Phosphorylated tau potentiates A?-induced mitochondrial damage in mature neurons

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Tau phosphorylated at the PHF-1 epitope (S396/S404) is likely involved in the pathogenesis of Alzheimer's disease (AD). However, the molecular mechanisms by which tau phosphorylated at these sites negatively impacts neuronal functions are still under scrutiny. Previously, we showed that expression of tau truncated at D421 enhances mitochondrial dysfunction induced by A? in cortical neurons. To extend these findings, we expressed tau pseudo-phosphorylated at S396/404 (T42EC) in mature and young cortical neurons and evaluated different aspects of mitochondrial function in response to A?. Expression of T42EC did not induce significant changes in mitochondrial morphology, mitochondrial length, or mitochondrial transport, compared to GFP and full-length tau. However, T42EC expression enhanced A?-induced mitochondrial membrane potential loss and increased superoxide levels compared to what was observed in mature neurons expressing full-length tau. The same effect was observed in mature neurons that expressed both pseudo-phosphorylated and truncated tau when they were treated with A?. Interestingly, the mitochondrial failure induced by A? in mature neurons that expressed T42EC, was not observed in young neurons expressing T42EC. These novel findings suggest that phosphorylated tau (PHF-1 epitope) enhances A?-induced mitochondrial injury, which contributes to neuronal dysfunction and to the pathogenesis of AD.

Alzheimer's disease

Mitochondria

Neuronal dysfunction

PHF-1

Tau

amyloid precursor protein

green fluorescent protein

presenilin 1

superoxide

tau protein

animal

animal embryo

brain cortex

C57BL mouse

cell culture

chemically induced

cytology

disorders of mitochondrial functions

drug effects

genetic transfection

genetics

metabolism

mitochondrial membrane potential

mouse

mutation

nerve cell

phosphorylation

rat

transgenic mouse

Amyloid beta-Protein Precursor

Animals

Cells, Cultured

Cerebral Cortex

Embryo, Mammalian

Green Fluorescent Proteins

Membrane Potential, Mitochondrial

Mice

Mice, Inbred C57BL

Mice, Transgenic

Mitochondrial Diseases

Mutation

Neurons

Phosphorylation

Presenilin-1

Rats

Superoxides

tau Proteins

Transfection