English abstract

Synapses and synaptic plasticity allows an efficient communication between neurons in the brain, which underlies of cognitive processes like memory and learning. Impairment of these processes is an essential feature in neurodegenerative diseases, particularly Alzheimer's disease (AD). AD accounts for about 60-70% of all forms of dementia. Despite many years of research, the disease is still incurable. Moreover, the long preclinical period characterized by the lack of visible clinical symptoms makes it impossible to detect it early enough. An increasingly important role in improving the diagnosis of this disease is played by biomarkers assessed in the cerebrospinal fluid (CSF), which provide evidence in vivo of the development of early neuropathological changes. Impairment of synaptic plasticity and transmission is one of the earliest neuropathological changes in AD, caused by amyloid-β deposits such as oligomers (Aβo) or senile plaques, one of the major features of AD. The synaptic connections and dendrites loss due to Aβ neuropathology can be detected and monitored by measuring synaptic proteins in the cerebrospinal fluid (CSF). Therefore, the study of proteins with specialized functions in synaptic transmission and plasticity seems to be an important direction of research that may find application in clinical practice. The aim of the research conducted as part of this doctoral dissertation was to quantify and analyze the potential diagnostic utility of selected proteins reflecting disorders of synaptic plasticity in the course of Alzheimer's disease and mild cognitive impairment (MCI). Neurongranin (Ng), neuronal pentraxin receptor (NPTXR) and fatty acid binding protein 3 (FABP3) were assessed by immunological methods (i.e. classical ELISA method and xMAP multiplexing technology on the Luminex 200 platform) in the cerebrospinal fluid (CSF) of patients with MCI, AD and non-cognitive controls. In addition, a bioinformatic analysis was performed using the Gene ontology (GO) enrichment tool to determine possible relationships between biological processes of synaptic pathology underlying AD, molecular functions of selected proteins reflecting synaptic and axonal pathology at the cellular level.

The studies showed a significantly increased concentration of Ng in both the AD and MCI groups compared to the control group without cognitive impairment (CTRL). The concentration of NPTXR in CSF was significantly lower in AD and MCI patients than in the CTRL group. A significantly higher concentration of FABP3 protein in CSF was observed in the group of AD patients compared to MCI and CTRL. The largest area under the curve (AUC) was observed for the NPTXR / Ng ratio compared between MCI and CTRL (AUC = 0.974). The highest AUC among all compared groups was found for the Aβ42 / Ng ratio, especially between patients with MCI versus AD (AUC = 0.909).

Bioinformatics analysis of common biological processes based on Gene Ontology (GO) terms for the candidate and classical biomarkers showed that both "modulation of chemical synaptic transmission" and "regulation of trans-synaptic signaling" are common for Ng, NPTXR, Tau and Aβ. By applying bioinformatics to experimental data, the understanding and interpretation of the results can be expanded in the context of the biological functions of the tested proteins.

In summary, the research included in this doctoral dissertation has shown that Ng, NPTXR, Ng / NPTXR ratio and FABP3 may be promising biomarkers reflecting processes related to synaptic dysfunction. Moreover, the combination of research results of potential new biomarkers with GO enrichment analysis seems particularly promising for the development of new research and therapeutic targets.