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Commentary

Cooling-Induced ER Stress is Good for Your Brain

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Therapeutic hypothermia has been widely used to treat acute brain injury. However, this approach is not risk-free, and the underlying protective mechanisms are poorly understood. In this issue of *EbioMedicine*, Rzechorzek et al. (2015) have studied the neuroprotective mechanisms induced by hypothermic preconditioning in functional cortical neurons differentiated from human pluripotent stem cells. They found that mild or moderate hypothermia induced an endoplasmic reticulum (ER) stress response and activation of the unfolded protein response (UPR), which are the cellular mechanisms that ensure correct folding of newly synthesized secreted and membrane proteins before they exit the ER (Hetz and Mollereau, 2014). This response was sufficient to protect the cells to more severe stress – an effect known as ER hormesis – in this case, to subsequent treatment with oxidative and ER stressors. Inhibition of the UPR during hypothermic preconditioning abrogated the protective response. Thus, exposure of the cortical neurons to cold stress prompted a UPR-dependent adaptive response that protected against oxidative and ER stresses.

How hypothermia induces the UPR and ER hormesis is unknown. One possibility is that it is simply due to aberrant folding of as yet unknown proteins at low temperatures. Alternatively, hypothermia may induce cold shock proteins such as the RNA binding motif protein 3 (RBM3), which has recently been shown to confer neuroprotection by increasing structural plasticity at the level of synapses (Peretti et al., 2015).

Restoration of protein homeostasis following ER stress requires activation of the three arms of the UPR, initiated by IRE1 (inositol-requiring enzyme 1), ATF6 (activating transcription factor 6), and PERK (protein kinase RNA-like endoplasmic reticulum kinase). These pathways induce expression of chaperone proteins to facilitate protein folding, attenuate translation and trigger ER-associated degradation (ERAD) to remove aberrantly folded proteins.

Interestingly, Rzechorzek et al. found that although cold stress activated the PERK pathway, induction of the downstream transcription factor CHOP did not lead to expression of Bax or to apoptosis. Instead, they found that PERK inhibitors abrogated the neuroprotection conferred by cold stress. This indicates that PERK contributes to the adaptive response induced by cold stress, possibly by stimulating an antioxidant response.

These results are particularly timely given the growing interest in the function of ER stress in physiological and pathological conditions (Mollereau et al., 2014). It is now recognized that while severe or prolonged ER stress can be deleterious, mild or moderate ER preconditioning is neuroprotective. For example, mutations in the chaperone *ninaA* induce an adaptive UPR-dependent response that protects *Drosophila* photoreceptor neurons (Mendes et al., 2009). This study was the first to use the term ER hormesis as an extension of the hormesis paradigm, which posits that exposure to a low dose of a toxic chemical agent or environmental factor induces an adaptive beneficial response that protects the cell or organism when exposed to higher doses of the agent (Calabrese et al., 2010). ER hormesis can also be elicited by treatment with the ER stress inducer tunicamycin, which confers neuroprotection by stimulating an autophagic response in *Drosophila*, mouse, and human neuroblastoma models of Parkinson's disease (Fouillet et al., 2012).

In empirical medicine, the concept that mild stress can be protective is not new. As Nietzsche said: "What does not kill you makes you stronger". For example, rapid cycles of ischemia are used to precondition the heart before surgery. Although the protective mechanisms behind the hormetic response are poorly understood, they have largely been attributed to increases in the levels of reactive oxygen species (ROS) in mitochondria following exposure to mild stress, which are thought to then trigger a protective antioxidant response (Luna-Lopez et al., 2014). Thus, identification of the mechanisms and targets that mediate hypothermic ER hormesis and other forms of hormetic tissue protection should mitigate the risks of preconditioning interventions while preserving their therapeutic effects.

Currently, there is intense focus on identifying molecules that can modulate the UPR (Hetz et al., 2013). Since the UPR can stimulate both pro- and anti-survival pathways, pharmacological modulation of the UPR could be used either to stimulate ER hormesis, which might be beneficial in treating neurodegenerative diseases, or to induce apoptosis, which could be useful for cancer treatment. A wide range of molecules has been developed that inhibit the pro-survival function of the UPR, and many have been used in preclinical or clinical studies in cancer. Fewer compounds have been shown to increase the UPR and ER folding capacity (Hetz et al., 2013). Tunicamycin is a broad inducer of UPR pathways, but more specific activating drugs have shown beneficial effects in models of neurodegeneration (Fouillet et al., 2012; Hetz et al., 2013). Examples include salubrinal and guanabenz, which increase phosphorylation of eIF2α by inactivating eIF2α phosphatase complexes. Salubrinal can reduce both neuronal cell death after excitotoxicity in the hippocampus and neurodegeneration in models of Parkinson disease and amyotrophic lateral sclerosis. Quercetin, another interesting candidate, activates IRE1 by specifically interacting with the IRE Ken domain (Wiseman et al., 2010). The goal of future

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research will be to further characterize the protective pathways of the UPR and to identify specific drugs capable of stimulating an adaptive ER stress response with minimal adverse side effects.

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