ENDOPLASMIC RETICULUM STRESS INDUCES TAU PATHOLOGY AND FORMS VICIOUS CYCLE IN PATHOGENESIS OF ALZHEIMER’S DISEASE

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Introduction: Accumulation and deposit of unfolded protein can disturb the functions of endoplasmic reticulum (ER), leading to ER stress or called unfolded protein responses (UPR). UPR is increased in post-mortem Alzheimer’s disease (AD) brains, and upregulation of UPR signaling can be found in neurons with diffuse phosphorylated tau. However, the relationship between UPR and tau pathology is still unclear.

Aim: The aim of this study is to investigate whether UPR and tau pathology form vicious cycle, promoting neurodegeneration.

Methods: We used aged transgenic mice bearing human mutated tau P301L. In addition, we used primary cultures of cortical neurons.

Results: We found that there were increased levels of phosphorylated PKR-like ER-resident kinase (p-PERK) and phosphorylated eukaryotic initiation factor 2α (p-eIF2α), which were UPR activation markers, in the hippocampus of aged P301L mice. The p-PERK immunoreactivity was found to be co-localized with that of phosphorylated tau. We further investigated whether tau phosphorylation can induce UPR and vice versa. By using protein phosphatase 2A (PP2A) inhibitor okadaic acid (OA) as a tau phosphorylation inducer, we found increased levels of p-PERK and p-eIF2α in cultured neurons. On the other hand, treatment of neurons with thapsigargin (Tg), an ER stress inducer, induced tau phosphorylation at Thr231, Ser262 and Ser396. Tg also induced the activation of caspase-3 and tau cleavage.

Conclusion: Theses findings suggest that ER stress and tau hyperphosphorylation could be induced from each other and may form a vicious cycle in AD pathogenesis.

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