GLIA

Aquaporin: not so swell?

Fluid accumulation — or oedema — in the brain is a potentially life-threatening condition. It increases intracranial pressure, which can damage brain tissue and restrict blood supply. Thrane *et al.* now reveal molecular effects of brain oedema in astrocytes that could contribute to the pathophysiological outcome of the condition.

The authors injected mice with water to induce hypo-osmotic stress and consequently, brain oedema; they had previously shown that this causes astrocytes to swell. The authors first established whether aquaporin-4 (AQP4), a membrane protein that conducts water through the cell membrane, mediates astrocyte swelling. In acute cortical slices from mice lacking AQP4 (*Aqp4*$^{-/-}$ mice) that were exposed to mild hypo-osmotic stress (20% reduction in osmolality), astrocyte swelling was greatly reduced compared with wild-type mice. *In vivo* two-photon imaging further revealed that mild hypo-osmotic stress increased Ca^{2+} spiking in astrocytes from wild-type animals but not from *Aqp4*$^{-/-}$ mice. However, a more severe hypo-osmotic stress (30% reduction in osmolality) was capable of inducing both astrocyte swelling and Ca^{2+} spikes in *Aqp4*$^{-/-}$ astrocytes, indicating that Ca^{2+} responses are triggered by AQP4-induced cell swelling and not directly by AQP4 itself.

As activation of purinergic receptors is known to trigger Ca^{2+} spikes in astrocytes, the authors assessed whether these receptors mediated the swelling-induced Ca^{2+} responses. They showed that wild-type astrocytes cultured in a hypo-osmotic medium released more ATP (which binds to purinergic P2 receptors) than cells cultured in an isotonic solution, whereas astrocytes from *Aqp4*$^{-/-}$ mice showed no such response. Furthermore, adding P2 receptor antagonists to the culture medium delayed the onset of hypo-osmotic stress-induced Ca^{2+} responses in cortical slices from wild-type mice. Together, this indicates that P2 receptor activation mediates hypo-osmotic stress-induced, AQP4-dependent Ca^{2+} responses in astrocytes.

Thus, AQP4 mediates water influx in astrocytes under conditions of hypo-osmotic stress, and thereby initiates intracellular signalling events. This finding suggests that, in addition to increased intracranial pressure, potential cytotoxic downstream effects of signalling pathways activated in astrocytes may have a role in the pathophysiology of brain oedema.

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ORIGINAL RESEARCH PAPER Thrane, A. S. *et al.* Critical role of aquaporin-4 (AQP4) in astrocytic Ca^{2+} signaling events elicited by cerebral edema. *Proc. Natl Acad. Sci. USA* 27 Dec 2010 (doi:10.1073/pnas.1015217108)