Clinical Pharmacy-2013
OMICS Group Conferences
Accelerating Scientific Discovery
International Summit on
Clinical Pharmacy & Dispensing
November 18-20, 2013 San Antonio, Texas, USA

Testing the two-hit hypothesis of Alzheimer disease: Cell cycle re-entry

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Abstract

The two-hit hypothesis of Alzheimer suggests cell cycle entry is a major factor in driving neuronal death in Alzheimer's disease (AD). We experimentally addressed this issue by driving c-myc expression specifically in neurons with an inducible cam-kinase promoter. We confirmed that c-myc was specifically inducible in large cortical/hippocampal neurons. We found expression of c-myc led to histone phosphorylation, DNA fragmentation (TUNEL), gliosis, and neuronal death. The effects were specific to brain areas of increased expression and did not involve the cerebellum. Consistent with neuronal specificity, behavior analysis showed the deficits were cognitive rather than motor function. These findings support cell cycle re-entry as a critical hit of the two-hit hypothesis of AD and point to the attractiveness of intervention to modify neuronal cell cycle re-entry as a therapeutic target.

Support provided by a National Institutes of Health grant from the National Institute on Minority Health and Health Disparities (G12MD007591), and by the Alzheimer's Association.

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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