NEURODEGENERATIVE DISORDERS

ASIC mind

The signalling pathways responsible for neuronal degeneration in multiple sclerosis (MS) are poorly understood. A study by Fugger and colleagues now shows that acid-sensitive ion channel 1 (ASIC1), a neuronally expressed, proton-gated cation channel, might contribute to the pathophysiology of this disease.

MS is a neuroinflammatory disease that leads to the demyelination and axonal degeneration of CNS neurons. The degeneration is thought to be caused by inflammation-induced mitochondrial dysfunction and by increased influx of Na⁺ and Ca²⁺ ions into the neurons. This led the authors to investigate the role of ASIC1 in a mouse model of MS.

The authors induced experimental autoimmune encephalomyelitis (EAE; a mouse model of MS) in wild-type mice and mice that lacked either one or both copies of *Accn2*, the gene that encodes ASIC1. They found that the *Accn2*^{-/-} mice displayed significantly reduced clinical symptoms compared with both the *Accn2*^{+/-} mice and the wild-type mice, implicating ASIC1 in the neurodegeneration.

As ASIC1 is proton-gated, the authors used micro pH meters to measure the acidity of mouse spinal cords, and found that the extracellular pH of EAE-induced mice, both wild-type and *Accn2*^{-/-}, was significantly lower than that of control mice. Furthermore, by contrast with

the control mice, the spinal pH levels in the EAE-induced mice were lower than the pH that is required for the opening of the proton-gated pores of ASIC1. This acidosis in the neural tissue of EAE-induced mice has been proposed to be the result of axonal hypoxia and inflammation-induced mitochondrial dysfunction. Indeed, the levels of hypoxia-inducible factor 1 α were elevated in the spinal cords of the EAE-induced mice.

To further examine ASIC1's role in the development of the neurodegenerative pathophysiology, the authors measured *Accn2* mRNA levels in retinal and cerebellar neurons throughout the course of EAE progression in wild-type mice. ASIC1 expression has previously been shown to be upregulated by proinflammatory mediators and, in accordance, the authors detected significantly elevated *Accn2* mRNA levels in both types of neurons 15 and 30 days after EAE induction.

Finally they investigated whether inhibition of ASIC1 after EAE induction might exert a neuroprotective effect *in vivo*. They showed that the clinical symptoms of wild-type, EAE-induced mice treated with amiloride, a non-specific ASIC blocker that is licensed for the treatment of hypertension, were reduced to a similar extent as in the *Accn2*^{-/-}, EAE-induced mice. Treatment of *Accn2*^{-/-}, EAE-induced mice with amiloride caused no further clinical improvement, suggesting

that the effect of the drug is mediated through ASIC1.

Together these results indicate that ASIC1 might contribute to the pathophysiology of MS, and that compounds that block the channel, such as amiloride, might be valuable therapeutics for slowing the progression of this disease.

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ORIGINAL RESEARCH PAPER Friese, M. A. et al. Acid-sensing ion channel-1 contributes to axonal degeneration in autoimmune inflammation of the central nervous system. *Nature Med.* 11 Nov 2007 (doi:10.1038/nm1668)