ABSTRACT

Alzheimer´s disease (AD) is a progressive brain disorder characterized by extracellular beta amyloid (Aβ) plaques, intracellular neurofibrillary tangles formed by hyperphosphorylated Tau protein and neuroinflammation. Since obesity and type 2 diabetes mellitus (T2DM) have been established as risk factors for the development of neurological disorders, anorexigenic and antidiabetic peptides, such as prolactin-releasing peptide (PrRP) seem to be potential neuroprotective agents.

In the first part of the study, the molecular mechanisms of action of natural PrRP31 and its lipidized analog palm^{11}-PrRP31 was studied in the human neuroblastoma cell line SH-SY5Y. Both compounds significantly activated the signaling pathways typical for insulin promoting cell survival and growth. Moreover, PrRP31 and palm^{11}-PrRP31 increased cell viability and suppressed apoptosis in methylglyoxal-stressed SH-SY5Y cells.

The second part of the thesis was focused on the neuroprotective and anti-inflammatory effects of 2-month-long subcutaneous administration of palm^{11}-PrRP31 in the brains of APP/PS1 mice, model of Aβ pathology. Palm^{11}-PrRP31 significantly reduced the Aβ plaque load and microgliosis in the hippocampi, cortices, and cerebella. Furthermore, palm^{11}-PrRP31 increased the synaptogenesis and attenuated neuroinflammation and apoptosis in the hippocampus of APP/PS1 mice.

In the third part of the thesis, a potential relationship between insulin resistance and AD was followed in the brains and periphery of APP/PS1 mice fed with high-fat diet (HFD), the model connecting obesity and AD-like pathology. HFD worsened the Aβ pathology in hippocampi and significantly affected both central and peripheral inflammation. Furthermore, mice on HFD developed substantial peripheral insulin resistance leading to central insulin resistance. The study revealed a deleterious effect of obesity-related inflammation and pre-diabetes on the development of Aβ pathology and neuroinflammation and confirmed peripheral and central inflammation and insulin resistance as potential mediators of brain dysfunction in AD.

In conclusion, my thesis proves beneficial effect of PrRP in the AD-like pathology, suggesting palm^{11}-PrRP31 as a promising agent for the treatment of AD.

KEY WORDS:

Alzheimer´s disease, obesity, inflammation, neuroinflammation, APP/PS1 mice, Aβ plaques, Tau, insulin resistance, SH-SY5Y cells, prolactin-releasing peptide