BLOCKADE OF TAU HYPERPHOSPHORYLATION BY A GSK3B INHIBITOR, IN THE AB25-35 MODEL OF ALZHEIMER'S DISEASE, CORRELATES WITH ATTENUATION OF FUNCTIONAL DEFICITS

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Introduction: Glycogen synthase kinase-3β (GSK-3β) is a Serine/Threonine kinase, playing an important role in Alzheimer's disease (AD) pathogenesis, by mediating hyper- and abnormal phosphorylations of Tau protein, generating neurofibrillary tangles. The central administration of oligomeric amyloid β25-35 peptide fragment (oAβ) in rodents, a nontransgenic model of AD, increased GSK-3β phosphorylation and activity.

Aims: We analyzed whether inhibition of GSK-3β by the potent inhibitor 2-thio(3-iodobenzyl)-5-(1-pyridyl)-[1,3,4]-oxadiazole (TIBPO) affected oAβ toxicity in mice.

Methods: Mice received 9 nmol of oAβ icv 7 days prior to behavioral analyses; spontaneous alternation in the Y maze and step-through passive avoidance. Lipid peroxidation was examined in hippocampus as an index of oxidative stress, cell death was assessed in brain slices using cresyl violet staining, and GSK-3β activity and Tau protein phosphorylation using western blotting.

Results: oAβ induced memory deficits, oxidative stress and hippocampus cell loss. oAβ increased hippocampal GSK-3β activity in a time-dependent manner, by increasing Tyr216 phosphorylation. Ser9 phosphorylation and total GSK-3β levels remained unchanged. oAβ increased hyper- and abnormal phosphorylation of Tau protein, as shown by increased AT8 and AT100 immunoreactivity. The GSK-3β inhibitor TIBPO concomittantly administered with oAβ blocked the induction of memory deficits, oxidative stress, hippocampus cell loss and Tau phosphorylation.

Conclusions: GSK-3β inhibition protected against the toxicity and behavioral deficits observed after oAβ injection in mice. Such oligomeric peptide preparation therefore rapidly provokes Tau protein hyperphosphorylation and this mechanism is involved, besides of neuroinflammation, endoplasmic reticulum stress and oxidative stress, in the functional deficits observed in this acute pathomimetic AD model.