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SYNAPTIC PLASTICITY

Cold-shocked synapses

Synapses are eliminated and formed continuously in healthy brains. This synaptic remodelling seems to be impaired in neurodegenerative diseases, as enduring synapse loss is a feature of these disorders. Peretti *et al.* now show that induction of RNA-binding motif protein 3 (RBM3), a cold-shock protein, promotes the formation of new synaptic contacts in mice, and that RBM3 expression protects against synaptic loss in two models of neurodegeneration.

Cooling and rewarming is known to trigger synaptic remodelling in hibernating animals. Here, the authors found that cooling decreased the number of synapses in the hippocampus in wild-type mice, and that synaptic connections could be formed with restoration of normal body temperature. The cooling process is known to induce cold-shock proteins, including RBM3, and indeed the authors found that hippocampal levels of RBM3 increased after cooling in these animals. This phenomenon lasted several days, leading the authors to hypothesize that RBM3 contributes to synapse regeneration upon rewarming.

The authors next examined this process in the 5XFAD transgenic mouse model of Alzheimer disease (AD) and in wild-type mice intracerebrally injected with prions (a model of prion disease). In both cases, cooling induced a loss of synapses in the hippocampus, followed by new synapse formation upon rewarming, but only in mice in the very early stages of disease (up to 3 months of age in the AD model, and up to 6 weeks post infection in the prion model). When cooling was carried out after these time points, synaptic loss occurred as normal, but synaptic regeneration did not occur after rewarming. Furthermore, increased RBM3 expression occurred only when cooling was carried out at the early time points. These findings suggest that impaired capacity to regenerate synapses after cooling and rewarming is an early feature of neurodegeneration, and is associated with a failure to induce RBM3.

Induced hypothermia has been shown to be neuroprotective in models of brain injury, and RBM3 has neuroprotective effects *in vitro*, but the potential benefits of cooling in neurodegenerative disease had not yet been explored. The authors found that repeated cooling of prion-infected mice, at 3 and 4 weeks post injection, was markedly neuroprotective, preventing neuronal loss, improving synaptic transmission and enhancing performance in memory tests at 7–9 weeks post injection. These improvements were associated with a rise in expression of RBM3, and were abolished by its knockdown, suggesting that early cooling has neuroprotective effects, largely via induction of this protein.

Furthermore, in the absence of cold-treatment, RBM3 overexpression in the hippocampus was sufficient to prevent early synaptic loss, synaptic dysfunction and behavioural deficits in the prion-infected mice. Conversely, knockdown of RBM3 in the hippocampus exacerbated synaptic loss and memory impairment in both the AD and prion-infected mice, and even induced these deficits in otherwise healthy animals. This suggests that in addition to cooling-induced plasticity, RBM3 also contributes to ongoing synaptic repair in mice, and may be impaired at an early stage in neurodegenerative disease.

These findings suggest that induction of RBM3 promotes synapse regeneration and is defective in two mouse models of neurodegeneration. Enhancing RBM3 expression by cooling or other methods could therefore have beneficial effects in these disease states.

Fiona Carr

> “RBM3 overexpression in the hippocampus was sufficient to prevent early synaptic loss, synaptic dysfunction and behavioural deficits in the prion-infected mice”

ORIGINAL RESEARCH PAPER Peretti, D. *et al.* RBM3 mediates structural plasticity and protective effects of cooling in neurodegeneration. *Nature* http://dx.doi.org/10.1038/nature14142 (2015)

FURTHER READING Yenari, M. A. & Han, H. S. Neuroprotective mechanisms of hypothermia in brain ischaemia. *Nature Rev. Neurosci.* **13**, 267–278 (2012)