Changes in PGC-1 α and Mfn1/Drp1 levels are indicative of amyloid β -induced mitochondrial dysfunction induced by P2X₂-mediated Ca²⁺ overload in a cellular model of Alzheimer's disease

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Soluble oligomers of Ab (SOAb) are the toxic agent in the pathogenesis of AD with multiple toxic effects. The aim of this work was to evaluate the effects of SOAb on the expression and levels of P2X₂R and its contribution on mitochondrial biogenesis and dynamics. Changes on P2X₂R was measured and Mitochondrial biogenesis was evaluated by changes on peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC-1 α), and by the silent mating type information regulation 2 homolog (SIRT1) protein. On the other hand, mitochondrial dynamics was evaluated by changes on the fusion protein Mitofusin 1 (Mfn1) and fission dynamin-related protein 1 (DRP1). P2X₂R increase (after 24 h) its expression and functional activity on neurons (over 25%). Through western blot and immunofluorescence, we observed decreased SIRT1 after SOAb treatments (about 50%). Conversely, an increment of PGC-1 α was detected after 5h incubations (218%), though reduced levels were obtained after 1 and 24 h treatments (30%, 42% respectively). The interaction between these two proteins after a 24 h SOAb exposure was lost, which correlates with a change in PGC-1 α distribution, increasing in the cytoplasm (177%) and decreasing in the nucleus (38%). After 2 h incubations we observed a reduction in Mfn1 levels (42%), and an increase in DRP1 (198%); additionally, DRP1 presented a distribution shift on hippocampal neurons, increasing its immunoreactivity in neuronal processes. Changes regarding mitochondrial proteins correlate with an alteration of mitochondrial network morphology and this dysfunction can be associated to the P2X₂R contribution. Finally, SOAb-induced imbalance on P2X₂R, mitochondrial dynamics, and decreased mitochondrial biogenesis, thus blocking the pathway that lead to the cell to have functional mitochondrias.