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

Cassano Tommaso, Serviddio G., Bellanti F., Tamborra R., Macheda T., Morgese M.G., Trabace L., Oddo S., LaFerla F.M., Cuomo V. and Vendemiale G.

1Dept. of Biochemical Sciences Univ. of Foggia, Italy; 2Dept. of Medical and Occupational Sciences, Univ. of Foggia, Italy; 3Dept. of Neurobiology and Behavior, Univ. of California, Irvine, U.S.; 4Dept. of Human Physiology and Pharmacology, Univ. of Rome “La Sapienza”, Italy

Alzheimer’s disease (AD) is characterized by two hallmark lesions: diffuse and neuritic plaques, which are predominantly composed of the amyloid beta (Aβ) peptide, and neurofibrillary tangles, composed of filamentous aggregates of hyperphosphorylated tau protein. Recent studies suggested that Aβ 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 Aβ-induced mitochondrial dysfunction.

In the present study, we used a triple-transgenic murine model of AD (3xTg-AD), which progressively develop Aβ 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 Aβ 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 Aβ 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.