Disengaging ATF6 from DREAM for neuroprotection

To study early changes in neuronal function during the pre-symptomatic phase of a given neurodegenerative disease is very important. It could deliver early diagnostic markers, offer prognostic clues about disease progression and uncover novel therapeutic targets for drug discovery. Deregulation of protein and calcium homeostasis, being considered critical events in early stages of neurodegeneration, are processes of special interest.

We have found that the expression of a member of the neuronal calcium sensor family of proteins, named DREAM – for Downstream Regulatory Element Antagonist Modulator- (also known as calsenilin or KChIP3) is significantly reduced in the brain of Huntington's disease patients, an inherited neurodegenerative disorder for which no cure is currently available. Notably, we also observed a significant decrease in DREAM levels in the brain of newly born asymptomatic R6/1 mice, a transgenic mouse model of the Huntington's disease that develops the symptoms in the adulthood. These results suggested that a reduction in DREAM levels could be an early marker of the disease. Since DREAM participates in the regulation of both protein and calcium homeostasis, we considered this finding highly encouraging.

Using genetic tools, transgenic mice expressing a constitutively active form of DREAM as well as DREAM deficient mice, we discovered that the decrease in DREAM expression in Huntington's neurons has a neuroprotective function. Accordingly, we reasoned that the pharmacological inhibition of the DREAM protein could result in a similar neuroprotective effect. To test this hypothesis we used repaglinide, a drug used in the clinic to reduce glucose levels in blood. It was known that repaglinide binds to other members of the neuronal calcium sensor family and affects their interaction with other proteins and their activity.

Chronic administration of repaglinide in the drinking water to R6/1 mice delayed the onset, slowed the progression of disease symptoms and reduced the loss of striatal tissue, the brain area that is primarily damaged in the mice and in Huntington's patients. At the molecular level, we found that repaglinide blocked the interaction between DREAM and ATF6 (Activating Transcription Factor 6), a protein that participates in the protein-quality control process. Releasing ATF6 from DREAM improved protein homeostasis in affected neurons, providing protection from neurodegeneration.

Taken together, our results identified DREAM as an early marker of the disease and as a new target for the treatment of Huntington's disease. Moreover, our results pave the way for the search for new inhibitors of the DREAM-ATF6 interaction with improved potency and longer lasting effects.

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