

3-3**SPHINGOSINE-1-PHOSPHATE ENHANCES α 1-ADRENORECEPTOR-MEDIATED VASOCONSTRICTION**

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Introduction. Sphingosine-1-phosphate (S1P) is a sphingolipid mediator, which is present in the human serum at low micromolar concentration as a product of endothelial cells, erythrocytes and activated platelets. It is known to influence a multitude of biological processes including vascular functions via its five G-protein-coupled receptors.

Aim. 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 α 1-adrenoreceptors.

Methods. To test the effects of S1P and the α 1-agonist vasoconstrictor phenylephrine (PE), myographic measurements were conducted under isometric conditions. Segments of the thoracic aorta were isolated from adult male mice and changes of the vascular tone upon administration of S1P and PE were detected. Responses of wild type (WT), S1P1, S1P2, and S1P3 receptor knock out (KO) vessels were determined. Tone changes were normalized to vasoconstriction evoked by 124 mM K⁺.

Results. Administration of 10 μ M 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 μ M S1P, however, the EC₅₀ of PE-induced vasoconstriction decreased from 145 $\pm$ 1 nM to 80 $\pm$ 1 nM, while E_{max} increased from 114 $\pm$ 3% to 133 $\pm$ 3% in WT vessels. Similar enhancement of the vascular reactivity was detected in S1P1- and S1P3 receptor KO segments. In S1P2 KO vessels, however, this phenomenon was absent, pointing at the role of this receptor in the signal transduction. The modulation of PE-induced vasoconstriction by S1P was also abolished by co-administration of the Rho-kinase inhibitor Y27632 (2 μ M).

In further experiments we aimed to evaluate the duration of the S1P-induced enhancement of α 1-adrenoreceptor-mediated vasoconstriction. Therefore, 80 nM PE was applied repeatedly every 20 minutes, following a 20 min long exposure of the vessels to 10 μ M S1P. Vasoconstrictor responses remained enhanced during the following 3 hours in WT segments, whereas this increase could not be detected in S1P2 KO vessels.

Conclusion. S1P does not directly modify resting vascular tone by itself, yet it significantly enhances α 1-adrenoreceptor-mediated vasoconstriction. The S1P2 receptor - Rho-kinase pathway is responsible for this effect. The sustained enhancement of vascular reactivity detected underlines the potential patophysiological significance of the phenomenon.

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