A Mechanistic Analysis of Intraneuronal Amyloid Beta Aggregation Caused by Cellular Dysfunction in Alzheimer's Disease

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Alzheimer's Disease (AD) affects tens of millions of people around the world as the most prevalent form of dementia. A hallmark of AD is the intracellular and extracellular aggregation of the misfolded amyloid beta protein, which contributes to neurodegeneration. While the formation of extracellular amyloid beta plaques is well characterized, pathways for intracellular accumulation and resulting cellular dysfunction are less clear. The goal of this study was to identify and characterize the dominant cellular mechanisms for amyloid beta aggregation. To do so, the SH-SY5Y neuroblastoma cell line was transfected with the APPSwe plasmid, which produces amyloid beta's precursor protein. Cell lines were treated with one of three chemicals to replicate stress conditions in cellular organelles: hydrogen peroxide to induce general oxidative stress, rotenone to induce mitochondrial stress, and tunicamycin to induce endoplasmic reticulum (ER) stress. Cells were then stained for amyloid beta-specific antibodies and for cell death. Microscopy, followed by analysis via ImageJ software, was used to determine the chemical, and therefore cellular stress pathway, that induced the most amyloid beta aggregation in cells. Tunicamycin most prominently promoted aggregation when measuring the proportion of cell clusters expressing amyloid beta. A significant difference was present compared to both rotenone and hydrogen peroxide for both transfected and non-transfected cells. These results indicate that the ER stress pathway, and thus the cellular protein folding response, most influence intracellular amyloid beta aggregation. This points to therapeutics and preventive options targeted at the ER as potentially viable for combating AD.

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