Tau Deletion Prevents Cognitive Impairment and Mitochondrial Dysfunction Age Associated by a Mechanism Dependent on Cyclophilin-D

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Abstract
Aging is an irreversible process and the primary risk factor for the development of neurodegenerative diseases, such as Alzheimer's disease (AD). Mitochondrial impairment is a process that generates oxidative damage and ATP deficit; both factors are important in the memory decline showed during normal aging and AD. Tau is a microtubule-associated protein, with a strong influence on both the morphology and physiology of neurons. In AD, tau protein undergoes post-translational modifications, which could play a relevant role in the onset and progression of this disease. Also, these abnormal forms of tau could be present during the physiological aging that could be related to memory impairment present during this stage. We previously showed that tau ablation improves mitochondrial function and cognitive abilities in young wild-type mice. However, the possible contribution of tau during aging that could predispose to the development of AD is unclear. Here, we show that tau deletion prevents cognitive impairment and improves mitochondrial function during normal aging as indicated by a reduction in oxidative damage and increased ATP production. Notably, we observed a decrease in cyclophilin-D (CypD) levels in aged tau−/− mice, resulting in increased calcium buffering and reduced mitochondrial permeability transition pore (mPTP) opening. The mPTP is a mitochondrial structure, whose opening is dependent on CypD expression, and new evidence suggests that this could play an essential role in the neurodegenerative process showed during AD. In contrast, hippocampal CypD overexpression in aged tau−/− mice impairs mitochondrial function evidenced by an ATP deficit, increased mPTP opening, and memory loss; all effects were observed in the AD pathology. Our results indicate that the absence of tau prevents age-associated cognitive impairment by maintaining mitochondrial function and reducing mPTP opening through a CypD-dependent mechanism. These findings are novel and represent an important advance in the study of how tau contributes to the cognitive and mitochondrial failure present during aging and AD in the brain.

Author keywords
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