PERK Inhibition: A Possible Therapeutic Option for Tauopathies

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Tau is a microtubule-associated protein predominantly found in axons. Under normal conditions, tau interacts with microtubules to stabilize the structure of the cell's cytoskeleton. In neurodegenerative diseases known as tauopathies, tau becomes abnormally misfolded and aggregates in the somatic compartment of the neuron. One of the most common tauopathies is Alzheimer's disease, where appearance of tau aggregates closely correlates with cognitive decline. It was recently discovered that abnormally folded tau causes stress in the endoplasmic reticulum (ER) and activates the unfolded protein response (UPR). When the UPR is triggered, RNA translation in the cell is diminished by the autophosphorylation and activation of the transmembrane protein PERK, a major mediator of the UPR. Upon activation, PERK phosphorylates the alpha subunit of the eukaryotic initiation factor 2 (eIF2), a protein involved in the initiation of translation. When eIF2α is phosphorylated, it cannot promote translation. The goal of this study is to identify whether PERK affects the rate of RNA translation in tau transgenic mice. To accomplish this goal, four-month-old tau transgenic mice were administered a PERK inhibitor (GSK2606414) or vehicle control for one, two, or four days. The transgenic mice were then injected with puromycin, an antibiotic that allows for quantification of the rate of RNA translation by using surface sensing of translation (SUnSET) and immuno-fluorescent tags. The cohort treated with the PERK inhibitor for four days showed mild changes in RNA translation rates. These data suggest that at least four days of treatment are necessary to initiate an effective modulation of protein synthesis. Therefore, this work further supports PERK inhibition as a therapeutic strategy and identifies an early therapeutic window for tauopathies.