A PREP inhibitor may help stop the progression of frontotemporal dementia

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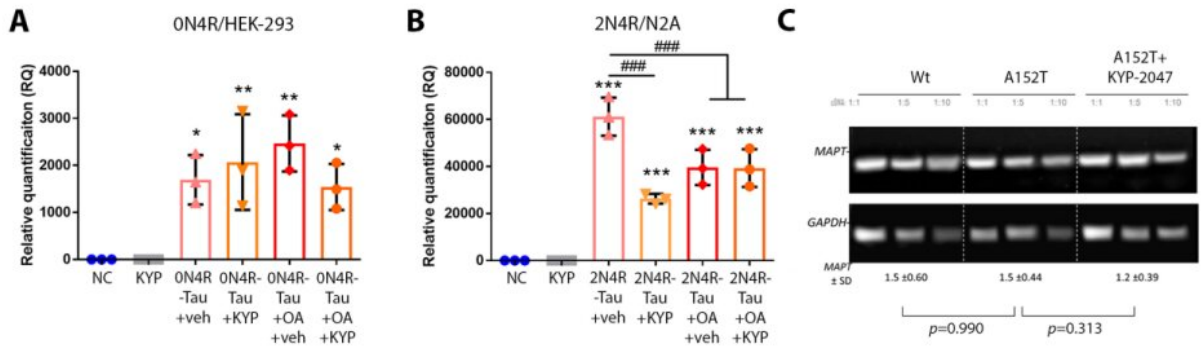

TAu (MAPT) mRNA in cell culture models and in FTD (tau-A152T) iNeurons. MAPT mRNA was measured from (A) 0N4R-tau transfected HEK-293 cells and (B) 2N4R-tau transfected N2A cells that were incubated 24 h with 10 µM KYP-2047, 10 nM OA or their combination. (C) RT-PCR analysis of control (tau-WT) and FTD (tau-A152T) iNeurons at 6 weeks of differentiation ± 0.1 µM KYP-2047 (24h). Three dilutions of cDNA were tested to ensure measurements within the detection range; densitometry quantification relative to the housekeeping gene control GAPDH (C). n=3 in each experiment.

Inhibition of the PREP enzyme was successful in stopping the progression of frontotemporal dementia in a mouse model of the disease, according to a new study published in *Science Translational Medicine*. PREP inhibitor treatment also reduced the accumulation of tau protein in neurons, which is typical of dementias.

Alzheimer's disease and other dementias affect more than 50 million patients worldwide, making them a major health problem. Current therapies are not able to stop or even delay disease progression, leading to increasingly difficult symptoms and disability of the patients.

A group led by Professor Timo Myöhänen at the University of Eastern Finland and the University of Helsinki has previously shown that by regulating an enzyme called prolyl oligopeptidase, PREP, with inhibitors, it is possible to reduce the toxicity of alpha-synuclein accumulation, a phenomenon related to Parkinson's disease. PREP inhibitors can enhance the cellular recycling systems to degrade the excessive protein aggregates, leading to reduced symptoms in Parkinson's disease mice.

Similar protein accumulation is also seen, for example, in Alzheimer's disease and other dementias where b-amyloid forms plaques and tau protein forms aggregates inside the cells. The current view is that formation of tau aggregates eventually leads to neuronal death, and tau accumulation correlates well with clinical symptoms. In frontotemporal dementia, tau aggregation appears to be the major driver for cellular death.

In the new study, the researchers showed that a PREP inhibitor reduces tau accumulation and toxicity also in cellular models, including patient-derived neurons from frontotemporal dementia patients. After promising cellular results, PREP inhibitor treatment was also tested in the mouse model of frontotemporal dementia. To follow the clinical situation, one-month treatment with the PREP inhibitor was initiated at the time of memory impairment.

After the treatment, mice in the control group were performing poorly in a memory test, while mice treated with a PREP inhibitor had normal cognitive skills. PREP inhibitor treatment had reduced tau accumulation

in the brain areas related to cognition and memory, also leading to reduced oxidative stress, which is common in neurodegenerative diseases.

"The performance of mice in the memory tests after PREP inhibitor treatment was surprisingly good since usually in similar studies, treatment is initiated before symptoms occur, not after the symptom onset. This supports the further development of PREP-targeting drugs, and we are currently looking for investors or collaborators for this," Professor Myöhänen says.

The study was mainly conducted by Professor Myöhänen's research groups at the University of Helsinki and the University of Eastern Finland, with groups from Harvard University, U.S., and University of Heidelberg, Germany, also participating in the study.

More information: Tony S. Eteläinen et al, A prolyl oligopeptidase inhibitor reduces tau pathology in cellular models and in mice with tauopathy, *Science Translational Medicine* (2023). DOI: 10.1126/scitranslmed.abq2915

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