9. Abstract

Introduction: Increased intake of lipids disturbs concentrations of glucose and insulin which affects central nervous system. Sphingolipids i. e. ceramide and sphingomyelin are directly involved in regulation of brain homeostasis through an impact on physico-chemical properties of plasma membrane and signal transduction. Metformin is a biguanide with a proven hypoglycemic properties used for treatment of type two diabetes. Its influence on sphingolipid concentration in central nervous system has not been tested in short term several week high fat diet models. Usage of metformin is reasoned due to its beneficial action towards cognitive defects in high fat diet models as well as, its effect on activating AMPK enzyme, which normalize cell metabolic balance and regulate level of sphingolipids.

Aims: The main objective of the study was to observe if high fat diet lasting for 3 or 6 weeks induces changes in ceramides and sphingomyelin levels in hippocampus and prefrontal cortex of rats, as well as if metformin used during high fat diet affect these parameters, and to determine morphological alterations of astrocytes in tested brain structures

Materials and methods: Male Wistar rats were used for the study. Rodents were divided to create following experimental groups: 1) control, 2) administrated with metformin, 3) fed with high fat diet for three weeks, 4) fed with high fat diet for six weeks, 5) fed with high fat diet for six weeks and administrated with metformin for 3 weeks. Material used for the study was collected from each group after six weeks from the start of experiment. Rat plasma was used for analysis of glucose, insulin concentrations and for measurement of lipid profile. Hippocampus and prefrontal cortex were isolated from brain tissue and used for measurement of concentration of fatty acids forming saturated (SAFA) and mono unsaturated (MUFA) Cers and SMs, using a gas liquid chromatograph. Morphological analysis was conducted in mentioned brain structures using optical microscope.

Results: High fat diet administered to rats induced rise of rat weight, incrased level of glucose and insulin proportionally to its duration. Moreover, we observed alterations of lipid profile under high fat diet towards reduction of HDL concentration, and elevation of levels of LDL and triglicerydes. Metformin administrated to healthy animals did not induce significant alterations of any tested parameters. Drug administered to animals fed with high fat diet for six weeks resulted in decrease of weight gain, glucose insulin and triglyceride concentrations. Fatty acid C18:0 (a backbone of tested SFs) dominated among SAFA-Cer and SAFA-SM in

hippocampus and prefrontal cortex of healthy rats. C18:1 was the most abundant fatty acid among Cers in hippocampus and C24:1 among Cers in prefrontal cortex. Metformin administered to the control group effected only in significant rise of MUFA-SM concentration in prefrontal cortex of rats. High fat diet increased concentration of SAFA and MUFA Cer and SM proportionally to the duration of diet, to the greater extent in prefrontal cortex than hippocampus. Six week high fat diet proportionally to its duration induced rise of SAFA and MUFA Cers and SM in greater extent in prefrontal cortex then in hippocampus. Six week high fat diet induced elevation of Cer-C18:0; SM-C16:0 and SM-C18:1 concentrations in hippocampus of rats, while in prefrontal cortex all particular species of SAFA and MUFA Cers and SM. Metformin administered to rats fed with high fat diet for six weeks induced moderate decrease of concentrations of all particular SAFA and MUFA Cer in hippocampus, while greater alterations were observed in terms of SM in this structure. Metformin induced decrease of SAFA-Cer i MUFA-Cer concentrations and rise of concentration of total MUFA-SM as well as particular C16:1 i C24:1 MUFA and C20:0 i C24:0 SAFA-SM. It was demonstrated that metformin had stronger influence on prefrontal cortex, in case of reduction of all particular SAFA and MUFA Cer and SM. Morphological analysis of prefrontal cortex and hippocampus considering number and morphology of astrocytes did not reveal significant differences among tested groups.

From the results tobtained he following conclusions were drawn:

1. Ceramide and sphingomyelin profiles in hippocampus and prefrontal cortex differ between control rats and rats fed with high fat diet.

2. Changes of tested sphingolipids depend on duration of high fat diet.

3. Hippocampus and prefrontal cortex of rats fed with high fat diet exhibit different profiles of ceramides and sphingomyelin.

4. Metformin exerts beneficial influence on selected brain structures by changing the concentrations of ceramide and sphingomyelin.

5. High fat diet did not induce significant morphological changes of hippocampus and prefrontal cortex in matters of astrocytes morphology.