Streszczenie w języku angielskim

Obesity is a chronic, relapsing disease associated with substantial morbidity and mortality. Due to the globally high prevalence and its negative impact on health, obesity and the accompanying insulin resistance are serious public health problems, and their prevention and treatment have become a priority in health plans in developed and developing countries.

Insulin resistance is a state of impaired biological response of important metabolic organs (liver, skeletal muscles, adipose tissue) to the stimulation of insulin circulating in the blood, which results in disturbances in the metabolism of carbohydrates, lipids and proteins. It is known that adipose tissue is the "center" of the body's energy balance, and the sensitivity of adipocytes to insulin indirectly regulates the metabolic activity of the liver and muscles. Accumulation of the energy surplus in the form of lipids in fat deposits leads to adipocyte hypertrophy and their hyperlipolytic phenotype, which is resistant to insulin.

Biologically active lipids that interfere with the intracellular insulin pathway include sphingolipids, of which ceramide and sphingosine-1-phosphate are of particular interest. It has been repeatedly confirmed that the excessive accumulation of these molecules contributes to the development of insulin resistance of adipose tissue.

Numerous studies confirm that the endocannabinoid (eCBome), the complex, internal signaling system involved in the regulation of the body's energy balance, plays a key role in the pathogenesis of metabolic diseases, e.g. obesity and type 2 diabetes. The endocannabinoidome includes the endocannabinoid system (ECS) composed of G protein-coupled CB1R and CB2R cannabinoid receptors, their lipid ligands, N-arachidonoyl-ethanolamine (AEA) and 2-arachidonoyl glycerol (2-AG), and the enzymes involved in their metabolism. The highest concentration of CB1R occurs in the central nervous system, while CB2R expression is visible mainly on the immune cells, therefore it plays an important role in inflammatory processes. In addition to the ECS, the components of the endocannabinoidom include numerous mediators derived from fatty acids that act, among others, on G protein-coupled receptors such as GPR55, transient potential vanilloid receptors (TRPV) and peroxisome proliferator-activated receptors α and γ (PPARα and PPARγ). It has been repeatedly confirmed that high-fat diets lead to excessive activation of the endocannabinoidome by modulating the expression of receptors, the level of endocannabinoids and causing changes in the expression of anabolic and catabolic enzymes, which in turn leads to the development of the features of metabolic syndrome such as dyslipidemia or insulin resistance. Currently, it is known that cannabidiol (CBD), a phytocannabinoid lacks of abuse potential, exhibits antidiabetic activity and it modulates the

lipid metabolism by targeting endocannabinoidome receptors. However, there are still no reports on the effect of this phytocannabinoid on the insulin sensitivity of adipose tissue.

The aim of the study was to evaluate the effect of CBD on the sphingolipid metabolism and insulin signalling pathway in subcutaneous (SAT) and visceral (VAT) adipose tissue in an animal model of insulin resistance induced by a high-fat diet (HFD) for 7 weeks.

The study was conducted on Wistar rats, randomly selected for the four groups - (I) control group fed with standard rodent chow, (II) HFD group fed with a high-fat diet, (III) CBD group fed with standard rodent chow receiving intraperitoneal injections of cannabidiol, (IV) HFD+CBD group fed HFD diet receiving intraperitoneal injections of cannabidiol. The content of sphingolipid fractions was determined by high-performance liquid chromatography (HPLC). The expression of proteins that were directly engaged in sphingolipid metabolism and the insulin signalling pathway was detected by using a routine Western blotting procedure.

The performed experiment shows that cannabidiol injected into insulin resistant rats caused a significant decrease in the concentrations of sphinganine and ceramide in visceral and subcutaneous adipose tissue. In VAT by reducing its *de novo* synthesis and increasing its catabolism. However, in SAT, CBD decreased the ceramide level through the inhibition of salvage and *de novo* synthesis pathways. All of these changes restored adipose tissues' sensitivity to insulin.

Considering all the above observations, it can be assumed that cannabidiol has a potentially beneficial impact on the metabolism of subcutaneous and visceral adipose tissue in conditions of increased bioavailability of fatty acids in the diet. Thus, performing more detailed research on CBD seems reasonable, because it may turn out to be used as a potential therapeutic strategy for treating or reducing insulin resistance, T2DM, and metabolic syndrome.