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Mitochondrial abnormalities at the origin of oxidative stress In Alzheimer's disease

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Abstract

Mitochondria may underlie oxidative stress in Alzheimer disease (AD) changes since dysfunction is a prominent and early feature of AD. Recent studies demonstrate that mitochondria are dynamic organelles that undergo continual fission and fusion events which regulate their morphology and distribution. Morphometry showed a small but significant reduction in mitochondria number and enlarged size in AD. Levels of the fission/fusion proteins DLP1, OPA1, Mfn1 and Mfn2C were significantly decreased in AD, yet levels of Fis1 were significantly increased. Interestingly, although all these proteins demonstrate even distribution in the cytoplasm and processes of pyramidal neurons in age-matched control hippocampus, they appeared to accumulate in the soma but not in the processes of pyramidal neurons in AD hippocampus. Given that OPA1, Fis1, and Mfn1/2 are all mitochondrial membrane proteins, the changes in their distribution to soma in AD neurons, suggest changes in mitochondria distribution in these neurons. The expression of fission/fusion proteins was manipulated in M17 cells and primary hippocampal neurons in a way that mimicked their expression changes in AD. These manipulations all reduced mitochondrial density in the cell periphery (M17 cells) or neuronal processes (primary neurons) which correlated with reduced spine numbers (primary neurons).

AβPP and Aβ caused reduced expression of DLP1 and OPA1 while increasing expression of Fis1, consistent with our findings in AD brains. Through time lapse study, we were able to demonstrate that mitochondria were able to fuse with each other but at a much slower rate in AβPP overexpressing cells.

Overall, we concluded that AβPP, through amyloid-β production impairs mitochondrial fission/fusion balance through regulation of expression of mitochondria fission and fusion proteins.

Biography

George Perry is dean of the College of Sciences and professor of biology at The University of Texas at San Antonio, and adjunct professor of Pathology and Neurosciences at Case Western Reserve University. Perry is recognized in the field of Alzheimer's disease research particularly for his work on oxidative metabolism. He is distinguished as one of the top Alzheimer's disease researchers with over 1000 publications, and one of the top 100 most-cited scientists in neuroscience and behavior. Perry is editor-in-chief for the Journal of Alzheimer's Disease, a Fellow of the American Association for the Advancement of Sciences, the Microscopy Society of America, the Royal Society of Chemistry, and past president of the American Association of Neuropathologists, as well as a member of the Dana Alliance for Brain Initiatives and a Fulbright Senior Specialist. Perry's research is primarily focused on how Alzheimer disease develops and the physiological consequences of the disease at a cellular level.

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