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Poster 27

SPHINGOSINE-1-PHOSPHATE ENHANCES ALPHA₁-ADRENORECEPTOR-MEDIATED VASOCONSTRICTION

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Sphingosine-1-phosphate (S1P) is a sphingolipid mediator known to influence a wide range of biological processes including vascular functions via its five G-protein-coupled receptors (S1P₁₋₅). In our present experiments we intended to examine the vasoactive effects of S1P. Our aim was to evaluate its capability to alter the basal vascular tone and to influence vasoconstriction mediated by alpha₁-adrenoreceptors.

Segments of the thoracic aorta were isolated from adult male wild type (WT) and knockout (KO) mice deficient in S1P₁ or S1P₂, or S1P₃ receptors. Isometric tension of the segments was measured via myography. Effects of S1P and the α₁-agonist vasoconstrictor phenylephrine (PE) were tested. Changes in tension were normalized to vasoconstriction evoked by 124 mM K⁺.

Administration of 10 μM S1P - that is in the concentration range of human serum - did not cause significant change in the resting vascular tone. Following a 20 min incubation of the segments with 10 μM S1P however, the EC₅₀ of PE-induced vasoconstriction decreased from 145±1 nM to 80±1 nM, while E_{max} increased from 114±3% to 133±3% in WT vessels. Similar enhancement of the vascular reactivity was detected in S1P₁- and S1P₃ KO segments. In S1P₂ KO vessels, however, this phenomenon was absent. The modulation of PE-induced vasoconstriction by S1P was also abolished by simultaneous administration of the Rho-kinase inhibitor Y27632 (2 μM).

In further experiments we aimed to evaluate the duration of the S1P-induced enhancement of α₁-adrenoreceptor-mediated vasoconstriction. Therefore, 80 nM PE was applied repeatedly every 20 minutes, following a 20 min long exposure of the vessels to 10 μM S1P. Vasoconstrictor responses remained enhanced during the following 3 hours in WT segments, whereas this increase could not be detected in S1P₂ KO vessels.

Although S1P does not directly modify resting vascular tone by itself, yet it significantly enhances alpha₁-adrenoreceptor-mediated vasoconstriction. The S1P₂ receptor - Rho-kinase pathway is responsible for this effect. The sustained enhancement of vascular reactivity detected underlines the potential pathophysiological significance of the phenomenon.

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