein Science Research Synergy Program.