PECULIARITIES OF THE EFFECT OF A HIGH-CALORIUM DIET ON THE STRUCTURE OF THE SPLEEN ON THE CORRECTION WITH ORLISTAT

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PECULIARITIES OF THE EFFECT OF A HIGH-CALORIUM DIET ON THE STRUCTURE OF THE SPLEEN ON THE CORRECTION WITH ORLISTAT

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Sodium glutamate is a food additive that is used worldwide in the food industry to enhance taste. The aim of the present study was to determine the morphometric and histological changes of the rat spleen parenchyma in experimental obesity and its correction with orlistat. The study was performed on 66 white rats of reproductive age. Eight weeks after the experimental animals were on a high calorie diet, a significant decrease in the relative area of the white pulp in the spleen parenchyma of white rats of males and females was observed and, accordingly, an increase in the relative area of red pulp, increase the number of secondary lymph nodes, but the zones are not clearly traced, the number of monocytes, macrophages and plasmocytes is increasing, numerous macrophages contain hemosiderin residues in the cytoplasm. Under the conditions of orlistat correction, fewer structural changes in the parenchyma of the spleen were detected.

Key words: experiment, spleen, sodium glutamate, ORLISTAT, lymphocyte.

Т.В. Гарапко, Л.Р. Матешук-Вацеба, А.С. Головацький, У.Є. Підвальна

ОСОБЛИВОСТІ ВПЛИВУ ВИСОКОКАЛОРІЙНОЇ ДІЄТИ НА СТРУКТУРУ СЕЛЕЗІНКИ ЗА УМОВ КОРЕКЦІЇ ОРЛІСТАТОМ

Глутамат натрію є харчовою добавкою, яка в усьому світі використовується в харчовій промисловості з метою підсилення смаку. Метою дослідження було вивчення морфометричних та гістологічних змін паренхіми селезінки щурів при впливі на організм глутамату натрію та корекції його дії орлістатом. Дослідження проведено на 66 білих щурах репродуктивного віку. Через вісім тижнів перебування експериментальних тварин на висококалорійній дієті спостерігається достовірне зменшення відносної площі білої пульпи в паренхімі селезінки білих щурів самців та самок та відповідно збільшення відносної площі червоної пульпи, зростання кількості вторинних лімфоїдних вузликів, проте зони прослідковуються не чітко, кількість моноцитів, макрофагів та плазмоцитів зростає, численні макрофаги містять у складі цитоплазми залишки гемосидерину. В умовах корекції орлістатом у паренхімі селезінки виявлено менше структурних змін.

Ключові слова: експеримент, селезінка, глутамат натрію, орлістат, лімфоцит

The work is a fragment the research project "Morphological characteristics of internal organs and vascular bed in ontogenesis in the norm and patterns of their restructuring in obesity and the impact on the body of physical factors". State registration number 0119U102059.

Sodium glutamate is a food additive that is used worldwide in the food industry to enhance taste [1]. Prolonged use of sodium glutamate causes a number of diseases and complications, the treatment of which causes significant difficulties [3]. Scientists conclude that this food supplement causes metabolic disorders and contributes to the development of obesity [1]. Studies in newborn mice and rats have shown that this supplement over time causes obesity and diabetes, so it is not recommended for use in the production of baby foods [2, 3].

Obesity has increased in recent years with the epidemic rate not only among adults but also among children. Obesity, type 2 diabetes mellitus, and other metabolic disorders are being reconceptualized as inflammatory conditions [4, 5]. Obesity is associated with multiple adverse health outcomes collectively summarized as the "metabolic syndrome", consisting of insulin resistance and dyslipidemia [11]. It is a well-known fact that obesity causes a number of comorbidities and complications of the chronic course (hypertension, type 2 diabetes, atherosclerosis, some cancers, etc.) [6, 14]. The urgent question remains the effect of sodium glutamate on the immune organs. However, there is insufficient data in the literature on the effects of sodium glutamate on lymphoid organs, which are of particular scientific interest because they protect the body from foreign cells and substances, ensuring homeostasis of the body, including the spleen. Accordingly, if the functional capacity of the immune organs suffers, the whole organism loses its protective mechanism and becomes sensitive to the action of antigens [13]. Spleen is the largest lymphoid organ in the body and has a critical role in the modulation of the immune system and differentiation and activation of inflammatory cells [4, 7]. Although the spleen is the main immune organ with a close anatomical relationship with the liver, its role in the progression of fatty liver disease remains uncertain [9, 13]. Further research is needed to study the effects of this supplement on the human body. Also no less important is the question of correction of changes caused by the action of sodium glutamate on the body.We used ORLISTAT to correct the changes caused by obesity. Orlistat is a potent, specific, long-acting and reversible lipase inhibitor, a member of a new class of drugs available for the treatment of obesity [10]. Diet plus Orlistat repeatedly showed significantly greater weight loss compared to diet plus placebo [12]. Moreover, the effects of the active substance of the drug, namely Orlistat, are significant and meet the standards for the effectiveness of prescription weight control drugs [10, 12].

The purpose of the study was to determine the morphometric and histological changes of the rat spleen parenchyma in experimental obesity and its correction with Orlistat.

Materials and methods. We carried out the study on 66 white rats of reproductive age (2.5–6.5 months) weighing 120-280 g.

Microanatomy of the spleen structural components in white rats under conditions of physiological norm was studied on 10 intact animals (first group). Experimental animals were divided into 5 groups: the second group (10 animals), being fed a high-calorie diet (HCD) for eight weeks; the third group (10 animals), fed high-calorie diet for two weeks followed by two weeks of HCD+ Orlistat; the fourth group (10 animals), fed high-calorie diet for two weeks followed by four weeks of HCD+ Orlistat; the fifth group (10 animals), fed high-calorie diet for two weeks followed by six weeks of HCD+ Orlistat.

Each group included 5 male and 5 female rats. High-calorie diet was achieved due to the fact that glutamate sodium was added into food in a dose of 0.07 g/kg of rat body weight. The dose of Orlistat was 4.5 mg/kg of body weight of the rat, administered orally daily at the same time.

Control was provided by 16 white rats, fed a standard diet of vivarium instead of a high-calorie diet. All experimental animals were kept under the vivarium of the Danylo Halytsky Lviv National Medical University. The study was performed in accordance with the provisions of the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes (Strasbourg, 1986), Council of Europe Directives 86/609 / EEC (1986), Law of Ukraine No. 3447-IV "On the Protection of Animals from Cruelty", the general ethical principles of experiments on animals adopted by the First National Congress of Ukraine on Bioethics (2001).

Morphometric studies were performed using a system of visual analysis of histological preparations. Images from histological specimens of the spleen on a computer monitor were taken from a MICROmed SEO SSCAN microscope and using a Vision CCD Camera. The studies were performed at certain times of the experiment in stained with hematoxylin and eosin. Morphometric studies were performed using VideoTest-5.0, CAAPA Image Base, Stepanizer, and Microsoft Excel on a personal computer. For all indices, the values of arithmetic mean (M), arithmetic mean error (m) and standard deviation (δ) were calculated. The significance of the difference in values between the independent quantitative values was determined at the normal distribution by Student's t-test. Differences at $p<0,05$ are considered reliable.

Results of the study and their discussion. The spleen is a secondary immune organ in which antigen-dependent proliferation and differentiation of T- and B-lymphocytes occurs. In animals of the intact and control groups, according to our histological studies, the structure of the spleen was compliant with the species norm. Externally, the spleen surrounded by a connective-tissue capsule, from which numerous trabeculae lead inside the spleen's parenchyma. The parenchyma is formed by white and red pulp (fig. 1).

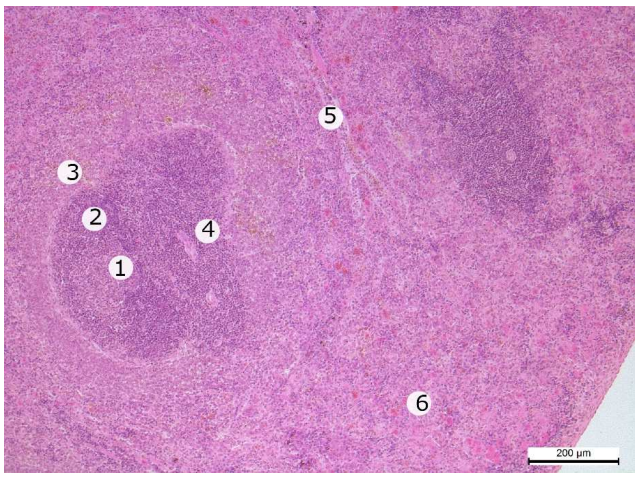

Fig. 1. A fragment of a spleen of an intact white rat male. Stained with hematoxylin and eosin. Magnif: obj.×10, ocul.×10. Designation: 1 – germinal center of the lymphoid nodule; 2 – mantle zone; 3 – marginal zone; 4 – central arteriole; 5 – periarterial lymphatic sheath; 6 – red pulp.

The white pulp consists of periarterial lymphatic sheath (PALS), and lymphatic nodules. The red pulp occupies the majority of the stromal tissue of the spleen. It consists of the cords of Billroth and splenic sinusoids. Red pulp is represented by clusters of blood cells that are surrounded by reticular cells.

Eight weeks after HCD, there is a significant decrease in the relative area of white pulp in the spleen parenchyma of white rats of males and females to 21.6±1.22 % and 21.78±1.3 %, which is 16.2 % and 17.4 % less parameters of intact group of animals (see table. 1). Accordingly, the relative area of the red pulp increases to 78.4±1.45 % in male rats and to 78.22±1.54 % in female rats. These figures are 5.6 % and 6.2 % higher than the parameters of the intact group of animals (table 1).

Table 1

Dynamics of changes in the relative areas of red and white pulp of the spleen of white rats of control and experimental groups (M ± m)

Group name	Male rats		Female rats	
	$S_{white\ pulp}$,%	$S_{red\ pulp}$,%	$S_{white\ pulp}$,%	$S_{red\ pulp}$,%
group I – intact animals	25.78±1.18	74.22±1.33	26.38±1.02	73.62±1.4
group II – 8 weeks HCD	21.6±1.22*	78.4±1.45*	21.78±1.3*	78.22±1.54*
group III – 2 weeks HCD, 2 weeks HCD+ Orlistat	26.99±1.09*	73.01±1.08*	27.84±1.2*	72.16±1.4*
group IV – 2 weeks HCD, 4 weeks HCD+ Orlistat	26.01±1.2	73.99±1.0	27.19±1.28	72.81±1.32
group V – 2 weeks HCD, 6 weeks HCD+ Orlistat	25.56±1.11	74.44±1.4	25.63±1.12	74.37±1.3

Notes: * – values that are statistically significantly different from those of the intact animal group ($p<0.05$)

Eight weeks of the high-calorie diet (second group of animals) in both male and female rats increases the number of secondary lymph nodes, but the zones are not clearly traced. The number of monocytes, macrophages and plasmocytes is increasing. Numerous macrophages contain hemosiderin residues in the cytoplasm (fig. 2).

The latter is also located in the intercellular spaces of the parenchyma of the organ. The presence of iron-containing pigment is evidence of erythrocyte death. The wall of the central artery is swollen, thickened. Vascular edema is observed. The proportion of reticular connective tissue increased in the thickness of the red pulp Billroth. The venous sinuses of the red pulp are full-blooded, enlarged and somewhat deformed. There is an immuno-inducing effect with enhanced proliferation of activated lymphocytes and their subsequent differentiation into plasma cells. Around small vessels, eosinophilic aggregation and lipid accumulation in the enlarged sinuses are found. Congestion in the spleen is manifested in the increased aggregation of blood cells in the sinuses and red pulp. In the white pulp, the perifollicular area of the lymphatic follicles looks looser, lighter than normal, that is, the number of lymphoid elements decreases compared to normal.

Morphometric indices in the third group of animals (two weeks of HCD, followed by two weeks of HCD+ Orlistat) indicate that the relative area of white pulp in the spleen parenchyma of white rats of males and females increased by 4.7 % and 5.5 % compared to the intact group of animals and was 26.99±1.09 % and 27.84±1.2 %, respectively (table 1). Accordingly, the relative area of the red pulp decreases to 73.01±1.08 % in male rats and 72.16±1.4 % in female rats. These figures are 1.6 % and 2.0 % less than the parameters of the intact group of animals. The structure of the spleen when consumed with Orlistat together with HCD for two weeks, with the previous two-week intake of HCD, did not change significantly, similar to that of intact animals (fig. 3).

Morphometric indices in the fourth group of animals (two weeks of HCD, followed by four weeks of HCD+ Orlistat) indicate that the relative area of white pulp in the spleen parenchyma of white rats in males and females decreased by 3.6 % and 2.3 %, respectively. Group of animals and is 26.01±1.2 % and 27.19±1.28 %. These figures are 0.9 % and 3.0 % higher than the parameters of the intact group of animals. Accordingly, the relative area of the red pulp increases by 1.3 and 0.9 % compared to the previous group of animals and is 73.99±1.0 % in male rats and 72.81±1.32 % in female rats. These figures are 0.3 % and 1.1 % less than the parameters of the intact group of animals.

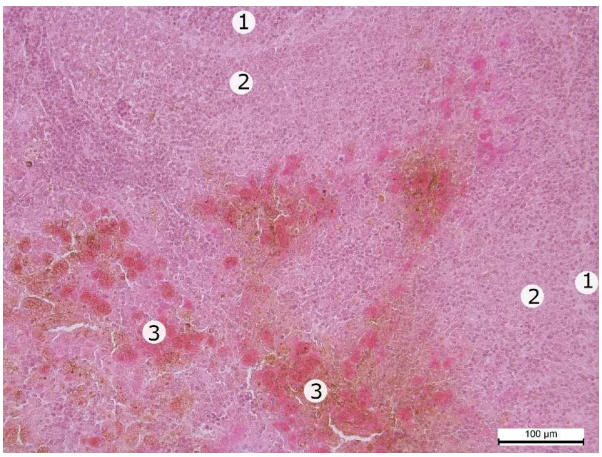

Fig. 2. A fragment of a spleen of an white rat male after eight weeks of HCD. Stained with hematoxylin and eosin. Magnif: obj.×20, ocul.×10. Designation: 1 – mantle zone of the lymphoid nodule; 2 – marginal zone of the lymphoid nodule; 3 – accumulation of hemosiderin and lipids in venous sinusoids of red pulp.

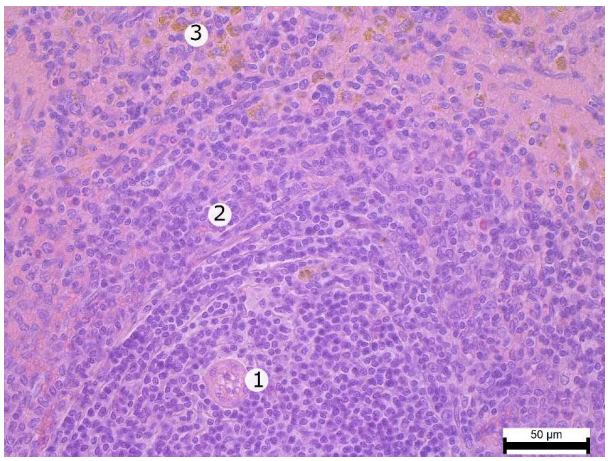

Fig. 3. A fragment of a spleen of an white rat female after two weeks of HCD, followed by two weeks of HCD+ Orlistat. Stained with hematoxylin and eosin. Magnif: obj.×40, ocul.×10. Designation: 1 – central arteriole; 2 – marginal zone of the lymphoid nodule; 3 – accumulation of hemosiderin and lipids in red pulp.

Histological preparations have a moderate amount of iron-containing pigment. Areas of lymph nodes are clearly demarcated. The artery and vein in the gland of the spleen are somewhat enlarged and full-blooded. The number of monocytes, macrophages and plasmocytes does not increase. The proportion of reticular connective tissue did not increase in the thickness of the red pulp Billroth. Single lymphocytes with signs of apoptosis occur (fig. 4 A).

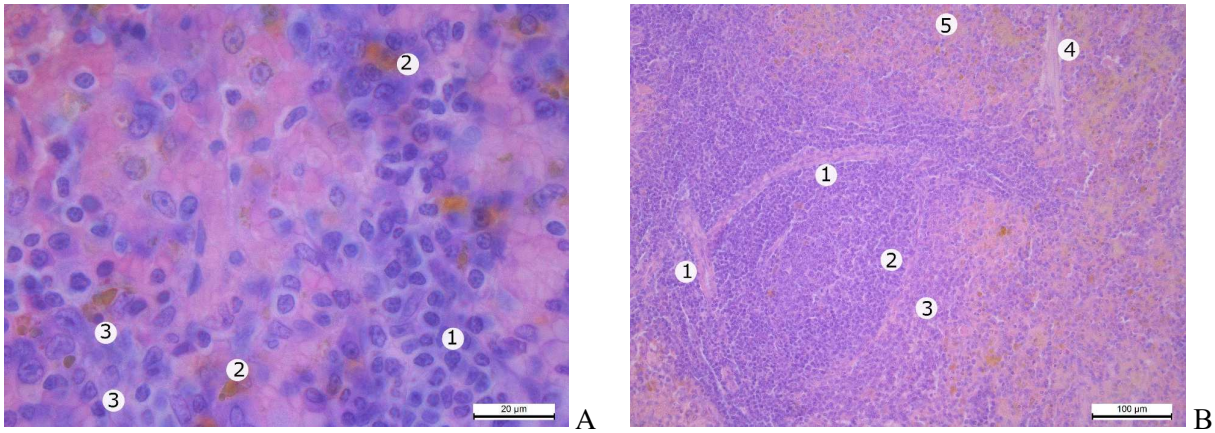

Fig. 4. A fragment of a spleen of an white rat female after two weeks of HCD, followed by four weeks of HCD+ Orlistat (A) and a fragment of a spleen of an white rat male after two weeks of HCD, followed by six weeks of HCD+Orlistat (B). Stained with hematoxylin and eosin. Magnif: A. obj.×100, ocul.×10; B. obj.×20, ocul.×10. Designation: A. 1 – lymphocytes; 2 – accumulation of hemosiderin; 3 – necrotic altered cells; B. 1 – periarterial lymphatic sheath; 2 – marginal zone of the lymphoid nodule; 3 – mantle zone of the lymphoid nodule; 4 – swollen cords in red pulp; 5 – hemosiderin in red pulp.

Morphometric indices in the fifth group of animals (two weeks of HCD, followed by six weeks of HCD+ Orlistat) indicate that the relative area of white pulp in the spleen parenchyma of white rats in males and females decreased by 1.7 and 5.7 %, respectively, with the previous group of animals and is 25.56±1.11 % and 25.63±1.12 %. These figures are 0.9 % and 2.8 % less than the parameters of the intact group of animals. Accordingly, the relative area of the red pulp is increased by 0.6 % and 2.1 % compared to the previous group of animals and is 74.44±1.4 % in male rats and 74.37±1.3 % in female rats. These figures are 0.3 % and 1.0 % higher than the parameters of the intact group of animals (table 1).

On histological preparations, the boundaries between nodules are clear; differentiation into zones is observed almost everywhere (fig. 4 B). Some veins are enlarged, full-blooded. The amount of hemosiderin in the parenchyma of the spleen is moderate.

The revealed changes in the morphological response of the spleen to the use of Orlistat under the conditions of modeling of obesity with the help of a high-calorie diet may be related to the spectrum of action of the constituents of the drug and the manifestation of the general adaptive reaction of the organism.

V.V. Bevzo found that prolonged administration (within 4 weeks) to rats of a 3 % solution of glutamate sodium at a dose of 30 mg/kg body weight leads to an increase in the serum content of total and tyrosine-containing peptides, substances of low and average molecular weight, as well as an increase in the values of the intoxication coefficient, which indirectly indicates the disturbance of the processes of detoxification of endogenous metabolites in the liver of animals [1].

Authors used 16 adult female Sprague Dawley rats, weighing between 150–200 g. They performed rat models, fed with normal or high-fat diet for duration of 3 months. After this controlled nutritional process, spleens are removed from all anesthetized rats and performed by routine histological process. Stereologically, estimated the spleen volumes in consecutive serial sections using Cavalieri method in control and treatment groups. Mean spleen volumes were 1.40 ml in the control and 2.03 ml in the treatment group, suggesting splenomegaly. Volumes of spleens in 2 groups revealed statistical significant difference ($p<0.05$, independent samples t-test). In studying spleen slices, many macrophages and necrotic figures were defined. In addition, sinusoidal dilatation and hemosiderin deposits were observed and found macrophages, filled with hemosiderin droplets. In some sections, especially around small vessels, eosinophilic aggregations and lipid accumulations in dilated sinusoids were detected [1].

Spleen-derived IL-10 had a protective effect against pathological inflammation in liver and IL-10 and improves liver fibrosis. However, obesity is associated with low IL-10 production by the spleen. The results indicate that preservation of the spleen contributes to the prevention of the progression of hepatic steatosis to steatohepatitis in obese rats [8, 9]. IL-10 is synthesized by several cell types in multiple organs, including the spleen. Authors noted spleen-derived IL-10 because the serum level of only IL-10, despite the significantly decreased expression of all cytokines in the spleens of HF-fed mice compared with standard-fed mice.

This suggested that large amounts of serum IL-10 are derived from the spleen and that obesity reduces IL-10 secretion from the spleen. Previous research showed that HF feeding compared with standard feeding, downregulated the expression of CD20, a surface molecule present on B cells, which play a large role in the immune response and produce IL-10 mainly in the spleen [7, 8]. Authors hypothesized that the obesity-induced reduction in IL-10 synthesis in the spleen could lead to inflammatory responses in the kidneys and to metabolic disorders.

The authors describe that obesity reduces the size of inguinal lymph nodes, impairs lymphatic fluid transport and migration of dendritic cells to peripheral lymph nodes, and reduces the number of T lymphocytes in lymph nodes. In general, obesity violates the integrity of the immune system and leads to changes in the development of leukocytes, their migration and diversity [6].

Taking orlistat at a dose of 120 mg 3 times a day was accompanied by an improvement in total cholesterol and low-density lipoprotein, glucose and blood pressure. Data from the XENDOS study (3305 patients treated with orlistat for 4 years at a dose of 120 mg 3 g/day) showed a weight loss of 2.7 kg over 4 years more than in the placebo group, and significantly reduced the risk of developing type 2 diabetes from 9.0 % in the placebo group to 6.2 %. Taking orlistat at a dose of 60 mg 3 times a day resulted in a 2.5 kg weight loss compared to placebo over 12 months [15].

Conclusions

1. After eight weeks of HCD, a significant decrease in the relative area of white pulp in the spleen parenchyma of white rats of males and females was observed by 16.2 % and 17.4 %, respectively, and an increase in the relative area of red pulp by 5.6 % and 6.2 %, respectively.

2. After two weeks of HCD, followed by six weeks of HCD+Orlistat the relative area of white pulp in the spleen parenchyma of white rats in males and females decreased are 0.9 % and 2.8 % less than the parameters of the intact group of animals. Accordingly, the relative area of the red pulp are 0.3 % and 1.0 % higher than the parameters of the intact group of animals. Under the conditions of Orlistat correction it is found that the boundaries between the lymph nodes are clear, differentiation to the zones is followed almost everywhere, some veins are enlarged, full-blooded, the amount of hemosiderin in the parenchyma of the spleen is moderate.

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METABOLIC POLYORGANIC DISORDERS IN RATS WITH INSULIN RESISTANCE ON THE BACKGROUND OF IODINE DEFICIENCY

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Impaired glucose tolerance leads to structural and functional restructuring of internal organs, that intensify under iodine deficiency conditions. Studies were carried on male rats (animals with insulin resistance under conditions of adequate iodine supply and iodine deficiency). Metabolic changes were studied in blood serum, homogenates of kidneys, heart, liver, teeth pulp and oral mucosa. It is established that development of insulin resistance is accompanied by activation of lipoperoxidation processes in studied organs, decrease of catalase activity and increased glutathione defense system. In animals signs of visceral obesity are developed, manifested by increase of atherogenic index and leptin level, decrease of ghrelin concentration in blood serum. Under conditions of combined endocrinopathy increase of lipoperoxide products in tissues on the background of antioxidant reserve inhibition, growth of proatherogenic lipid fractions relative to data in animals with isolated insulin resistance are observed, that reflects potentiation of pathological changes under conditions of combined endocrinopathy.

Key words: thyroid hormones, insulin, ghrelin, leptin, lipids, oxidative stress, antioxidant system.

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МЕТАБОЛІЧНІ ПОЛІОРГАННІ ПОРУШЕННЯ У ЩУРІВ ІЗ ІНСУЛІНОРЕЗИСТЕНТНІСТЮ НА ТЛІ ЙОДОДЕФІЦИТУ

Порушення толерантності до глюкози призводить до структурно-функціональної перебудови внутрішніх органів, що може посилюватися за умов йододефіциту. Дослідження проведені на щурах-самцях (тварини з інсулінорезистентністю за умов належного забезпечення йодом та йододефіциту). Метаболічні зміни вивчали у сироватці крові, гомогенатах нирок, серця, печінки, пульпи зубів і слизової оболонки порожнини рота. Встановлено, що розвиток інсулінорезистентності супроводжується активацією процесів ліпопероксидації у досліджуваних органах, зниженням активності каталази та підвищенням глутатіонової системи захисту. У тварин розвиваються ознаки вісцерального ожиріння, що проявляються зростанням коефіцієнта атерогенності та рівня лептину, зменшенням концентрації греліну у сироватці крові. За умов комбінованої ендокринопатії спостерігається збільшення продуктів ліпопероксидації у тканинах на тлі пригнічення антиоксидантного резерву, зростання проатерогенних фракцій ліпідів щодо даних у тварин із ізольованою інсулінорезистентністю, що відображає потенціювання патологічних змін за умов комбінованої ендокринопатії.

Ключові слова: тиреоїдні гормони, інсулін, грелін, лептин, ліпіди, оксидативний стрес, антиоксидантна система.

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The maintaining of internal environment stability of organism and ensuring of adaptation processes are carried out due to a complex multi-component system of regulation of proteins, fats and carbohydrates metabolism. Each of the nutrients not only independently, but also comprehensively, through a series of biochemical transformations, provides energy, plastic, trophic, regulatory, protective and many other vital functions. Regulation of metabolism and energy exchange is carried out by a hierarchical neuro-humoral