Novel role of peroxisome proliferator-activated receptor α in the regulation of amyloid β peptide metabolism and mitochondrial function in an animal model of Alzheimer's disease

The project focuses on the role of peroxisome proliferator-activated receptor α (PPAR –α) in molecular and biochemical alterations that are associated with pathogenesis of Alzheimer's disease (AD). This disease is classified as the most severe form of dementia. The number of people with dementia rapidly increasing during last decades. According to World Alzheimer Report (2018), 50 million of people worldwide are living with dementia. The number will be tripled to 152 million in 2050. This disease affects patients and their families and are serious social and economic problem. One of the main characteristic features of AD are alteration of amyloid precursor protein (APP) metabolism which lead to Aβ accumulation and oligomerisation and in consequence to mitochondrial dysfunction. Mitochondria are the main source of ROS and their alterations may lead to activation of oxidative stress. Additional, in the past decade several studies shown that activation of oxidative stress is related to disturbances of PPAR-α signalling. A few data showed reduced expression of PPAR-α in Alzheimer's disease brain. However, till now there is no data available on the role of PPAR-α that are involved in APP/Aβ metabolism and mitochondrial function in animal model of AD.

The fundamental goal of present project is to provide new insights into the protective role of PPAR-α receptor agonists (fenofibrate and GW7647) on the levels of gene transcription and enzyme activity in APP/Aβ metabolism. Moreover, we will evaluate the effect of pharmacological modification of PPAR-α agonist signaling on mitochondrial dynamic and the function of electron transport chain (ETC) complexes in an animal model of AD.

In this project molecular/ biochemical analysis in animal model of AD (mice model of AD with the "London" APP mutation, Tg AD mice) will be applied to examine the effect of PPAR-α agonists in different brain regions in Tg AD mice (cortex, hippocampus). The molecular and biochemical analyzes of genes expression, proteins level and enzymes activity in APP/Aβ protein metabolism will be investigated. Then analysis of genes expression that encode proteins that are involved in mitochondrial function and dynamics and in signaling pathway leading to cell death will be determined. In addition, in this project the study of ATP level and free radicals, will be carried out. In our research following molecular/biochemical methods will be applied: real-time RT-PCR analysis, Western Blot (WB) analysis, enzymes activity by spectrophotometric/fluorometric methods. Activation of apoptotic processes by WB analysis.

Alzheimer's disease is nowadays the most important challenge for researchers and health system. Every year, the number of people with AD increased and AD become clinical, economic and social problem. Until now, no one has undertaken to document the relationship between PPAR-α agonists, APP/Aβ metabolism and mitochondrial function in AD models. This study seems to be an interesting and innovative approach.

The main objective of the presented research project does therefore not only focus on molecular mechanisms, which may be responsible for the pathomechanism of AD, but it also provides a solid basis for continuing research in the future and for developing novel therapeutic strategies in AD, whose main purpose may be pharmacological modulation of PPAR-α signaling.