P3-005 PESTICIDE EXPOSURE INDUCES COGNITIVE ABNORMALITIES AND TAU HYPERPHOSPHORYLATION IN MALE RATS

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Background: Since the sporadic cases accounted for 90% of the composition of the AD pathogenesis, it is generally believed that genetic factors play a small role in the etiology of AD, the roles of pesticides, air pollution, some metal elements and head injuries, lifestyle, dietary habits and other environmental factors play in the process of AD can not be ignored. Pesticide exposure has neurotoxic and can affect neural development and neurobehavior in rats. Neurodegenerative diseases are reported to aggregate in employees frequently exposed to pesticides. The populations living in areas with high pesticide use were found to have an increased risk for developing AD, independently of age and gender. All of these epidemiological studies suggest that pesticide exposure has a tight association with AD, but until now, the specific impacts of pesticide on the mechanism of AD pathogenesis is still obscure. Methods: Deltamethrin or carbofuran was administered into SD rats once a day for 28 days by gavage. Morris water maze test, Western blot, Immunohistochemistry and Nisil staining. Results: Pesticide exposure induced spatial memory deficits with simultaneous decreases in synaptic proteins of N-methyl-D-aspartate receptor 1 (NR1), synaptophysin and synapsin I, the immediate early gene cAMP response element binding (CREB) protein, all of which are memory-related proteins. Pesticide exposure also caused neuron loss in the hippocampus and cortex, and induced tau hyperphosphorylation at multiple Alzheimer-related phosphorylation sites with activation of glycogen synthase kinase-3 b (GSK-3 b) and inhibition of protein phosphatase-2A (PP)-2A. Conclusions: In summary, we have firstly found in the present study that pesticide treatment induced spatial memory deficits with possible mechanisms that may involve the expression of several memory-related proteins, including NR1, synaptophysin and synapsin I. It also increased tau phosphorylation with inhibition of PP-2A as well as activation of GSK-3 b.

P3-006 ENDOGENOUS TAU CONTRIBUTES TO ALZHEIMER’S-LIKE TAU PATHOLOGY IN 3XTG MICE

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Background: Abnormal tau aggregates, also known as neurofibrillary tangles (NFTs), and amyloid-beta (Aβ) plaques are pathological hallmarks of Alzheimer’s disease (AD). Recent studies have shown contradictory results about the role of endogenous mouse tau in the pathological events observed in AD models. On one hand, it has been suggested that the concomitant expression of the endogenous murine tau might interfere with the disease progression and the neurodegenerative processes by delaying pathological accumulation of human mutant tau in neurons. On the other hand, other studies strongly indicate that mouse tau is a critical downstream mediator of Aβ toxicity. Methods: To clarify the role of endogenous murine tau in the pathological events that occur in AD models, we developed a novel transgenic mouse model by crossing 3xTg-AD with mttauKO mice, referred as 3xTg-AD/mttauKO. This new model (3xTg-AD/mttauKO) allows us to determine the specific pathological role of murine tau. Results: Here, we show that 3xTg-AD/mttauKO mice exhibit lower tau loads in both soluble and insoluble fractions and reduced tau hyperphosphorylation in the soluble fraction when compared with 3xTg-AD mice. These results indicate that mouse tau is hyperphosphorylated and significantly co-aggregated with human tau in 3xTg-AD mice. Interestingly, both transgenic models showed similar tau kinase activity as well as comparable Aβ pathology. Furthermore, both models exhibited equivalent cognitive dysfunction when tested on a spatial memory task. Conclusions: These results provide relevant insights for developing new models to better understand the link between β-amyloid and tau.

P3-007 DEVELOPMENT OF TAU PROTEOLYTIC ACTIVITY AS A TARGET FOR DRUG DISCOVERY


Background: Tau is a microtubule binding protein that normally functions in axons to maintain microtubule structure. It is hyperphosphorylated in AD facilitating its dissociation from microtubules and accumulation in the somatodendritic compartment where it can aggregate (Iqbal et al. 2010). Neurofibrillary tangles, primarily composed of tau protein are a pathological hallmark in Alzheimer’s disease (AD). However, the oligomeric forms of tau appear to be most closely associated with neuronal loss and memory impairment in mouse models of tauopathy (Berger et al. 2007; Yoshiyama et al. 2007). Tau oligomers were also found to accumulate in human AD brain specimens (Maeda et al. 2006; Patterson et al. 2011; Lasagna-Reeves et al. 2012). Importantly, extracellular tau oligomers have been shown to cause memory impairment and toxicity in mice inhibiting formation of long-term potentiation in hippocampal slices and formation of associative fear memory (Fá et al. 2010) and to induce neurodegeneration by affecting mitochondrial and synaptic function (Lasagna-Reeves et al. 2012). Here, we describe tau protease activity, screening of inhibitors and the development of HTS assays for drug discovery targeting tau protease. Methods: Tau oligomers prepared from recombinant human 4R/2N tau protein were highly purified and used for protease assays. Reverse-phase HPLC was used to assay tau protease activity on peptides from tau and other proteins. An Envision plate reader was used for a peptide-based FRET assay of protease inhibitors. Results: The class of tau protease was determined using protease inhibitors. Autoproteolytic cut sites were characterized by mass spectrometry. Tubulin