Revealing Consequences Of Progressive Inhibition Of Protein Phosphatase 2A Activity In An Alzheimer-Like Phenotype Induced By Okadaic Acid In Mice.

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INTRODUCTION. Accumulation of β-amyloid plaques, hyperphosphorylated tau and oxidative stress are contributors to cognitive decline in Alzheimer’s disease (AD). Recently, hypothetical models have been used to describe AD temporal evolution. However, biological basis behind these models still remains largely unknown. Here we propose an AD-like model induced by okadaic acid (OA), an inhibitor of protein phosphatase 2A (PP2A) activity, as a suitable tool for the study of the progression of AD in mice. Inhibiting PP2A, OA mimics a common scenario of PP2A reduced activity in AD patients. MATERIAL AND METHODS: An infusion of OA was made on right ventricle (25, 50, 100 and 200ng) in CF1 mice. We analyzed behavioral and neurochemical responses of OA increasing doses on AD specific outcomes as well as lipid peroxidation, oxidative stress, tau phosphorylation and spatial memory performance in the Morris Water Maze task (MWM). RESULTS AND DISCUSSION: Our results showed that the impairment in spatial memory, increase in lipid peroxidation levels (TBARS) and in tau phosphorylation is dependent on OA dose. Also, increased lipid peroxidation and tau phosphorylation levels are correlated with spatial memory impairments on MWM. CONCLUSIONS: Our study demonstrated that increasing PP2A inhibition by OA in mice is able to replicate important features of AD. Also, the progressive phosphatase inhibition provides a model that mimics AD phases (mild to severe) representing a powerful tool to study AD progression supported by PP2A abnormal activity.

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