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Effect of Oxidative Stress and Tau protein in Alzheimer's Disease

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About the Study

Oxidative stress appears to be one of the earliest events and a major determinant of the pathogenesis and progression in Alzheimer's disease. In experimental models and human brain studies of Alzheimer's disease, oxidative stress has also been shown to play an important role in neuronal degeneration. Several risk factors for Alzheimer's disease may cause or promote oxidative damage, such as advanced age, apolipoprotein E epselon4 alleles, and medical risk factors, environmental and lifestyle-related risk factors and so on. Generally, oxidative stress is caused by the imbalance between reactive oxygen species, which is associated with both the chronic formation of reactive oxygen species derived from the mitochondrial electron transport chain and the acute and high output formation of reactive oxygen species derived from nicotinamide adenine dinucleotide phosphate oxidase, and the breakdown of chemically reactive species by reducing agents and antioxidant enzymes, such as superoxide dismutase. This disequilibrium may result from disease, stressors or environmental factors. High ROS levels lead to the accumulation of oxidized proteins, lipids and nucleic acids due to the mitochondrial dysfunction, increased metal levels, inflammation and Aβ peptides, thereby directly impairing cellular function if not be removed or neutralized. Oxidative damage to cellular components is likely to result in the alteration of membrane properties such as fluidity, ion transport, enzyme activities, protein crosslinking and eventually cell death.

Structurally and functionally damaged mitochondria are more proficient at producing reactive oxygen species. Mitochondrial dysfunction may be an initial trigger for enhanced Aβ production during the aging process. Oxidative stress can promote Aβ deposition, tau hyperphosphorylation, and the subsequent loss of synapses and neurons in the development of Alzheimer's disease. Several studies suggest that reactive oxygen species are involved in Aβ fibrilization and NFT formation in Alzheimer's disease and increase with Aβ and NFT pathology in Alzheimer's disease. Both soluble and fibrillar Aβ may further accelerate oxidative stress as well as mitochondrial dysfunction. The transgenic Thy1-APP751 mouse model of Alzheimer's disease shows increased proteolytic cleavage of APP, increased production of Aβ and impaired Cu/Zn-SOD activity. Furthermore, oxidative stress is considered as a primary factor of NFT formation in Alzheimer's disease. However, the relationship between oxidative stress and tau hyperphosphorylation remains unclear. Okadaic acid is used as a research model to induce tau phosphorylation and mitochondrial SOD2 deficiency also increases the levels of Ser396 phosphorylated tau in the Tg2576 mouse model of Alzheimer's disease.

Tau protein plays a large role in the outgrowth of neuronal processes and the development of neuronal polarity. Tau protein in the central nervous system is predominantly expressed in neurons, with its main function to promote microtubule assembly, stabilize microtubules, affect the dynamics of microtubules in neurons and inhibit apoptosis particularly in axons. However, recent reports suggest that excess intracellular tau is released into the extracellular culture medium *via* membrane vesicles. In the adult human brain, tau consists of six isoforms and the tau gene contains 15 exons. The isoforms are generated by alternative splicing of exons 2, 3 and 10. Depending on the alternative splicing of exon 10, tau isoforms are termed 4R or 3R, Terminal exon, two N-terminal exons or no N-terminal exons at the N-terminal inserts mainly depend on the inclusion exon 2, exon 2 and 3 or the exclusion of both. Biochemical analyses of postmortem Alzheimer's disease brains indicate that 4R-tau is more abundant than 3R isolated NFTs.

Tau protein normally stabilizes axonal mictrotubules in the cytoskeleton and plays a vital role in regulating the morphology of neurons. It has more than 30 phosphorylation sites. When tau is abnormally hyperphosphorylated, it destabilizes microtubules by decreasing the binding affinity of tau and resulting in its aggregation in NFTs. NFTs are composed of paired helical filaments of abnormally hyperphophorylated tau. The severity of dementia in Alzheimer's disease was shown to correlate well with NFT load. In the transgenic mouse model, conditionally expressing the human tau P301L mutant, age-related NFTs develop along with neuronal loss and behavioral impairment. After the suppression of transgenic tau, memory function recovered and neuron numbers stabilized. The pathogenesis of tau-mediated neurodegeneration is unclear but hyperphosphorylation, oligomerization, fibrillization and propagation of tau pathology has been proposed as the likely pathological processes that induce the loss of function or gain of tau toxicity, which caused neurodegeneration. Tau phosphorylation has been investigated at Alzheimer's disease related sites by using recombinant human tau phosphorylated by DNA damage-activated checkpoint kinase 1 and checkpoint kinase 2 *in vitro*. Recent studies identified a total of 27 Ser/Thr residues as Chk1 or Chk2 target sites. Among these sites, 13 sites have been identified to be phophorylated in Alzheimer's disease brains. The generation of a Tg mouse line overexpressing human tau 441 *via* V337M and R406W tau mutations has been shown to accelerate the phosphorylation of human tau, inducing tau pathology and cognitive deficits.