Obesity is a significant public health problem affecting almost every country in the world with mortality reaching approximately 2.8 mln people each year. The latest epidemiological studies have shown the association between obesity, insulin resistance and type 2 diabetes development with the occurrence of cognitive disorders, dementia, depression, as well as an increased incidence of Alzheimer's disease. Although the brain has long been considered an insulin-insensitive organ, recent research has demonstrated that insulin has significant effects on the brain, where it plays a role in maintaining neuronal growth and energy homeostasis. Early triggers of brain insulin resistance remain incompletely understood but can be related to increased delivery of fatty acids trough the blood brain barrier in the course of obesity followed by mitochondrial dysfunction and activation of inflammatory process.

The brain has limited capacity of storing surplus energy substrates in the form of triacylglycerols, which are considered neutral and relatively safe lipid pool in the peripheral tissues such as skeletal muscles or adipose tissue. Instead, excessive fatty acid redirection to form lipid fractions such as ceramides and diacylglycerols reduces oxygen consumption and underlies cell inability to metabolize other energy sources, such as amino acids and glucose, ultimately resulting in the cerebral damage. Therefore, an explanation of the brain's insulin resistance mechanisms and the attempt to develop new therapeutic strategies have arisen as key issues. In the light of the abovementioned evidence, the main purpose of this project is to evaluate the possibility of overcoming cerebral insulin resistance through the administration of β-hydroxy-β-methylbutyrate (HMB), a leucine metabolite, known to stimulate mitochondrial respiration. Previously published literature data clearly indicate HMB potential to enhance the efficacy of antidiabetic drugs and mitigate metabolic abnormalities linked to peripheral insulin resistance. The mechanisms of cerebral HMB actions remain, however, largely unexplored. To fulfill this gap, we will be the first to examine HMB effects on the interplay between lipid, amino acid and carbohydrate metabolism. These assessments will be performed in the rat's brain structures that regulate energy balance (hypothalamus) and cognitive functions (cerebral cortex). Additionally, the introduction of cell culture model of neurons and astrocytes will enable to assess the discrete changes in both cell populations in response to HMB.

Importantly, the proposed study is not only original, but also has a high potential for application in the development of effective methods for prevention and/or treatment of obesity. If HMB proves to be an important regulator of cerebral fatty acid handling, it may allow to amend excessive fatty acid accumulation in the brain. Therefore, HMB may fulfill an urgent so far unmet clinical need for treatments that can directly target cerebral metabolic defects and their comorbidities.