The role of mitochondrial impairment in alzheimer´s disease neurodegeneration: The Tau connection

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Abstract
Accumulative evidence has shown that mitochondrial dysfunction plays a pivotal role in the pathogenesis of Alzheimer's disease (AD). Mitochondrial impairment actively contributes to the synaptic and cognitive failure that characterizes AD. The presence of soluble pathological forms of tau like hyperphosphorylated at Ser396 and Ser404 and cleaved at Asp421 by caspase 3, negatively impacts mitochondrial bioenergetics, transport, and morphology in neurons. These adverse effects against mitochondria health will contribute to the synaptic impairment and cognitive decline in AD. Current studies suggest that mitochondrial failure induced by pathological tau forms is likely the result of the opening of the mitochondrial permeability transition pore (mPTP). mPTP is a mitochondrial mega-channel that is activated by increases in calcium and is associated with mitochondrial stress and apoptosis. This structure is composed of different proteins, where Ciclophilin D (CypD) is considered to be the primary mediator of mPTP activation. Also, new studies suggest that mPTP contributes to Aβ pathology and oxidative stress in AD. Further, inhibition of mPTP through the reduction of CypD expression prevents cognitive and synaptic impairment in AD mouse models. More importantly, tau protein contributes to the physiological regulation of mitochondria through the opening/interaction with mPTP in hippocampal neurons. Therefore, in this paper, we will discuss evidence that suggests an important role of pathological forms of tau against mitochondrial health. Also, we will discuss the possible role of mPTP in the mitochondrial impairment produced by the presence of tau pathology and its impact on synaptic function present in AD.

Author keywords
Alzheimer´s disease
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