

MITOCHONDRIAL DYSFUNCTIONS IN A TRANSGENIC MURINE MODEL OF ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is characterized by two hallmark lesions: diffuse and neuritic plaques, which are predominantly composed of the amyloid beta (A β) peptide, and neurofibrillary tangles, composed of filamentous aggregates of hyperphosphorylated tau protein. Recent studies suggested that A β can directly interact with mitochondria causing leakage of reactive oxygen species (1), but no evidences have been produced so far on the mechanisms involved in A β -induced mitochondrial dysfunction.

In the present study, we used a triple-transgenic murine model of AD (3xTg-AD), which progressively develop A β and tau pathology, with a temporal- and regional-specific profile that closely mimics the human pathology (2). To directly test the hypothesis of whether the regional-specific development of A β and tau pathologies interfere with mitochondrial respiratory chain, brain mitochondria were isolated from frontal cortex, hippocampus, striatum, and cerebellum of 18-months old 3xTg-AD and Non Tg mice. The following parameters were measured: 1) state 4 and state 3 respiration rates in the presence of either Complex I or Complex II substrates; 2) respiratory control ratio (RCR); 3) membrane potential.

Results revealed that, excepted for the cerebellum, all the mitochondria isolated from 3xTg-AD mice and monitored in state 4 and state 3, showed an alteration in Complex I. In particular, adding glutamate/malate as substrate a higher oxygen consumption was found in state 4 vs state 3, which accounts for a lower RCR in 3xTg-AD mice with respect to Non Tg mice. When the respiratory activity of Complex II in state 4 and state 3 was monitored in mitochondria incubated with succinate as substrate and rotenone as inhibitor of Complex I, a significant increase of oxygen consumption was observed in mitochondria isolated from striatum, cortex and hippocampus of 3xTg-AD mice compared to Non Tg mice. Such increase was observed both in state 4 and state 3 and the RCR resulted similar to that obtained in mitochondria of Non Tg mice. Our results suggest that the mitochondria isolated from brain regions of 3xTg-AD mice displaying higher A β and tau lesions showed an alteration in Complex I, which might account for a mitochondrial uncoupling between respiratory chain complexes and ATP synthesis. This hypothesis is supported by a lower inner mitochondrial membrane potential found in 3xTg-AD mice compared to Non Tg mice.

1. Reddy P.H. (2006) *J Neurochem.* 96: 1-13.
2. Oddo S., et al. (2003) *Neuron.* 39: 409-21.