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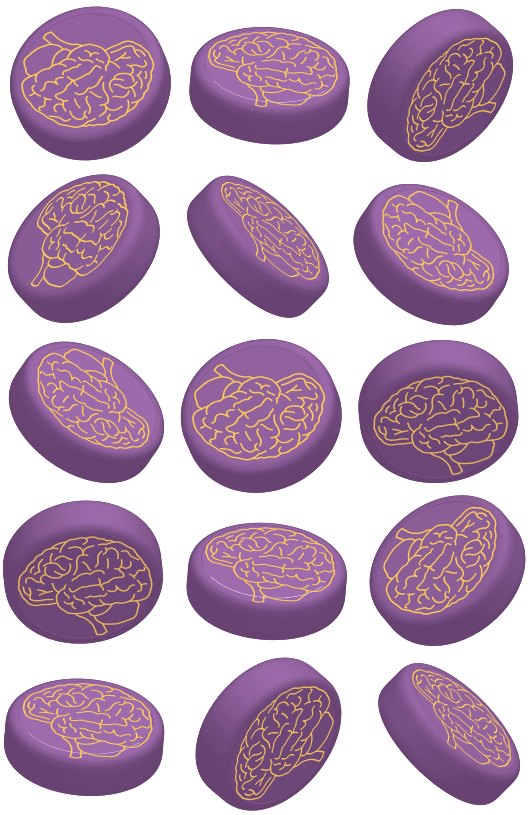
NEURODEGENERATIVE DISEASE

Halting neurodegeneration — are repurposed drugs the answer?

> "trazodone and dibenzoylmethane inhibited neurodegeneration"

The PERK/eIF2α-P branch of the unfolded protein response (UPR) is implicated in the pathogenesis of a number of neurodegenerative diseases, but the drugs developed specifically to target this pathway have proved unsuitable for use in humans. A new study, published in *Brain*, has identified two pre-existing drugs — one of which is already licensed for the treatment of depression — that act on this UPR branch and have the potential to be repurposed as neuroprotective agents.

The UPR is a stress response to accumulation of unfolded or misfolded proteins in the endoplasmic reticulum. Overactivation of the UPR — in particular, a branch that involves signalling through PERK (pancreatic endoplasmic reticulum kinase) and eIF2α-P (phosphorylated eukaryotic initiation factor 2 subunit α) — has been observed in the brains of patients with various neurodegenerative diseases, including Alzheimer disease (AD), frontotemporal dementia (FTD) and prion disease. Consequently, PERK and/or eIF2α-P inhibition is being actively pursued as a therapeutic strategy for these conditions, and experimental treatments have proved very effective in mouse models.



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To identify compounds with anti-UPR activity but without toxicity to humans, Mark Halliday and colleagues initially screened a library of 1,040 small molecules in the nematode *Caenorhabditis elegans*. "*C. elegans* have many experimental advantages as a model organism, many of which pertain to drug screening," state the authors in their new paper. "In contrast to cell lines, they contain many cell types … and have easily observable phenotypes, increasing the likelihood of detection of representative and translatable effects of drugs on signalling pathways."

The *C. elegans* screen yielded 20 'hit' compounds, which were further screened in mammalian cells to identify inhibitors of eIF2α-P signalling. Five compounds emerged from this additional screen, and two — trazodone hydrochloride and dibenzoylmethane — were selected for further study in animal models of neurodegeneration. Trazodone is a licensed antidepressant of the serotonin antagonist and reuptake inhibitor class, and dibenzoylmethane is a liquorice constituent with well-documented anticancer properties.

In a mouse model of prion disease, trazodone and dibenzoylmethane markedly reduced neurodegeneration and ameliorated cognitive and behavioural deficits, as well as prolonging survival. Similar neuroprotective effects were observed in a mouse model of FTD. In addition, trazodone reduced the burden of hyperphosphorylated tau protein in the brains of FTD mice, indicating that this drug could be particularly beneficial for the treatment of diseases characterized by tau pathology.

Previous attempts to target the UPR, using the PERK inhibitor GSK2606414, were hampered by pancreatic toxicity. However, no such toxicity was evident in the mice treated with trazodone or dibenzoylmethane, suggesting that eIF2α-P inhibition is indeed a viable prospect for clinical translation.

"[Trazodone and dibenzoylmethane] represent an important step forward in the pursuit of disease-modifying treatments for AD and releated disorders," the researchers conclude. "These drugs should now be tested in clinical trials in the treatment of dementia."

Heather Wood

ORIGINAL ARTICLES Halliday, M. *et al.* Repurposed drugs targeting eIF2α-P-mediated translational repression prevent neurodegeneration in mice. *Brain* http://dx.doi.org/10.1093/brain/awx074 (2017)

FURTHER READING Moreno, J. A. *et al.* Oral treatment targeting the unfolded protein response prevents neurodegeneration and clinical disease in prion-infected mice. *Sci. Transl. Med.* **5**, 206ra138 (2013) | Halliday, M. *et al.* Partial restoration of protein synthesis rates by the small molecule ISRIB prevents neurodegeneration without pancreatic toxicity. *Cell Death Dis.* **6**, e1672 (2015)