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THE ROLE OF DYSMETABOLIC MECHANISMS IN THE DEVELOPMENT OF NEURODEGENERATIVE PROCESSES IN AN EXPERIMENTAL METABOLIC-COGNITIVE SYNDROME MODEL

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ИЗУЧЕНИЕ РОЛИ ДИСМЕТАБОЛИЧЕСКИХ МЕХАНИЗМОВ В РАЗВИТИИ НЕЙРОДЕГЕНЕРАТИВНЫХ ПРОЦЕССОВ ПРИ ЭКСПЕРИМЕНТАЛЬНОМ МОДЕЛИРОВАНИИ МЕТАБОЛИКО-КОГНИТИВНОГО СИНДРОМА

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This article describes the role of dysmetabolic mechanisms in the development of neurodegenerative processes in an experimental animal model of metabolic-cognitive syndrome. Cognitive decline and neurodegenerative changes in experimental animals were revealed in the form of decreased cortical thickness in the temporal and parietal lobes of the brain. Administration of polyphenol preparations prevented morphological and functional changes in animals. Neuroprotection in individuals with metabolic syndrome can be individualized using drugs with different polyphenol compositions.

Keywords: neurodegeneration, metabolic syndrome, cognitive impairment, polyphenols

Описаны результаты изучения роли дисметаболических механизмов в развитии нейродегенеративных процессов при экспериментальном метаболико-когнитивном синдроме. Выявлены когнитивное снижение и нейродегенеративные изменения у экспериментальных животных в виде уменьшения толщины коры в височно-теменных долях головного мозга. При коррекции полифенольными препаратами наблюдалось нивелирование морфофункциональных из-

менений в эксперименте. Нейропротекция при метаболическом сидроме может быть индивидуализирована за счет ипользования препаратов с различным составом полифенолов.

Ключевые слова: нейродегенерация, метаболический синдром, когнитивные нарушения, полифенолы

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AD – Alzheimer's disease
FFM – fructose feeding model
MS – metabolic syndrome

According to the results of recent studies, the occurrence of many neurological diseases can be associated with metabolic syndrome (MS) and insulin resistance [1, 2]. Different degrees of obesity at the age of 40–45 years are associated with a two- to three-fold increase in the risk of developing Alzheimer's disease (AD). The risk of developing AD among women is 6.57 times higher in the presence of MS; moreover, 80 % of patients with AD have either type 2 diabetes or impaired glucose tolerance [2, 3].

Investigations of correlative relationships between cognitive functions and insulin resistance and morphological assessments of various areas of the cerebral cortex have contributed to the understanding of the functional state of the brain in neurological and endocrine diseases. In particular, a decrease in the prefrontal cortex volume was found in individuals with neurological and endocrine diseases compared with the control group [4].

Experimental studies indicated that memory and learning in rats deteriorated during tasks requiring activation of the prefrontal cortex after 8 weeks on a high-fat diet. Morphologically, cognitive deficits associated with obesity were accompanied by a decrease in the apical dendritic process density of pyramidal cells in the prefrontal cortex, a decrease in the number of dendritic spines, and significantly lower levels of presynaptic and postsynaptic proteins such as spinophilin, synaptophysin, vesicular gamma-aminobutyric acid, and vesicular glutamate. These changes were correlated with morphological changes in the microglia located in layers I and II/III of the prefrontal cortex [5, 6].

Researchers are interested in determining the role of the hippocampus and its functional and organic disorders in the development of MS. Because the hippocampus, especially the dorsal part, contains insulin receptors, it becomes a target in the development of MS, which manifests itself in the form of cognitive deficits, memory disorders, and spatial orientation deficits [7, 8].

Taking into account the role of metabolic disorders in the pathogenesis of neurodegenerative disorders, the development and implementation of new preventive and therapeutic-restorative technologies for early endocrinopathies and, accordingly, the initial forms of higher neuronal function disorders has become particularly relevant. Medicinal products of plant origin with a high polyphenol content (flavonoids, lignans, and stilbenes) are of interest in the prevention and treatment of these pathological conditions [9, 10].

The aim of the study was to examine the dysmetabolic and inflammatory mechanisms of metabolic-cognitive syndrome development in an experimental model and to examine the effectiveness of treatment with polyphenolic drugs.

Material and Methods. The experimental study was performed on 32 Wistar white rats (6–12 months old, body weight 400–440 g) housed under specific pathogen-free conditions.

The fructose feeding model (FFM), with 60 % fructose content based on standard solid feed (Research Diet, USA), was used to generate the MS model [11]. The duration of feeding was 16 weeks. The International Diabetes Federation, 2005 criteria were used to confirm the development of MS.

Rats were divided into the following groups consisting of eight animals each:

Group 1 – MS+Natural Resveratrol (Now Foods, USA), administered from the 5th week of FFM induction;

Group 2 – MS+Fenokor (Ressfud, Russia), administered from the 5th week of FFM induction;

Group 3 – MS, 16 weeks of FFM induction without drug treatment;

Group 4 – Control, intact animals.

Natural Resveratrol was used in the recommended dose (2 mg/kg, Food and Drug Administration). For Fenokor, 2.5 ml/kg, equivalent to 87.5 mg of polyphenolic compounds (delphinidin, malvidin, cyanidin, petunidin, peonidin, and quercetin), together with 0.5 ml of water was used. The drugs were administered once per day as a ready-made solution using a gastric tube. The MS group without drug administration received the corresponding amount of distilled water in the same manner.

Euthanasia was performed at the end of the experiment by inhalation of 96 % diethyl ether to study the structure of the brain and visceral system organs.

The following research methods were used: somatometric–weighing of visceral fat (VLTE-500 laboratory electronic scales, Akvilon, Russian Federation); biochemical–routine methods for determining blood glucose, total cholesterol, triglyceride, and high-density lipoprotein levels using commercially available kits (automatic biochemical analyzer ERBA XL-180; Erba Lachema, Czech Republic); cognitive tests–assessment of the distance (cm) and speed (cm/sec) of finding the true mink in the Barnes test (Labyrinth of Barnes, NPK Open Science, Russian Federation). The preliminary selection of animals was carried out using an open field test (Open Field for Rats Installation, Open Science Research and Development Center, Russian Federation). General methods to examine morphology were also used; brain sections of experimental rats were examined with hematoxylin and eosin and toluidine blue staining using light microscopy, followed by morphometric measurements of the thickness and density of layers 2–3 and 4–5 of the temporal and parietal cortex.

Morphometric calculations were performed using the Aperio ImageScope program (Leica Biosystems Division of Leica Microsystems Inc., Buffalo Grove, IL, USA), followed by statistical processing using the Statistica 10.0 program (StatSoft, USA) using parametric (Student's T-test) and nonparametric (Wilcoxon's W test) tests.

All measurements were made using measuring equipment that had undergone metrological verification and auxiliary equipment that had undergone certification.

Results and Discussion. This study revealed that experimental modeling of MS using the FFM results in the development of characteristic MS features, namely visceral obesity, hyperglycemia, and hypertriglyceridemia. The visceral fat weight of rats in the MS model group was 11.21 g, which was two times higher than the control group value ($p<0.001$). Additionally, MS development was accompanied by rapid development of hyperglycemia; by the end of the 4th week of feeding, a significant increase in the glucose level to 8.32 mmol/l ($p<0.01$) was observed compared with the control group.

Administration of polyphenol-containing compounds to animals in the MS group led to decreases in the visceral fat mass of 47.3 % ($p<0.001$) and 60.7 % ($p<0.001$) (Fig. 1), and a pronounced hypoglycemic effect was observed after 4 weeks of Natural Resveratrol administration ($p<0.01$). Because resveratrol is partially metabolized by the gut microbiota, the hypoglycemic potential of this compound may be attributable to changes in the bacterial composition associated with favorable metabolic outcomes [12].

The authors state that there is no potential conflict of interest that requires disclosure in this article.

The main criterion used to assess cognitive abilities in rats was the distance and the speed of achieving the goal in the Barnes test. Reliable data on distance and speed reduction were recorded in animals with MS without pharmacological intervention ($p<0.05$). The use of Fenokor and Natural Resveratrol resulted in 2.02-fold and 2.91-fold decreases in the distance and 2.27-fold and 3.25-fold increases in the speed of finding the target in the Barnes test, respectively, in relation to the control group ($p<0.01$).

Morphometric studies of brain sections showed a significant difference in the thickness and density of the cortex in the temporal and parietal lobes in the MS group of rats without drug treatment (737.94 μm) compared with the control animals (923.86 μm) ($p<0.00001$). MS development was accompanied by a decrease in the density of neurons in layers 2–3 and 4–5 of the temporal-parietal cortex, indicating the development of neurodegenerative changes in the framework of the brain in metabolic-cognitive syndrome (Fig. 2).

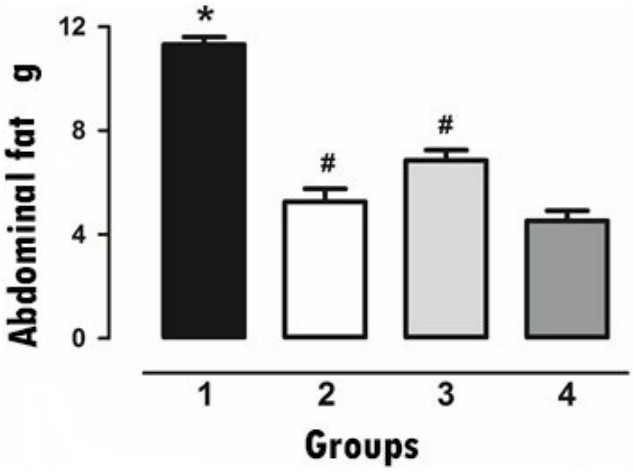

Fig. 1. Changes in the weight of abdominal fat in metabolic syndrome (MS) rat models administered polyphenols: 1 – MS group without drug administration; 2 – Fenokor group; 3 – Natural Resveratrol group; 4 – control group. *$p<0.05$ compared with the control group, #$p<0.05$ compared with the MS group without drug administration

Rats administered Fenokor showed a significant increase in the thickness and density of the cortex (by 1.34-fold to 876.71 μm, $p<0.0001$) compared with MS rats without drug treatment. There were no significant differences in the thickness and density of the cortex in the MS group administered Natural Resveratrol compared with the MS group without drug treatment, but pronounced tendencies of increases in the number of neurons in the visual field and cortical thickness (752.85 μm, $p=0.66$) were observed. Additionally, administration of

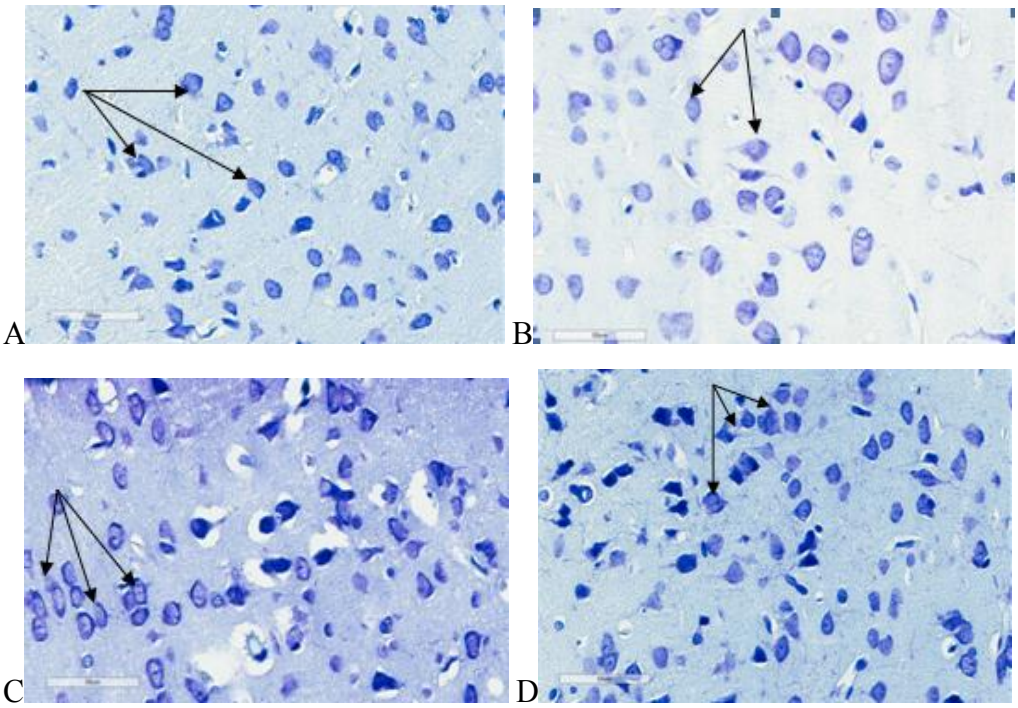

Fig. 2. The density of neurons in the parietal cortex of the rat brain (neurons are indicated by arrows). The control group (A) and metabolic syndrome (MS) group without drug administration (B) show a decrease in the number of neurons in the field of view and weak staining of intercellular fluid; the MS+Natural Resveratrol group (C) and the MS+Fenokor group (D) show an increase in the number of neurons in the field of view and intense staining of nuclei and intercellular fluid. Staining: toluidine blue, magnification x40

polyphenol preparations resulted in more intense staining of neuronal nuclei and intercellular fluid, indicating an increase in the synthetic activity of neuronal cells. A significant increase in the thickness and density of the temporal-parietal cortex (91 % greater, $p<0.001$) was also observed in the Fenokor group compared with the Natural Resveratrol group.

The absence of significant changes in the cortex structure in rats administered resveratrol can be explained by the short duration of administration in this study because cognitive changes are mediated by epigenetic mechanisms [13]. The cumulative and summative potential of the polyphenol complex seems to result in a more pronounced and early effect of Fenokor because of its multicomponent effect on brain cells [14, 15], which may be a justification for its use for obtaining a rapid therapeutic effect, while pure resveratrol can be used for long-term prevention of brain dysfunction in patients with MS.

Conclusions. The development of experimental metabolic-cognitive syndrome in rats is associated with the development of cognitive deficits and impaired memory, learning, and orientation in space in experimental animals. Morphologically, experimental metabolic-cognitive syndrome manifests as a decrease in the thickness and density of the temporal and parietal lobe cortex in the rat brain, which indicates the involvement of this structure as a target organ. Administration of drugs with a high polyphenol content eliminates the symptoms of MS, eliminating the manifestations of insulin resistance and obesity, and has a hypoglycemic as well as a neuroprotective effect. These results can be used in further studies for treatment and prevention of metabolic and cognitive syndrome development.

Experimental animal procedures. The maintenance and care of experimental animals corresponded to the standards given in the Order of the Ministry of Health of the Russian Federation No. 708n of 23.08.2010 «On Approval of the Rules of Laboratory Practice in the Russian Federation» and the ethical principles established by the European Convention for the Protection of Vertebrates Used for Experimental and Other Scientific Purposes (adopted in Strasbourg on March 18, 1986 and confirmed in Strasbourg on June 15, 2006). The study was approved by the institutional ethics committee (Protocol No. 1 of 17.01.2018).

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ANTICATALEPTIC ACTIVITY OF 2-SUBSTITUTED DERIVATIVES OF 3(H)-QUINAZOLIN-4-ONE

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АНТИКАТАЛЕПТИЧЕСКАЯ АКТИВНОСТЬ 2-ЗАМЕЩЕННЫХ ПРОИЗВОДНЫХ 3(H)-ХИНАЗОЛИН-4-ОНА

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The anticataleptic effect of 2-substituted derivatives of 3(H)-quinazolin-4-one in male rats was examined using a haloperidol catalepsy test. Compounds I, II, III, IV, V, VI, and VII (laboratory codes) were administered at a dose of 0.2 of the molecular weight in mg/kg. Catalepsy was induced by administration of haloperidol (1 mg/kg). Control animals were injected with a neuroleptic solvent. In male rats, compounds IV and V limited the severity of motor disorders and showed anticataleptic activity, suggesting their possible use as antiparkinsonian treatments.

Keywords: 2-substituted derivatives of 3(H)-quinazolin-4-one, anticataleptic effect, haloperidol catalepsy

Изучено антикаталептическое действие 2-замещенных производных 3(H)-хиназолин-4-она у самцов крыс в тесте галоперидоловой каталепсии. Соединения I, II, III, IV, V, VI, VII (лабораторные шифры) вводились в дозе 0,2 от молекулярной массы в мг/кг. Каталепсию вызывали введением галоперидола (1 мг/кг). Контрольным животным вводили нейролептик и растворитель. Соединения IV, V у самцов крыс ограничивают выраженность двигательных нарушений, проявляя антикаталептическую активность. Это позволяет предположить перспективность их изучения как антипаркинсонических средств.

Ключевые слова: 2-замещенные производные 3(H)-хиназолин-4-она, антикаталептическое действие, галоперидоловая каталепсия

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