

GLUTATHIONE DEPLETION LEADS TO SYMPTOMS OF PARKINSON'S DISEASE IN MICE

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Buck Institute study provides new model for the study of the neurodegenerative disease while highlighting the role of aging in disease development

Scientists at the Buck Institute have shown that mice suffering from a depletion of the antioxidant glutathione in dopamine-producing neurons developed nerve damage and symptoms associated with Parkinson's disease (PD) in humans. Dopamine is a neurotransmitter produced in the mid-brain which facilitates many critical functions, including motor skills. Past studies have shown that depletion of the naturally occurring antioxidant in the affected area of the brain is one of the earliest signs of PD, but this study shows that glutathione depletion may be a causal factor in the disorder. Results of the study, led by faculty member Julie Andersen, are to be published in the December 19, 2007 issue of The Journal of Neuroscience.

In the course of their research, Buck Institute scientists created a new model for studying PD, a progressive, incurable neurodegenerative disorder that affects 1.5 million Americans and results in tremor, slowness of movement and rigidity. They bred mice that can be chemically induced to develop a depletion of glutathione in the dopaminergic neurons as adults (animals unable to create glutathione would not survive in the womb). By inducing the depletion at various stages of the adult lifecycle scientists researchers also highlighted the connection between aging and PD. Mice induced to have glutathione depletion as young adults did not develop Parkinsonian-like nerve damage and symptoms, while those who suffered from the depletion in late middle age did develop a loss of dopaminergic neurons specifically related to PD.

In addition, the study suggests that loss of glutathione in the affected neurons may impact on energy production in the mitochondria, the "power plant" of the cells. This appears to involve a particular enzyme complex called mitochondrial complex I. Enzymatic activity of this complex has been found to be compromised in PD patients, but to date it has not been clear how this inhibition occurs.

Glutathione is recognized as a detoxifying antioxidant that helps the body repair damage from stress, pollution, infection and damage. While available in supplemental form, the antioxidant does not easily cross the blood-brain barrier. A pilot study in 1996 in which a small group of untreated PD patients were given daily intravenous infusions of glutathione over the period of a month reportedly resulted in a significant improvement in disability. "Whether such treatment was effective in altering brain levels of glutathione or in having lasting effects is unclear," said Andersen. "However, our data suggests that maintaining glutathione levels is critical for protecting neurons associated with PD from neurodegeneration. This work also points to glutathione replacement as a possible therapeutic avenue for PD and other related disorders."

"The novelty of this study is in finding a way to decrease glutathione synthesis in neural tissue by genetic manipulation and in demonstrating that this appears to allow inactivation of a critical component of mitochondrial function through the same mechanism that could only be previously demonstrated in a cell culture model," said Henry Jay Forman, PhD, Professor, School of Natural Sciences, UC Merced. "The implications for the role of glutathione depletion in the mechanism of Parkinson's disease are clear."

Joining Andersen in the study were Shankar Chinta, Jyothi Kumar, Mike Hsu, R. Subramanian, Deepi Kaur, Anand Rane and David Nicholls, also of the Buck Institute, along with Jinah Choi, from the University of California at Merced. The project was supported by NIH grant AG121141 to J.K.A.; S. J. Chinta is a recipient of a postdoctoral fellowship from the American Parkinson's Disease Association.

The Buck Institute is an independent non-profit organization dedicated to extending the healthspan, the healthy years of each individual's life. The National Institute of Aging designated the Buck a Nathan Shock Center of Excellence in the Biology of Aging, one of just five centers in the country. Buck Institute scientists work in an innovative, interdisciplinary setting to understand the mechanisms of aging and to discover new ways of detecting, preventing and treating age-related diseases such as Alzheimer's and Parkinson's disease, cancer, stroke, and arthritis. Collaborative research at the Institute is supported by genomics, proteomics and bioinformatics technology.

