ER STRESS IS ASSOCIATED WITH THE PHOSPHORYLATION OF TAU - AN IN VITRO STUDY

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Introduction: The unfolded protein response (UPR) is a protein quality control mechanism that protects cells against endoplasmic reticulum (ER) stress. Previous studies in our group and others have demonstrated that involvement of the UPR in Alzheimer's disease (AD). UPR markers (e.g. Bip and pPERK) were found in pre-tangle neurons containing hyperphosphorylated tau. This indicates that UPR activation proceeds and might initiate tau phosphorylation.

Aims: In this study we investigate the link between UPR activation, the major tau kinase glycogen synthase kinase (GSK) 3β and tau phosphorylation in an in vitro cell model.

Methods: ER stress was induced in the SK-N-SH neuroblastoma cell model using tunicamycin and thapsigargin. Specific antibodies for (phosphorylated) tau and GSK3β were used in westernblot and in cell ELISA assays.

Results: We find that ER stress decreases the inactive serine 9 (S9) and increases the active tyrosine 216 (Y216) phosphorylation mark on GSK3β, indicating the enzyme is more active. In addition, westernblot and In Cell Elisa assays demonstrate increased tau phosphorylation in these settings. In order to further investigate this connection, we generated inducible PC12 cell lines containing tau and mutant tau associated with frontotemporal lobar degeneration (FTLD).

Conclusions: Our data indicate a connection between UPR activation, increased GSK3β activity and tau phosphorylation in vitro. UPR mediated in vivo tau phosphorylation might initially be a protective event aimed at modulating cellular transport by modulating tau bound to the microtubules.