12. Streszczenie w języku angielskim

Nowadays, metabolic pathologies, e.g., obesity or type 2 diabetes mellitus are one of the major medical concerns that widely occur among different populations. Consequently, obesity and its associated disorders constitute a serious threat to global health and might be considered as a worldwide epidemic. Insulin resistance, a condition with impaired insulin action and response in both peripheral tissues, e.g. liver or skeletal muscles, and central nervous system, e.g. brain cortex, is one of the major factors leading to the development of metabolic disorders. First defined as a main regulator of peripheral glucose concentration, insulin also was recognized as a key factor in synaptic transmission, memory and other cognitive processes.

Alzheimer's disease (AD) is a chronic neurodegenerative disease that is the most common type of dementia causing 60–70% of dementia cases. In 2020, the global number of patients who suffered from dementia was about 55 million. The development of systemic insulin resistance and attenuated brain insulin signaling are common features of AD, T2DM and obesity. A substantial correlation between brain IR, type 2 diabetes mellitus and dementia with cognitive impairment was widely demonstrated in numerous basic studies, including clinical trials.

Insulin resistance and T2DM are associated with higher tissue concentration of sphingolipids, a class of lipids that, in addition to having an important structural function in cellular membranes, are also known to be widely involved in intracellular signaling pathways. Moreover, certain research, both in vitro and in vivo, as well as clinical trials showed that disturbances in the sphingolipid pathway may contribute to the development of not only insulin resistance, but also neurodegenerative disorders via alterations in the phosphorylation of tau protein. It is believed that changes in metabolism of sphingolipids may provide a unique treatment strategy for both metabolic and neurological disorders.

Data from numerous studies indicated a substantial correlation between the endocannabinoid system (ECS), a key regulator of energy homeostasis, and the development of metabolic pathologies e.g. obesity, type 2 diabetes mellitus (T2DM). The endocannabinoid pathway includes elementarily G-protein-coupled receptors, known as cannabinoid receptor type 1 and 2 (CB1R and CB2R) and the endogenous agonists of these receptors, known as endocannabinoids, mainly anandamide (AEA) and 2-arachidonoylglycerol (2-AG). It is known that the CB1 receptor is predominantly found in the brain, whereas CB2 principally expressed on the cells of the immune system. Cannabidiol (CBD), a non-psychoactive

Cannabis plant-derived compound and a core of this project, was widely found to show neuroprotective properties.

In order to assess the outcomes of cannabidiol effect on sphingolipids metabolism, insulin resistance, and its aftermath, this project was carried out on male Wistar rats. An obesity and insulin resistance in this animal model was induced by feeding animals with a high fat diet (HFD) for a period of 7 weeks. The rats were divided and randomly assigned to four groups – (1) Control group fed with a standard chow for rodents, (2) HFD group fed with a high fat diet, (3) CBD group treated with cannabidiol with standard chow feeding (4) HFD+CBD group fed with high fat diet feeding. In this project different analytical techniques, including Western Blot, high performance liquid chromatography, and gas liquid chromatography, were used.

This study demonstrated that cannabidiol in an animal model of high-fat diet-induced obesity leads to significant changes in the content of the major sphingolipids such as ceramide, sphingosine, sphinganin and sphingomyelin in the brain cortex of insulin resistant Wistar rats. The main routes affected by this phytocannabinoid, under condition of high-fat diet, were ceramide *de novo* synthesis and the salvage pathway. Moreover, we indicated innovatively that CBD might be considered as an essential factor that leads to the reduction of brain insulin resistance, as well as tau protein phosphorylation, two essential factors predisposing to the occurrence of neuropathologies, e.g. Alzheimer's disease.

The proposed research introduced a comprehensive assessment of cannabidiol action on various aspects of brain metabolism. The novelty and originality of this project are compounded by the fact that preventing metabolic and neurodegenerative pathologies is a very alarming issue since the number of individuals suffering from those diseases increases annually among different populations. So far, extremely little amount of data demonstrated the effects of phytocannabinoids on brain both glucose and lipid metabolism. Thus, we believe that our research will concern a new possible therapeutic approach with a Cannabis-plant derived compounds and within a few years, those substances will be considered as prominent compounds for targeting both metabolic and neurodegenerative pathologies.