Caspase-Cleaved Tau Impairs Mitochondrial Dynamics in Alzheimer?s Disease

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Alzheimer?s disease (AD) is characterized by the presence of aggregates of tau protein. Tau truncated by caspase-3 (D421) or tau hyperphosphorylated at Ser396/S404 might play a role in the pathogenesis of AD. Mitochondria are dynamic organelles that modify their size and function through mitochondrial dynamics. Recent studies have shown that alterations of mitochondrial dynamics affect synaptic communication. Therefore, we studied the effects of pathological forms of tau on the regulation of mitochondrial dynamics. We used primary cortical neurons from tau(?/?) knockout mice and immortalized cortical neurons (CN1.4) that were transfected with plasmids containing green fluorescent protein (GFP) or GFP with different tau forms: full-length (GFP-T4), truncated (GFP-T4C3), pseudophosphorylated (GFP-T42EC), or both truncated and pseudophosphorylated modifications of tau (GFP-T4C3-2EC). Cells expressing truncated tau showed fragmented mitochondria compared to cells that expressed full-length tau. These findings were corroborated using primary neurons from tau(?/?) knockout mice that expressed the truncated and both truncated and pseudophosphorylated forms of tau. Interestingly, mitochondrial fragmentation was accompanied by a significant reduction in levels of optic atrophy protein 1 (Opa1) in cells expressing the truncated form of tau. In addition, treatment with low concentrations of amyloid-beta (A?) significantly reduced mitochondrial membrane potential, cell viability, and mitochondrial length in cortical cells and primary neurons from tau(?/?) mice that express truncated tau. These results indicate that the presence of tau pathology impairs mitochondrial dynamics by reducing Opa1 levels, an event that could lead to mitochondrial impairment observed in AD.

Alzheimer?s disease

Mitochondria

Neurodegeneration

Opa1

Tau

amyloid beta protein

caspase

green fluorescent protein

mitochondrial protein

optic atrophy protein 1

tau protein

unclassified drug

tau protein

Alzheimer disease

animal cell

Article

brain cell

cell size

cell viability

controlled study

disorders of mitochondrial functions

down regulation

immortalized cell line

mitochondrial membrane potential

mouse

nonhuman

protein cleavage

protein expression

protein modification

protein phosphorylation

Alzheimer disease

animal

brain

genetics

knockout mouse

metabolism

mitochondrial dynamics

mitochondrion

nerve cell

phosphorylation

physiology

Alzheimer Disease

Animals

Brain

Green Fluorescent Proteins

Membrane Potential, Mitochondrial

Mice

Mice, Knockout

Mitochondria

Mitochondrial Dynamics

Neurons

Phosphorylation

tau Proteins