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**Titel des Beitrags:**
The unfolded protein response is activated in disease-affected brain regions in progressive supranuclear palsy and Alzheimer’s disease.

**Abstract:**
Progressive supranuclear palsy (PSP) is a neurodegenerative disorder pathologically characterized by intracellular tangles of hyperphosphorylated tau protein distributed throughout the neocortex, basal ganglia, and brainstem. A genome-wide association study identified EIF2AK3 as a risk factor for PSP. EIF2AK3 encodes PERK, part of the endoplasmic reticulum's (ER) unfolded protein response (UPR). PERK is an ER membrane protein that senses unfolded protein accumulation within the ER lumen. Recently, several groups noted UPR activation in Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis, multiple system atrophy, and in the hippocampus and substantia nigra of PSP subjects. Here, we evaluate UPR PERK activation in the pons, medulla, midbrain, hippocampus, frontal cortex and cerebellum in subjects with PSP, AD, and in normal controls. We found UPR activation primarily in disease-affected brain regions in both disorders. In PSP, the UPR was primarily activated in the pons and medulla and to a much lesser extent in the hippocampus. In AD, the UPR was extensively activated in the hippocampus. We also observed UPR activation in the hippocampus of some elderly normal controls, severity of which positively correlated with both age and tau pathology but not with A? plaque burden. Finally, we evaluated EIF2AK3 coding variants that influence PERK activation. We show that a haplotype associated with increased PERK activation is genetically associated with increased PSP risk. The UPR is activated in disease affected regions in PSP and the genetic evidence show that this activation increases risk for PSP and is not a protective response.

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