

IN VIVO CHARACTERIZATION OF DKK-1 EXPRESSION IN TRANSGENIC ANIMAL MODELS OF ALZHEIMER'S DISEASE

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Senile plaques, made of fibrillary β -amyloid ($A\beta$) peptide deposits, and neurofibrillary tangles, made of hyperphosphorylated tau protein are the histopathological hallmarks of Alzheimer's disease (AD). GSK-3 β appears to be responsible for tau hyperphosphorylation in AD brain. Several intracellular signal transduction pathways negatively regulate the activation of this kinase. Dysfunction of one such pathway, the Wnt signaling, leads to GSK-3 β activation and to increased levels of tau phosphorylation in AD. DKK-1 protein negatively modulates the canonical Wnt pathway and might therefore be a component of the sequence of events leading to neuronal toxicity. Lithium salts, through inhibition of GSK-3 activity, induce a significant reduction in aggregated tau and degeneration. The aim of this study was to characterize the expression pattern of DKK-1 and to test the effectiveness of LiCl treatment in ameliorating the AD-like pathology in transgenic animal models of AD. Western Blotting and immunohistochemical techniques were used to reveal protein of interest. The expression of DKK-1 was investigated in the brain of 7- and 12-month-old TgCRND8 mice, expressing double mutated human amyloid precursor protein (APP) and in 12-month-old APP^{swe}/PS1-dE9 transgenic mice, expressing mutated human APP and presenil-1, the variant dE9. Non-Tg wild type mouse littermates were used as controls. A group of 2-month-old-TgCRND8 ($n=8$) and control mice ($n=8$) received i.p. injections of either 0.6 M LiCl (10 μ l per gram of body weight) or sterile 10 mM PBS (10 μ l per gram of body weight) daily for 30 days. A marked induction of DKK-1 immunoreactivity was found in the II, III, V and VI layers of secondary motor cortex, in the piriform cortex and in the CA1 area of hippocampus of TgCRND8 mouse brain, as compared to controls. DKK-1 staining was localized in the cytoplasm and processes of neurons. Western blot analysis with DKK-1 antibody confirmed the immunohistochemical data. Double-labeling immunohistochemistry with DKK-1 and $A\beta(1-42)$ antibodies revealed DKK-1 immunopositive neurons in the vicinity of amyloid plaques. Numerous DKK-1 immunopositive neurons were detected in the CA3 area of hippocampus and in the entorhinal cortex of APP^{swe}/PS1-dE9 mice. These findings demonstrate that Wnt signaling is impaired in the brain of aged transgenic mouse models of AD. The effect of lithium salts treatment on DKK-1 expression, GSK-3 β activity and β -catenin levels is under investigation. Supported by a grant from the European Commission FP6 (ADIT, contract n.LSHB-CT-2005-511977)