Sphingosine-1-phosphate receptor 3 signaling is a critical modulator of stroke outcome [Abstract]

Hana Matuskova, Frank Matthes, Gabor Petzold, Anja Meissner

Angaben zur Veröffentlichung / Publication details:

Matuskova, Hana, Frank Matthes, Gabor Petzold, and Anja Meissner. 2023. "Sphingosine-1-phosphate receptor 3 signaling is a critical modulator of stroke outcome [Abstract]." Journal of Vascular Research 60 (Supplement 1): 19. https://doi.org/10.1159/000533846.

29
Sphingosine-1- phosphate receptor 3 signaling is a critical modulator of stroke outcome

Hana Matuskova[1,2,3,4], *Frank Matthes*[1,2,5], *Gabor Petzold*[3,4], *Anja Meissner*[1,2,4,5]

[1]Department of Experimental Medical Science, Lund University, Lund, Sweden, [2]Wallenberg Centre for Molecular Medicine, Lund University, Lund, Sweden, [3]Department of Neurology, University Hospital Bonn, Bonn, Germany, [4]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany, [5]Department of Physiology, Institute of Theoretical Medicine, University of Augsburg, Augsburg, Germany

Introduction: The complex pathogenesis of stroke is characterized by a deleterious cycle of vascular dysfunction and inflammation for which treatment options remain sparse. Recently, the bioactive phospholipid sphingosine-1-phosphate (S1P) has gained increasing attention in cardiovascular diseases due to its involvement in both vascular function and immune responses. Its action is mediated via specific G protein-coupled receptors (S1pr1-5). Previously published RNA sequencing data revealed a high S1pr3 expression particularly in astrocytes and endothelial cells under healthy conditions. As both play a critical role in the regulation of vascular integrity and function, we investigated the role of S1P/S1pr3 signaling in astrocytes and endothelial cells in ischemia-induced brain damage.

Method and Material: Stroke was induced in wild-type or S1pr3 knockout mice by middle cerebral artery occlusion. Stroke outcome was determined by infarct size evaluation, neuroscore, and assessment of cerebral blood flow by magnetic resonance imaging. Brain vessels were isolated using an improved vessel-parenchyma fractionation protocol. Expression analyses were performed by RNAscope in situ hybridization, qPCR, and Western blotting. CAY10444 was used as S1pr3 antagonist.

Results: In a murine stroke model, we detected increased S1pr3 expression in the ischemic hemisphere 24- and 72-hours post-ischemia. Vessel-parenchyma fractionation of brain tissue further revealed the majority of S1pr3 associated with cerebral vessels. Increased expression of astrocytic S1pr3 was confirmed by RNAscope and in a RiboTag mouse line as early as 24-hours post-ischemia, while endothelial S1pr3 was increased at later stages. Single administration of an S1pr3 antagonist 4 hours post-stroke led to significant improvements of cerebral blood flow and reduction of infarct size in the ischemic hemisphere 24-hours post-ischemia, persisting up to 72 hours. However, later administration at 8 hours post-stroke did not improve cerebral blood flow or reduce infarct size. Results obtained from the S1pr3 knockout mouse line revealed an improved functional outcome during the acute phase after ischemia.

Conclusion: Our findings point to an important cell-type specific involvement of S1P/S1pr3 signaling during stroke, rendering the modulation of S1pr3-mediated vascular responses a viable target to improve stroke outcome.