UKE Paper of the Month December 2012
Nature Medicine, December 2012, (PMID: 23160238)

TRPM4 cation channel mediates axonal and neuronal degeneration in experimental autoimmune encephalomyelitis and multiple sclerosis

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ABSTRACT: In multiple sclerosis, an inflammatory disease of the central nervous system (CNS), axonal and neuronal loss are major causes for irreversible neurological disability. However, which molecules contribute to axonal and neuronal injury under inflammatory conditions remains largely unknown. Here we show that the transient receptor potential melastatin 4 (TRPM4) cation channel is crucial in this process. TRPM4 is expressed in mouse and human neuronal somata, but it is also expressed in axons in inflammatory CNS lesions in experimental autoimmune encephalomyelitis (EAE) in mice and in human multiple sclerosis tissue. Deficiency or pharmacological inhibition of TRPM4 using the antidiabetic drug glibenclamide resulted in reduced axonal and neuronal degeneration and attenuated clinical disease scores in EAE, but this occurred without altering EAE-relevant immune function. Furthermore, Trpm4−/− mouse neurons were protected against inflammatory effector mechanisms such as excitotoxic stress and energy deficiency in vitro. Electrophysiological recordings revealed TRPM4-dependent neuronal ion influx and oncotic cell swelling upon excitotoxic stimulation. Therefore, interference with TRPM4 could translate into a new neuroprotective treatment strategy.

STATEMENT: *Our paper demonstrates the involvement of transient receptor potential melastatin 4 (TRPM4) ion channels in inflammation-induced axonal degeneration in a well-established animal model of multiple sclerosis (EAE). We show for the first time a functional expression of these channels in murine neurons but can also provide data from human MS patient's brain autopsies and biopsies showing neuronal TRPM4 expression but also a strong up-regulation on axons in inflamed areas of the brain. Using the EAE model and TRPM4-antagonists in wild-type and TRPM4 knock-out mice, we show that inflammation-induced neuronal and axonal degeneration and subsequent clinical disability is dependent on TRPM4. Thus, our manuscript provides experimental support for a potentially new therapeutic target for multiple sclerosis and maybe other neurodegenerative diseases in the hope of preventing, or at least reducing, the patients' long-term disabilities.*

BACKGROUND: This work was performed at the ZMNH in the Research Group Neuroimmunology headed by Dr. Manuel Friese in collaboration with the Institute for Neural Signal Transduction (Prof. Pongs), the Institute for Molecular Neurogenetics (Prof. Kneussel) and with colleagues from Heidelberg, Göttingen, Homburg, Leuven and Geneva. The study was part of the PhD thesis of Dr. Benjamin Schattling and was supported by the DFG (FR1720/3-1) and the Gemeinnützige Hertie-Stiftung (1.01.1/11/003). Dr. Friese's group is interested in the pathomechanisms of neuroimmunological diseases.