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CARBACETAM EFFECT ON OXIDATIVE STRESS MARKERS IN DIFFERENT GENDER RATS WITH METABOLIC SYNDROME

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Introduction. Many factors are known to influence metabolic syndrome pathology. Meanwhile, certain scientific evidence indicates that oxidative stress with chronic inflammatory conditions is the base promoting the development of metabolic diseases.

Objective of the research is to study carbacetam effect, as a GABA-receptor modulator, on pathogenic mechanisms of metabolic syndrome according to the oxidative stress markers of the hippocampus of different gender rats.

Materials and methods. The experiments were conducted on non-linear laboratory albino male and female rats. To reproduce the metabolic syndrome model, the rats were kept on a high-fat diet enriched with the addition of solid pork lard and free access to fructose solution. Carbacetam was injected into the peritoneum in the dose of 5 mg/kg during 14 days. The state of oxidative stress was estimated by the parameters of the pro-oxidant-antioxidant system.

Results. When carbacetam was administered, the activity of antioxidant protection enzymes was found to increase, and the content of products of lipid and protein peroxidation processes in the hippocampal neurons of rats of both genders with metabolic syndrome decreased.

Conclusions. Carbacetam as a modulator of GABA-receptors in rats with metabolic syndrome decreases the content of products reacting with 2-thiobarbituric acid and the products of protein oxidation modification confirmed by histochemical method; increases the activity of antioxidant protection enzymes in rats of both genders with metabolic syndrome.

Keywords: metabolic syndrome, carbacetam, lipid and protein peroxide oxidation.

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ВПЛИВ КАРБАЦЕТАМУ НА МАРКЕРИ ОКСИДАТИВНОГО СТРЕСУ У ЩУРІВ РІЗНОЇ СТАТІ З МЕТАБОЛІЧНИМ СИНДРОМОМ

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Відомо, що окислювальний стрес у поєднанні з хронічними запальними станами є основою розвитку метаболічних захворювань. Метою дослідження було вивчення впливу карбацетаму як модулятора ГАМК-рецепторів на патогенетичні механізми метаболічного синдрому за даними маркерів оксидативного стресу гіпокампа щурів різної статі. Експерименти проводили на нелінійних лабораторних білих щурах самцях і самицях, яким моделювали метаболічний синдром, утримуючи щурів на високожировій дієті, збагаченій жирами з вільним доступом до розчину фруктози. Карбацетам вводили внутрішньоочеревинно дозою 5 мг/кг (14 днів).

Висновки. Модулятор ГАМК-рецепторів карбацетам зменшує вміст продуктів, що реагують із 2-тіобарбітуровою кислотою, і продуктів окиснювальної модифікації білків, які підтверджено гістохімічним методом; підвищує активність ферментів антиоксидантного захисту в щурів різної статті із метаболічним синдромом.

Ключові слова: метаболічний синдром, карбацетам, перекисне окиснення ліпідів та білків.

Introduction. Metabolic syndrome is characterized by a number of several disorders that increase the risk of chronic cardiovascular diseases of metabolic origin including myocardial infarction, cerebral circulation disorders, diseases of the peripheral vessels, insulin resistance and type 2 diabetes mellitus.

According to the latest scientific data, occurrence of the syndrome is closely associated with an increasing rate of obesity and type 2 diabetes mellitus. Metabolic syndrome, in particular, afflicts about 25% of the world population. The rates are much higher in urban regions due to consumption of high-calorie diet with a low content of nutrients as well as decreased physical activity [1].

Many factors are known to influence metabolic syndrome pathology. Meanwhile, certain scientific evidence indicates that oxidative stress with chronic inflammatory conditions is the base promoting development of metabolic diseases [2, 3]. Imbalance between oxidants and antioxidants, often in favor of oxidants, is a cause of oxidative stress. In its turn, it causes disorders of redox signal transmission and regulation, as well as molecular and cellular damage [4, 5]. Therefore, imbalance between pro-oxidant and antioxidant mechanisms is considered one of the most important pathophysiological mechanisms of chronic diseases. Available scientific evidences confirm the hypothesis that oxidative stress may be considered an early diagnostic sign in the metabolic syndrome mechanisms, but not its consequence [6, 7]. Protein peroxide oxidation products, in particular, are known to be an appropriate index to determine oxidative stress in patients with the above disorders [7].

The current scientific data present understanding of neurochemical and neuromorphological bases of the cerebral activity concerning relations between different systems of neurotransmitters. It opens wide possibilities for more specific and targeted treatment followed by less amount of side effects. In particular, it is known about the wide distribution of GABAergic receptors in the brain and their physiological significance. It is GABAergic synapses that affect the rate of glucose utilization, and in critical cases this amino acid acts as an alternative substrate in the tricarboxylic acid cycle [8]. And since carbacetam, as a modulator of GABA receptors, which in our previous studies has shown itself as a means of relieving anxiety and improving memory processing, we were interested in finding out its role in the processes of lipid and protein peroxidation in metabolic syndrome in rats of different breeds [9].

Objective of the research is to study the carbacetam effect, as a GABA-receptor modulator, on pathogenic mechanisms of metabolic syndrome according to the oxidative stress markers of the hippocampus of different gender rats.

Materials and methods. The research was conducted on non-linear laboratory albino male and female rats weighing 0.18–0.25 kg (6 groups of 7 males and 7 females per group), kept under standard vivarium conditions with a natural change of day and night. The group consisted of rats of the same sex, so pregnancy in females was excluded. The experiments were carried out keeping to the main principles of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (18.03.1986); the EU Directives No. 609 of 24.11.1986 and the Orders of the Ministry of Health of Ukraine No. 690 of 23.09.2009, No. 944 of 14.12.2009, No. 616 of 03.08.2012. In addition, they were confirmed by the Board on Biomedical Ethics Bukovinian State Medical University (Protocol No. 5 of 15.02.24).

To reproduce the metabolic syndrome model, the rats were kept during 60 days on a high-fat diet enriched with the addition of solid pork lard and free access to fructose solution (100 g/L) [9]. The development of the syndrome was confirmed by the fasting blood glucose concentration in the blood serum higher than 7.0 mmol/L and positive glucose tolerance test. The control group of rats was on the standard diet and free access to water. After the syndrome was confirmed, all the rats were divided into two groups by the random sampling method. The group with metabolic syndrome model including animals with metabolic syndrome injected with carbacetam into the peritoneum in the dose of 5 mg/kg during 14 days. The studied compound is a derivative of β-carbolines, is characterized by a rapid onset of action, an optimal range of therapeutic doses, and belongs to the class of low-toxic compounds. Experimental data from leading domestic scientists indicate the pronounced nootropic and antihypoxant properties of carbaracetam [10, 11]. The groups of comparison included the control one and rats with the simulated pathology (7 rats in each group) injected 0.9% NaCl solution into the peritoneum.

Euthanasia of rats was performed under chloroform. The brain was immediately removed, placed on ice, and thoroughly washed with chilled 0.9% NaCl solution. The topographic boundaries of the hippocampus were determined using a stereotaxic atlas [12]. The cytoplasmic fraction was isolated by means of differential centrifugation of the hippocampus homogenates on the refrigerator centrifuge: 700 g during 10 min followed by 1400 g during 10 min (4 °C).

Lipid peroxide oxidation intensity was assessed by the content of products reacting with 2-thiobarbituric acid active products (TBA AP) [13]. TBA AP amount was calculated in μmol per 1 gram of tissue. The content of protein oxidation modification (POM) in homogenates was determined by spectrophotometric method with the wavelength of 370 and 430 nm [14]. The scientific literature evidences that protein oxidation results in aldehyde or keto derivatives of a neutral or basic character possessing different absorption spectrum ranges [15]. Neutral keto dinitrophenylhydrazines are determined with the wavelength of 370 nm. Basic aldehyde dinitrophenylhydrazines are registered with the wavelength of 430 nm respectively. POM was presented in units per gram of tissue. The state of the antioxidant defense system was estimated according to the enzymatic activity SOD [EC 1.15.1.1] and catalase [EC 1.11.1.6] [16].

Brain samples for histological examination were fixed in 10% neutral formalin solution, and after standard histological processing, the tissue was embedded into paraffin. Paraffin histological sections of cerebral cortex tissues 5 μm thick were made with a sledge microtome MC-2. Quantitative assessment of the state of proteins in histochemical

samples stained with bromophenol blue according to Mikel Calvo, was carried out by computer microspectrophotometry based on R/B ratio [17].

To process the results of the research, the arithmetic mean and its error were calculated. Differences in average tendencies were checked by means of Student's unpaired test after positive testing of the sample for normal distribution in it, by the Shapiro-Wilk test [18].

Results and discussion. The research we have conducted found that TBA AP content increased in the hippocampus of rats with metabolic syndrome of both genders (Table 1). Thus, in comparison with the control group, TBA AP content 85.4% ($p < 0.05$) and 82.3% ($p < 0.05$) increased in males and females respectively.

Analyzing the scientific data of other scientists, we can admit that the obtained results correspond to their conclusions. TBA AP content increase, in particular, is associated with the increase of highly reactive forms of oxygen to polyunsaturated fatty acids. These are the components of phospholipids of all the cellular membranes. Therefore, this index can be used as a marker of neuron membrane damage [19].

At the same time, protein peroxide oxidation processes increased in rats with metabolic syndrome with different wavelengths. Thus, POM 370 content was 81.4% ($p < 0.05$) higher than in males of the control group and 26.5% ($p < 0.05$) higher in females. POM 430 content was 35.8% ($p < 0.05$) higher in males and 53.5% ($p < 0.05$) – in females. These parameters inform about intensification of oxidation destruction of proteins, as important components of neuronal membranes, which disrupts their functional activity [20].

Considering the increase in the activity of peroxidation processes, we were interested in the state of antioxidant protective enzymes. Based on the information that SOD and catalase are among the launching enzymes of the antioxidant defense system of the body, their activity in male and female rats was studied first. They play an important role in the intracellular protection against oxygen active forms, maintain stable concentration of superoxide radicals on an appropriate level under condition of normal metabolism, and protect cellular structures against a harmful action of oxygen and hydroxyl radicals [20].

In rats with metabolic syndrome in comparison with the control group, SOD activity in males became 28.1% ($p < 0.05$) lower, and 18.7% ($p < 0.05$) lower in females. Catalase activity decreased on an average by 31.9% ($p < 0.05$) in both groups of rats. Thus, the activity of antioxidant protection enzymes decreases in rats with metabolic syndrome, and changes are more marked in males.

After carbacetam administration TBA AP content decreased by 28.2% ($p < 0.05$) and 12.1% ($p < 0.05$) in males and females respectively. POM content decreased in males and females as well. Thus, the content of neutral keto dinitrophenylhydrazines on an average 16.9% ($p < 0.05$) decreased, and basic aldehyde dinitrophenylhydrazines – 15.4% ($p < 0.05$) decreased.

At the same time, the activity of antioxidant protection enzymes increased. Thus, SOD activity in males 44.4% ($p < 0.05$) increased, and in females – 19.7% ($p < 0.05$).

Table 1

Carbacetam effect on free radical lipid and protein oxidation in different gender rats with metabolic syndrome (M ± m, n = 7)

Indices	Males		
	Control	Metabolic syndrome	Metabolic syndrome + carbacetam
TBA AP mcmol/g of tissue	41.097 ± 1.508	76.187 ± 2.791*	54.686 ± 1.995*,**
POM, λ = 370, units/g of tissue	20.571 ± 1.703	37.314 ± 1.081*	28.657 ± 0.824*,**
POM, λ = 430, units/g of tissue	19.429 ± 0.541	26.386 ± 0.929*	22.971 ± 0.415*,**
SOD units/mg of protein	0.327 ± 0.015	0.232 ± 0.006*	0.335 ± 0.005**
Catalase mcmol H_2O_2/min mg of protein	175.236 ± 3.847	118.611 ± 5.292*	158.717 ± 4.269*,**
Females			
TBA AP mcmol/g of tissue	43.735 ± 2.002	79.740 ± 1.397*	70.107 ± 2.215*,**
POM, λ = 370, units/g of tissue	31.457 ± 1.362	39.8 ± 1.028*	35.529 ± 0.544*,**
POM, λ = 430, units/g of tissue	30.371 ± 0.585	46.614 ± 0.727*	38.357 ± 0.772*,**
SOD units/mg of protein	0.225 ± 0.012	0.183 ± 0.010*	0.219 ± 0.003**
Catalase mcmol H2O2/min mg of protein	145.193 ± 5.678	99.403 ± 7.288*	121.219 ± 4.257*,**

Notes: * – reliability of differences compared with the control group of rats;

** – reliability of differences compared with the group of rats with metabolic syndrome.

Catalase activity 33.8% ($p < 0.05$) increased in males and – 21.9% ($p < 0.05$) in females.

After we received and processed the data, we were interested in studying the quantitative assessment of proteins in the hippocampus in the histochemical samples stained with bromophenol blue according to Mikel Calvo. The R/B ratio was the indicator of correlation between amino- and carboxyl groups in the proteins of certain localization, that is, it was a dimension for protein oxidation modification. Then arithmetic mean and its error were calculated for the R/B ratio.

The following data were obtained on the base of our research (Fig. 1A; 1B). In the control group of male rats the R/B ratio in the neurons was 1.11 ± 0.009, in females – 1.08 ± 0.006.

At the same time, in male rats with simulated metabolic syndrome this indicator 45.9% ($p < 0.05$) increased, and in females it 70.4% ($p < 0.05$) increased as compared to the control group (Fig. 2A; 2B).

Analysis of the obtained data showed that carbacetam administration during 14 days promoted decrease of the indicator in comparison with the data obtained from rats with modeled pathology (Fig. 3A; 3B).

Thus, the R/B ratio in the neurons of the hippocampus of rats of both genders decreased on an average by 77.5% ($p < 0.05$). Therefore, the data of histochemical examination of proteins in the hippocampus of rats confirm biochemical changes in the neurons obtained in our studies. That is, after metabolic syndrome modeling the amino groups of proteins in the neurons of the hippocampus of rats of both genders are damaged, especially in females.

A possible pathogenic mechanism of these changes is that GABA as the main inhibiting neurotransmitter in the central nervous system decreases glutamate excretion due to induced depolarization and ischemia [21]. It is not unthinkable that effect on GABA-receptors can promote neuron hyperpolarization through the anion channels (GABA A-receptors) and pre-synaptic receptors bound with G-protein (GABA B-receptors) [22]. This hyperpolarization counteracts depolarization, which is an inductor in biochemical ischemic cascade. It should

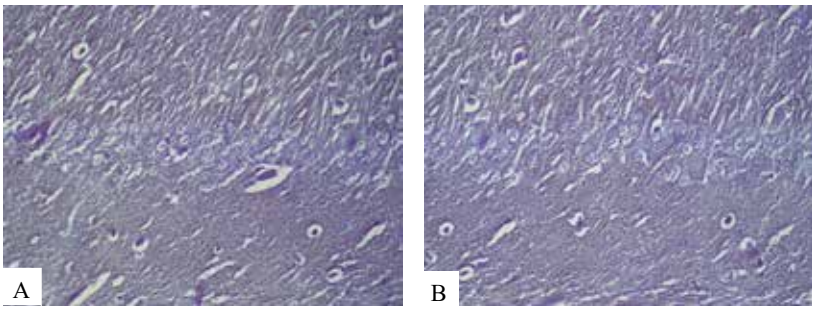

Fig. 1. Hippocampus of rats from the control group: A – male, B – female. Bromophenol blue staining of histological sections by Mikel Calvo. Obj. 40x Oc. 10x

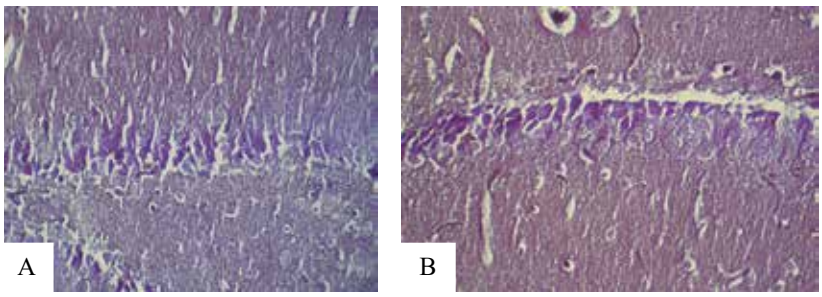

Fig. 2. Hippocampus of rats with metabolic syndrome: A – male, B – female. Bromophenol blue staining of histological sections by Mikel Calvo. Obj. 40x Oc. 10x

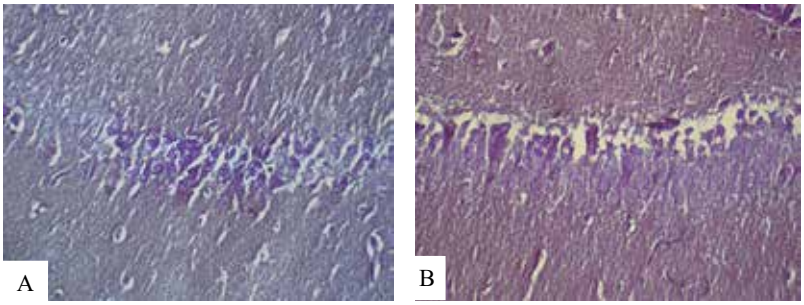

Fig. 3. Hippocampus of rats with metabolic syndrome after carbacetam administration: A – male, B – female. Bromophenol blue staining of histological sections by Mikel Calvo. Obj. 40x Oc. 10x

be kept in mind that due to activation of GABA-receptors respiratory rate decreases, optimal glucose level is maintained, acidosis decreases, and local blood circulation improves [23].

Therefore, based on the obtained results we can suggest that modulation of GABA-receptors promotes the increase of the activity of antioxidant protection enzymes and decreases the processes of lipid and protein peroxide oxidation in the hippocampal neurons of rats with metabolic syndrome. At the same time, with more pronounced changes in females than in males. Such results may be associated primarily with different hormonal backgrounds in males and females. That is, it can be assumed that females are more sensitive to metabolic disorders. At the same time, we observe positive dynamics when modulating GABA receptors with carbacetam. However, further studies are needed, such as studying the functional state of mitochondria of hippocampal neurons, in order to substantiate approaches to the prevention and treatment of negative consequences of metabolic disorders and the development of complex pathogenetic therapy of this pathology.

Conclusions

1. Under conditions of simulated metabolic syndrome in the hippocampus of male and female rats, the content of lipid and protein peroxide oxidation products increases; the activity of catalase and superoxide dismutase decreases which indicates a weakening of the antioxidant system with more pronounced changes in females.

2. Carbacetam administration during 14 days as a modulator of GABA-receptors in rats with metabolic syndrome decreases the content of products reacting with 2- thiobarbituric acid and the products of protein oxidation modification, confirmed by histochemical method; increases the activity of antioxidant protection enzymes.

3. The results obtained are indicative of a correcting effect of carbacetam through modulation of GABA-receptors of the hippocampal neurons on the markers of oxidative stress in rats of different genders with metabolic syndrome, with better results in males.

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