Streszczenie w języku angielskim

Many studies have indicated the relationship between peripheral insulin resistance and cognitive disorders, dementia, depression and/or increased incidence of Alzheimer's disease. It is postulated that the mechanisms linking metabolic disorders and neurodegeneration may be redox imbalance as well as oxidative stress. The term "oxidative stress" is defined as a state in which oxidative damage to cellular components occurs through increased production of free radicals and/or alterations in antioxidant defense mechanisms. However, the role of oxidative stress in the pathogenesis of brain complications of insulin resistance is still unclear.

The aim of the study was to evaluate the enzymatic and non-enzymatic antioxidants as well as oxidative damage to proteins, lipids and DNA in selected brain structures (hypothalamus and cerebral cortex) of rats with insulin resistance induced by a high-fat diet compared to the control group.

The experiment was performed on male Wistar rats with an initial body weight of 65-75 g. Rats were randomly divided into 2 groups of 8 individuals each:

- **group I** – rats fed a high-fat diet (HFD) containing 60 kcal% fat, 20 kcal% carbohydrates and 20 kcal% of proteins for 8 weeks.
- **group II** – rats fed a standard diet (control) containing 10.3 kcal% of fats, 65.5 kcal% carbohydrates and 24.2 kcal% of proteins for 8 weeks.

After 8 weeks, blood from the abdominal aorta as well as hypothalamus and brain cortex were collected. In order to assess insulin resistance, glucose was determined in the rat tail blood, whereas in the plasma - insulin concentration (by ELISA method) and free fatty acids (by gas chromatography). HOMA-IR index (homeostasis model assessment of insulin resistance) was also calculated.

In homogenates of the hypothalamus and cerebral cortex as well as serum/blood plasma were determined:

- the activity of **pro-oxidant enzymes**: oxidase NADPH (NOX) and xanthine oxidase (XO) using colorimetric/fluorimetric methods,
- the activity of **antioxidative enzymes**: glutathione peroxidase (GPx), glutathione reductase (GR), catalase (CAT) and superoxide dismutase-1 (SOD-1) using colorimetric methods,
- the concentration of **non-enzymatic antioxidants** (uric acid (UA)) and **redox status** (total antioxidant capacity (TAC), total oxidative status (TOS)) using colorimetric methods. The oxidative stress index (OSI) was also calculated,
- the concentration of **oxidative modification products of proteins** (advanced glycation end products (AGE)), **lipids** (4-hydroxynonneal (4-HNE), malondialdehyde (MDA)) and **DNA** (8-hydroxy-2'-deoxyguanosine) using colorimetric methods and ELISA.

All determinations were measured in duplicate/triplicate samples and standardized to 1 mg of total protein. The statistical analysis was performed using

the Student's t-test and Pearson's correlation coefficient, assuming the $p<0.05$ value as statistically significant.

The increase in plasma free fatty acids of HFD-fed rats led to peripheral insulin resistance, which was confirmed by a significantly higher concentration of glucose and insulin, as well as a significantly higher HOMA-IR index in comparison to the control group.

The activity of NOX and XO was significantly higher in both the cerebral cortex and the hypothalamus of HFD-induced insulin-resistant rats compared to the control group. The activity of brain antioxidative enzymes (GPx, CAT and SOD-1) was significantly higher in the cerebral cortex of insulin resistant rats, while GPx and GR activity was significantly lower in the hypothalamus of these animals compared to controls. The UA concentration was significantly higher in both the cerebral cortex and hypothalamus of HFD-fed animals. Insulin resistance induced by a high-fat diet also disturbed the redox status in both cerebral structures observed as the increase in TAC, TOS, FRAP and OSI in the cerebral cortex, as well as the increase in TAC, TOS and FRAP in the hypothalamus of these animals. The concentration of all assessed oxidative damage markers (i.e. AGE, 4-HNE, MDA and 8-OHdG) was significantly higher in the cerebral cortex of rats with insulin resistance, whereas in the hypothalamus of HFD rats only the concentration of 4-HNE and MDA was increased.

Based on the research, the following **conclusions** were drawn:

1. A high-fat diet induces systemic insulin resistance and results in redox imbalance and oxidative stress both at the plasma/serum level as well as at the brain.
2. Higher activity of pro-oxidant enzymes may be responsible for increased oxidative damage in the brain of HFD-induced insulin resistant rats.
3. HFD-induced insulin resistance causes oxidative stress in both brain structures; however, the cerebral cortex is more sensitive to oxidative damage compared to the hypothalamus.
4. Systemic insulin resistance affects the cerebral redox homeostasis, although it is not the only determinant of oxidative damage to the hypothalamus and cerebral cortex.