Influence of neurotoxic factors on aspartate *N* – acetyltransferase activity in cholinergic neurons

RESEARCH PROJECT OBJECTIVES: Alzheimer's Disease (AD) is the most common neurodegenerative disease, affecting as estimated 15 million people worldwide. Moreover, the disease is expected to affect 1 in 85 people in the world by 2050. This neurodegenerative disease affects their mental and physical health. However, the mechanism of this pathology remains not entirely elucidated According to the literature, with the development of AD is observed the increase of accumulation of amyloid-β, resulting in overproduction of nitric oxide (NO) and free radicals (ROS). Moreover, AD development is associated with *N*-acetylaspartate (NAA) depreciation and progressing impairment of septal cholinergic neurons. Metabolically, NAA is synthesized from acetyl-CoA and aspartate in the presence of hardly known enzyme aspartate *N*-acetyltransferase (Asp-NAT or NAT8L). In cholinergic neurons, acetyl-CoA is also used for energy and acetylcholine (cholinergic neurotransmitter) production. Consequently, this relatively high level of acetyl-CoA utilization could be a responsible for particular cholinergic susceptibility. According to one of the AD hypothesis, their particular sensitivity to cytotoxic agents may be resulted from acetyl-CoA consumption pathways observed in cholinergic neurons. In this research project, we assumed that particular cholinergic neurons susceptibility could be due to both extra acetyl-CoA consumption for acetylcholine synthesis and changes of aspartate *N*-acetyltransferase activity / level, which consequently could led to reduction of intracellular NAA level. Thereby, **the aim of this project** is to provide sufficient data about possible influence of the neurotoxic factors, involved in pathomechanisms of AD, on aspartate N-acetyltransferase activity.

METHODOLOGY: For our project, we plan to used human cellular model of cholinergic neurons with different cholinergic phenotype expression. This cells will be exposed chronically on neurotoxic factors (Aβ and NO in toxic concentrations). After experimental steps, cells will be used for selected assays. We will determinate the metabolic and enzymatic studies. Afterwards, Asp-NAT activity and protein level will be assayed. Proposed project should give us information about possible influence of used neurotoxin on NAA synthesis.

EFFECT: This project should reveal whether the accumulation of common AD neurotoxin may evoked NAA substrates shortages and Asp-NAT inhibition in neuronal cells with different expression of cholinergic phenotype.