Leaky receptors in stressed brains

Chronic stress damages neurons in the hippocampus and impairs cognitive function, but the mechanisms that lead to this damage are not clear. Liu *et al.* now show that neuronal ryanodine receptors have a key role in the pathological process.

Ryanodine receptors on the endoplasmic reticulum contribute to intracellular calcium release and are important for calcium homeostasis in neurons and other types of cell. In heart cells, chronic stress conditions lead to phosphorylation, oxidation and nitrosylation of the type 2 ryanodine receptor (RYR2) calcium release channels so that they become unbound from the subunit calstabin 2 and subsequently become 'leaky' — they release excessive intracellular calcium, which damages cardiac cells. RYR2s are also expressed in hippocampal neurons, so the authors investigated whether stress-induced hippocampal damage was mediated by these channels.

Liu *et al.* used chronic restraint to induce stress in mice and discovered that RYR2s in the hippocampi of these mice were phosphorylated by protein kinase A, oxidated and nitrosylated, just as in heart cells. Binding of calstabin 2 to the channels was reduced, and they became leaky. The mice also showed impaired cognitive performance in various behavioural tests, such as the Morris water maze, that are known to depend on hippocampal function, and long-term potentiation (LTP) was reduced in their hippocampi.

All of these effects were reversed when mice were treated before and during restraint with a drug, S107, that prevents the dissociation of calstabin 2 from RYR2s. The authors also used transgenic mice in which RYR2s lacked the protein kinase A phosphorylation site. These mice are protected against the harmful effects of stress on cardiac cells and were also immune to the effects of chronic stress on hippocampal neurons; furthermore, they showed normal cognitive function and LTP induction.

These results show that chronic stress induces leakiness in hippocampal RYR2s and that this impairs cognitive function. Stress-induced cognitive impairment shares many features with post-traumatic stress disorder in humans, and so the pathway that Liu *et al.* describe could be a potential therapeutic target for these disorders.

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