ABSTRACT

Alzheimer's disease (AD) is neurological disorder characterized by extracellular beta amyloid plaques and intracellular neurofibrillary tangles formed by hyper-phosphorylated Tau protein.

Since type 2 diabetes mellitus (T2DM) is a risk factor of AD development, in the first part of the thesis, a potential relationship between hyper-phosphorylation of Tau protein and central insulin resistance was followed in hippocampi of two models of obesity-induced pre-diabetes, fa/fa rats, and mice with monosodium glutamate (MSG) induced obesity. In both 8-month-old fa/fa rats and 6-month-old MSG mice a decreased phosphorylation of insulin signaling cascade resulted in an increased activation of main Tau kinase glycogen-synthase kinase-3Beta (GSK-3β) and an increased Tau phosphorylation at epitopes Ser396 and Thr231. This phenomenon was less developed in 2-month-old animals.

The second part of the thesis was focused on a potential neuroprotective anorexigenic neuropeptide, prolactin-releasing peptide (PrRP), designed at our Institute. Palmitoylation enabled PrRP to cross the blood-brain barrier and employ its central anorexigenic activity.

In the third part of the thesis, an effect of 14-day-long SC administration of liraglutide, the most used anti-T2DM drug with central anorexigenic effect, and palmitoylated PrRP31 on insulin signaling cascade and Tau hyper-phosphorylation was examined in the hippocampi of 6-month-old MSG mice. Both compounds streamlined insulin signaling cascade, and also attenuated Tau phosphorylation at Thr212, Thr231, and Ser396. The effect of 2-month-long SC administration of palmitoylated PrRP31 was examined also in a model of AD-like Tau pathology, Thy-Tau22 mice overexpressing mutated human Tau protein. The treatment resulted in decreased Tau protein phosphorylation at Thr231, Ser396 and Ser404.

Our study revealed a deleterious effect of obesity-related pre-diabetes on the development of Tau pathology, and the beneficial effect of anorexigenic compounds on the hyper-phosphorylation of Tau. Anorexigenic peptides thus showed potency for possible treatment of neurodegenerative disorders.

KEY WORDS:

Alzheimer's disease, insulin resistance, obesity, glycogen-synthase kinase – 3Beta, Tau protein hyper-phosphorylation, fa/fa rats, MSG mice, Thy-Tau22 mice, prolactin-releasing peptide, liraglutide