Mitochondrial bioenergetic dysfunction in tauopathy-linked autophagy defects for pathological tau clearance

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Hyperphosphorylation and aggregation of tau are a pathogenic hallmark of tauopathies and a defining feature of Alzheimer's disease (AD). Pathological tau is targeted by macroautophagy/autophagy for clearance after being sequestered within autophagosomes, but autophagy dysfunction is indicated in tauopathy. While mitochondrial bioenergetic deficits have been shown to precede tau pathology in tauopathy brains, it is unclear whether mitochondrial energy metabolism deficiency is involved in the pathogenesis of autophagy defects. Here, we reveal that stimulation of anaplerotic metabolism restores defective oxidative phosphorylation (OXPHOS) in tauopathy neurons, which, strikingly, leads to pronounced tau clearance by boosting autophagy functionality through enhancements of mitochondrial biosynthesis and supply of phosphatidylethanolamine for autophagosome biogenesis. Furthermore, early anaplerotic stimulation of OXPHOS elevates autophagy activity and attenuates tau pathology, thereby counteracting memory impairment in tauopathy mice. Taken together, our study sheds light on a pivotal role of mitochondrial bioenergetic deficiency in tauopathy-related autophagy defects and suggests a new therapeutic strategy to prevent the buildup of pathological tau in AD and other tauopathy diseases.

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