# INVESTIGATION OF Wnt SIGNALING FACTORS IN ANIMAL MODELS OF ALZHEIMER DISEASE

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Senile plaques and neurofibrillary tangles (NFTs) are the histopathological hallmarks of Alzheimer's disease (AD). Several kinases, among which GSK-3β, appear to be responsible for tau hyperphosphorylation and increased levels of GSK-3β have been found in AD brain associated with NFTs. Several intracellular signal transduction pathways negatively regulate the activation of GSK-3β and recently one such pathway, the Wnt signaling, has been extensively studied. Dysfunction of Wnt signaling, leading to GSK-3β activation, to increased levels of tau phosphorylation and to the deposition of insoluble Aβ peptide, links amyloid plaques biogenesis and neurofibrillary changes, thus opening new possibilities for therapeutic intervention in AD. Dickkopf-1 (DKK-1) protein negatively modulates the canonical Wnt pathway and might be a component of the sequence of events leading to neuronal toxicity in response to β-amyloid. In order to discover new drug targets in AD, we studied Wnt signaling pathway and, in particular, the expression pattern of DKK-1 and GSK-3β in vivo in transgenic animal models of AD. Western Blotting and immunohistochemical techniques were used. 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 APPswe/PS1-dE9 transgenic mice, expressing mutated human APP and presenil-1, the variant dE9. The expression of GSK-3β was investigated in the brain of TgCRND8 mice. Non-Tg mouse littermates were used as controls. A marked induction of DKK-1immunoreactivity was found in the motor and piriform cortex, 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-labelling experiments revealed a co-localization between DKK-1 and phospho-tau immunoreactivities in neurons in the vicinity of amyloid plaques. Numerous DKK-1-immmunopositive neurons were detected in the CA3 area of hippocampus and in the entorhinal cortex of APPswe/PS1-dE9 mice. Immunoreactivity of GSK-3β was increased in the motor cortex and in the CA3 area and dentate gyrus of the hippocampus of 12-month-old TgCRND8 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 and GSK-3β is under investigation. Supported by a grant from the European Commission FP6 (ADIT, contract n.LSHB-CT-2005-511977)