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CANNABIDIOL AND SPHINGOLIPID SIGNALING PATHWAY – A ROBUST DUO IN THE NOVEL THERAPEUTIC APPROACH TOWARD HIGH FAT DIET INDUCED-INSULIN RESISTANCE IN THE LIVER OF WISTAR RATS

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Relevance. Unhealthy diet and sedentary lifestyle result in rapidly increasing worldwide prevalence of obesity and its related disorders e.g. hypertension, metabolic syndrome, and type 2 diabetes mellitus. Thus, studies involving a new preventive and therapeutic approach to these diseases are still in high demand. Cannabidiol (CBD) as a natural phytocannabinoid widely occurring in *Cannabis sativa* plant, constitutes the main component of medical marijuana. A body of evidence suggests that chronic administration of CBD influences either lipid and glucose metabolism in the liver and subsequently, alleviates insulin resistance (IR) development what may exert beneficial effects in the treatment of various metabolic disorders.

Target: our study was conducted in order to evaluate whether CBD affected sphingolipid pathway components and changed insulin signalling during high-fat diet induced-lipid overload state in the liver of Wistar rats.

Materials and methods. The experiments were carried on male Wistar rats, divided into the following groups: control group (standard diet), CBD-treated group (standard diet + CBD), HFD group (rats fed with high-fat diet), and HFD+CBD group (rats fed with high-fat diet + CBD). Cannabidiol was administrated intraperitoneally in a dose of 10 mg/kg of body mass for last 14 days from 7-week feeding period. At the end of experiment, liver samples were collected. The concentrations of sphingolipids were assessed with high-performance liquid chromatography whereas, the expression of pivotal enzymes involved in sphingolipid metabolism were evaluated using Western blot. The expression of phosphorylated proteins from insulin signalling pathway were assessed using BioRad Multiplex immunoassay.

Results and its discussion. In the liver of rats fed with HFD, we observed a notably increased concentration of ceramide (CER) and decreased concentration of sphingosine-1-phosphate (S1P). The excessive accumulation of CER was caused by enhanced ceramide de novo synthesis pathway what resulted in inhibited phosphorylation of proteins participating in the insulin signalling. In the liver of animals from HFD+CBD group, decreased accumulation of CER and increased concentration of S1P were detected. Furthermore, the simultaneous combination of HFD and CBD reduced the expression of enzymes participating in the ceramide de novo synthesis pathway as well as enhanced insulin signalling.

Findings. Our results revealed that administration of CBD not only decreased the concentration of prodiabetic CER, but also diminished ceramide de novo synthesis pathway. Moreover, CBD enhanced insulin signalling what resulted in the overall reduction of the high fat diet-induced IR development in the liver. This study highlights the potential role of CBD administration as an alternative and adjuvant treatment method for metabolic disorders among which IR may be distinguished.

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