*Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

# ISRIB

**Evidence Summary**

ISRIB improves cognition in young, healthy mice, but it has yet to show benefits in mouse models of disease and may potentially be harmful.

**Neuroprotective Benefit:** Preclinical studies suggest ISRIB might provide acute cognitive benefits, but chronic administration might be detrimental.

**Aging and related health concerns:** N/A

**Safety:** No evidence for long-term usage, but cell culture studies suggesting ISRIB may exacerbate cell death in response to ER stress are concerning.

**What is it?**

ISRIB was discovered in a screen for molecules that could prevent the upregulation of ATF4, a protein upregulated by the integrated stress response (ISR) and the unfolded protein response (UPR), two pathways that sense cellular stress signals and react by initiating a number of protective programs (Sidrauski et al, 2013). PERK, and its effector eIF2a, lie at the intersection of the ISR and the UPR and maintain protein homeostasis in the endoplasmic reticulum (ER).

When misfolded proteins accumulate in the ER, PERK phosphorylates eIF2a which halts protein synthesis, preventing further accumulation of misfolded proteins in the ER. However, protein synthesis is important for learning and memory. Studies report an increase in phosphorylated eIF2a in post-mortem Alzheimer's brains and Alzheimer's animal models. In addition, genetic attenuation of eIF2a phosphorylation in Alzheimer's mice partially rescues the decrease in protein synthesis, synaptic plasticity, and spatial memory (Ma et al, 2013). Thus, preventing the phosphorylated eIF2a-induced brake on protein synthesis might improve memory formation.

ISRIB has a half-life of 8 hours and has excellent brain penetration. A single injection improved spatial memory and fear memory in 8-10 week old mice compared to placebo (Sidrauski et al, 2013; Di Prisco et al, 2014). Other cell culture studies reported that ISRIB reduced UPR-induced stress granule formation (globules of RNA and protein that appear under cellular stress), attenuated amyloid beta-induced cell death, reduced markers of inflammation, and prevented mGluR-mediated long-term depression (Sidrauski et al, 2015; Di Prisco et al, 2014; Hosoi et al, 2016, Guthrie et al, 2016). However, in aged Alzheimer's mice, a single ISRIB injection failed to provide cognitive benefit (Johnson and Kang, 2016).

Long-term modulation of the ISR or UPR might have a dark side though. In a mouse model of prion disease, treatment with a PERK inhibitor, GSK2606414, was neuroprotective, but the study had to be cut short because of pancreatic toxicity. Pancreatic cells produce insulin, thus homeostatic regulation of ER-protein synthesis load by the UPR is important. Short-term treatment (5 weeks) with ISRIB was not found to be toxic to the pancreas, but long-term studies have not been conducted (Halliday et al, 2015). In fact, in cell culture studies where ER-stress was artificially induced, 24 hours of ISRIB treatment accelerated cell death (Sidrauski et al, 2013). This suggests that in diseases characterized by increased ER-stress, UPR or ISR modulators such as ISRIB might be toxic. Additional long-term studies are needed.

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