Title

Caspase-3 cleaved tau impairs mitochondrial function through the opening of the mitochondrial permeability transition pore

Abstract

Mitochondrial dysfunction is a significant factor in the development of Alzheimer's disease (AD). Previous studies have demonstrated that the expression of tau cleaved at Asp421 by caspase-3 leads to mitochondrial abnormalities and bioenergetic impairment. However, the underlying mechanism behind these alterations and their impact on neuronal function remains unknown. To investigate the mechanism behind mitochondrial dysfunction caused by this tau form, we used transient transfection and pharmacological approaches in immortalized cortical neurons and mouse primary hippocampal neurons. We assessed mitochondrial morphology and bioenergetics function after expression of full-length tau and caspase-3-cleaved tau. We also evaluated the mitochondrial permeability transition pore (mPTP) opening and its conformation as a possible mechanism to explain mitochondrial impairment induced by caspase-3 cleaved tau. Our studies showed that pharmacological inhibition of mPTP by cyclosporine A (CsA) prevented all mitochondrial length and bioenergetics abnormalities in neuronal cells expressing caspase-3 cleaved tau. Neuronal cells expressing caspase-3-cleaved tau showed sustained mPTP opening which is mostly dependent on cyclophilin D (CypD) protein expression. Moreover, the impairment of mitochondrial length and bioenergetics induced by caspase-3-cleaved tau were prevented in hippocampal neurons obtained from CypD knock-out mice. Interestingly, previous studies using these mice showed a prevention of mPTP opening and a reduction of mitochondrial failure and neurodegeneration induced by AD. Therefore, our findings showed that caspase-3-cleaved tau negatively impacts mitochondrial bioenergetics through mPTP activation, highlighting the importance of this channel and its regulatory

protein, CypD, in the neuronal damage induced by tau pathology in AD. © 2023 Elsevier B.V.

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Chemicals/CAS

caspase 3, 169592-56-7; cyclosporine, 59865-13-3, 63798-73-2, 79217-60-0; cyclophilin A, ; cyclophilin B, ; cyclophilin C, ; cyclophilin D, ; peptidylprolyl isomerase, ; Caspase 3, ; Cyclophilin D, ; Mitochondrial Permeability Transition Pore,

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