

## ALTERATIONS OF TAU PROTEIN AND EFFECT OF LITHIUM SALTS TREATMENT ON TgCRND8 MICE

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Extracellular senile plaques, made of  $\beta$ -amyloid ( $A\beta$ ) peptide deposits, and intraneuronal neurofibrillary tangles, made of hyperphosphorylated microtubule-associated tau protein are the main histo-pathological changes seen in the Alzheimer's disease (AD) brain. Although much evidence suggest that  $A\beta$  deposition is a critical initiation factor, the relationship between amyloidosis and tau accumulation remains unclear. In this study the onset of neuropathological tau alterations was examined in the transgenic mouse TgCRND8, expressing double mutated human amyloid precursor protein and exhibiting enhanced cerebral  $A\beta$ -plaque burden. Non-Tg wild type mouse littermates were used as controls. Western Blotting and immunohistochemical techniques were used. Hyperphosphorylated tau was detected by using site-specific phosphorylation-dependent tau antibodies. Cognitive impairments were evaluated in the Step-Down and Morris Water Maze tasks. We found that, in the cortex and hippocampus of 7- and 12-month-old TgCRND8 mice, tau is hyperphosphorylated at different sites recognised by PHF-1, AT100, AT8 and CP13 antibodies. Thioflavin S- and Bielshowsky Silver staining indicate the occurrence of fibrillary inclusions within hyperphosphorylated tau bearing neurons. Phosphorylated SAPK/JNK levels were increased in the cortex (+ 40%,  $P < 0.01$  Student's t test) and the hippocampus (+ 58%,  $P < 0.001$  Student's t test) of tg mouse brain, where activated SAPK/JNK colocalizes with PHF-1-positive cells. Moreover, TgCRND8 mice displayed an increased immunoreactivity for the active form of GSK-3 $\beta$  in the motor cortex and in the CA3 subfield and the dentate gyrus of the hippocampus. To investigate whether GSK-3 $\beta$  inhibition can affect AD pathology *in vivo*, two-month-old-TgCRND8 ( $n=8$ ) and control mice ( $n=8$ ) received i.p. injections of either 0.6 M lithium chloride (10  $\mu$ l per gram of body weight) or sterile 10 mM PBS (10  $\mu$ l per gram of body weight) daily for 30 days. Lithium-treated Tg mice showed a significant improvement ( $p < 0.001$ , Bonferroni's test) in working memory performance in the Step-Down inhibitory avoidance task with respect to vehicle-treated animals. In addition, a significant improvement in learning ability ( $*P < 0.05$ , Bonferroni's test) as well as in spatial memory performances ( $**P < 0.01$ ) was found in the lithium treated TgCRND8 mice with respect to the vehicle treated Tg controls, when assessed in the Morris Water Maze task. The effect of lithium salts treatment on  $A\beta$ -plaque burden and tau alterations is under investigation. Supported by MIUR 2005.