ABSTRACT

Numerous epidemiological and experimental studies have shown that patients suffering from metabolic disorders such as type 2 diabetes mellitus (TDM2), insulin resistance or obesity are at a higher risk of cognitive functions impairment and developing Alzheimer´s disease (AD). Impairment of insulin signalling in the brain could contribute to two pathological changes which leads to AD development that include insoluble senile plaques and neurofibrillary tangles, containing an abnormally hyperphosphorylated tau protein (Tau).

This work is focused on investigating of insulin signaling in hippocampi in the brains of mice models of insulin resistence, impact of disturbed insulin signaling on hyperphosphorylation of Tau, and possible benefical efect of insulin sensitizing agents on insulin signaling and Tau phosphorylation in the hippocampi of diabetic mice.

The first, we examined insulin signaling and phosphorylation of Tau in hippocampi in two mouse models of TDM2 - lipodystrofic A-ZIP F-1 mice and monosodium glutamate obese mice (MSG mice). We did not observe any changes in insulin signaling and Tau phosphorylation in hippocampi of A-ZIP F-1 mice compared to controls. In the hippocampi of MSG mice there was attenuated phosphorylation of kinases of insulin signalling including Ser9 of glycogen synthase kinase-3β (GSK-3β). Attenuated phosphorylation of Ser9 inhibits kinase activity of GSK-3β and augmented phosphorylation of Ser9 conversely activates kinase activity GSK-3β. GSK-3β is one of the most important kinases of Tau, so activation seems to lead to phosphorylarion of Tau at Ser396 and Thr231 in comparison with control mice.

We tested impact of analogue of glucagon like peptide (GLP-1) liraglutide which is used for TDM2 treatment and lipidized analogue of prolactin releasing peptide (PrRP31), an anorexigenic neuropeptide, in MSG mice. After 14 days of subcutaneous injections of these peptides, a significant increase in phosphorylations of kinases in insulin signaling (PDK1 (Ser241), Akt (Thr308) and GSK-3β (Ser9)) occured and phosphorylations of Tau at Ser396, Thr231 and Thr212 were attenuated in the hippocampi in MSG mice. Our results show that insulin resistance could be involved in development of neurodegenerative changes in AD and insulin sensitising agents such as liraglutide and PrRP31 analogue could prevent these changes.