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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.

The study is a fragment of the research projects "Ontogenetic features of organs and tissues under conditions of iodine deficiency states, hypothyroidism", state registration No 0119U002847 and "Complex morphofunctional research and substantiation of modern technologies application for treatment and prevention of dental diseases", state registration No 0121U109242.

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

system, an important role in which belongs to biologically active substances. Therefore, impaired incretory function of endocrine glands or reduced sensitivity of target cells to the action of hormones can cause metabolic imbalance and multiorgan failure. So, the development of insulin resistance (IR) on the background of all components of metabolism's disorder causes the changes in the functional activity of many organs and systems of the body [13]. In particular, disorders of carbohydrate metabolism cause structural and functional reorganization of glomerular and tubular apparatus of kidneys, which gradually leads to the development of renal failure [5]. Hepatic manifestation of IR is associated with dyslipidemia, obesity, which are the reason of steatosis and steatohepatosis [1]. Impaired glucose tolerance is a trigger for microcirculatory changes in the teeth pulp and oral mucosa (OM), damage of connective tissue proteins and reduction of mineralizing ability of bones and teeth [15]. Important factors that determine the progression of pathological changes, may be the development of secondary dyslipidemia and violation of prooxidant-antioxidant homeostasis. A number of studies suggest that metabolic changes in case of IR are associated with the development of chronic inflammation and elevated levels of adipocytokines. In particular, the elevation of leptin content in blood plasma causes a reduction of the vascular wall's elasticity and the contractile ability of myocardium. At the same time, it is known that the hormone ghrelin has a cardioprotective effect, regulates the metabolism of glucose and insulin, the values of which are inversely correlated with each other. Therefore, a decrease of ghrelin concentration is accompanied by more pronounced manifestations of IR [2]. It is believed that mutations of signal receptors to insulin and leptin molecules are common in the pathogenetic mechanism of impaired glucose tolerance and obesity development [14]. It should be noted that the manifestations of combined endocrinopathy are diagnosed more often. Thus, IR or diabetes mellitus in combination with thyroid pathology is a common example of comorbidity in clinical practice [6].

The purpose of the study was to study the changes of hormonal profile, carbohydrate and lipid metabolism, prooxidant-antioxidant homeostasis in rats under conditions of impaired glucose tolerance on the background of adequate iodine supply and iodine deficiency for the determination of aggravating factors of insulin resistance.

Material and methods of research. The studies were carried on male rats weighing 150-180 g, which were divided into control and two research groups. The 1st group (n=30) included rats with IR, which received 10 % fructose solution instead of drinking water during 8 weeks [11]; to the 2nd (n=30) – rats with IR on the background of ID. ID was reproduced using an iodine deficiency diet, which included products with limited trace element content [3]. The control group (n=30) included intact animals, which were kept on a standard diet, normal temperature and light regime of the vivarium.

The development of IR was determined by HOMA-IR (Homeostasis Model Assessment Insulin Resistane) index, which was calculated due to the serum content of insulin and glucose, and the level of glycosylated hemoglobin (HbA1c) in whole blood was detected. Insulin content was examined by using reagent ELISA RIT (USA). Serum glucose level and HbA1c content were determined by using kits "Reagent" (Dnipro, Ukraine). The measurements were performed on a plate enzyme-linked immunosorbent assay STAT FAX 2100 (China). Leptin and ghrelin levels were tested by using Rat Lpt (Leptin) ELISA Kit (Elabscience, USA) and Rat GHRL (Ghrelin) ELISA Kit (Elabscience, USA) reagents respectively on an ER-500 Microplate Reader device. For the evaluation of thyroid status of animals, the content of free triiodothyronine (fT_3), thyroxine (fT_4), thyroid-stimulating hormone (TSH) in blood serum was determined by enzyme-linked immunosorbent assay on the ER-500 analyzer (Sinnowa, China) by using the kit "ELISA" (Elabscience, USA) with the following calculation of fT_3/fT_4 index. To determine the state of iodine supply of animals in single portions of urine, which were collected by the method of metabolic cells, the concentration of iodine was determined [12]. Blood lipid spectrum was characterized by the level of total cholesterol (TC), low-density (LDL) and high-density lipoprotein cholesterol (HDL), triglycerides (TG) in blood serum by using "Filisit-Diagnostics" kits (Dnipro, Ukraine) on a spectrophotometer LV/VIS ULAB with the following calculation of atherogenic index (AI). The processes of lipid peroxidation (LP) were studied by the accumulation of diene conjugates (DC) and products that react to thiobarbituric acid (TBA-AP) [10] on a spectrophotometer SPECORD M 40 (Germany) in blood serum, homogenates of kidneys, heart, liver, teeth pulp and OM. The state of antioxidant system was characterized by the activity of catalase (K) [CF 1.11.1.6], superoxide dismutase (SOD) [CF 1.15.1.1], glutathione peroxidase (GP) [CF 1.11.1.9], glutathione reductase (GR) [CF 1.8.1.7], ceruloplasmin (CP) content and transferrin saturation by iron (Tr), which were determined in blood serum [4]. The keeping, feeding and withdrawal of animals from the experiment were carried out in compliance with the basic provisions of the Rules for the experiments with the using of laboratory animals (1977), the Council of Europe Convention for the Protection of Vertebrate Animals Used in Experiments and Other Scientific

Purposes (1986), the Order of the Ministry of Health of Ukraine No. 281 of 01.11.2000 "About measures to further improve the organizational standards of work with the use of experimental animals" and the Law of Ukraine No. 3447-IV "About the protection of animals from cruelty" (2006).

Data Processing. Statistical analysis of digital results of the study was performed using the computer program Excel package Microsoft Office 365 ProPlus. For each of the samples, the distribution of the studied indicator was checked using the Kolmogorov-Smirnov and Liliefors criteria. Considering that the obtained data corresponded to Gauss's law, the results were presented by the interval M±m. Student's t-criterion was used to assess the significance of differences between groups. The difference in parameters at $p<0.05$ was considered as statistically significant.

Results of te study and their discussion. The changes of thyroid status of experimental animals are represented in table 1.

Table 1.

Indexes of thyroid status of intact animals, rats with insulin resistance under conditions of adequate iodine supply and iodine deficiency (M±m)

Indexes	Control, n=30	1st group, n=30	2nd group, n=30
fT_3, pmol/l	6.54±0.37	5.28±0.52*	3.48±0.23**** $p_{1-2}<0.01$
fT_4, pmol/l	29.84±0.65	26.31±2.48****	17.11±1.52**** $p_{1-2}<0.05$
TSH, mIU/l	0.13±0.02	0.10±0.01	0.15±0.01***
fT_3/fT_4	0.19±0.01	0.17±0.01	0.15±0.02***
Iodine in urine, mcg/l	105.17±3.12	96.13±5.27	58.64±4.29**** $p_{1-2}<0.001$

Note: Here and in the following tables and figures: * – $p<0.05$; *** – $p<0.01$; **** – $p<0.001$ – a reliable difference between the indexes to similar values in intact animals; p_{1-2} – a reliable difference between the indexes in animals of research groups.

As a results of the study a violation of thyroid homeostasis in insulin-resistant animals was found: decrease of fT_3 secretion by 19 % ($p<0.05$) and fT_4 – by 12 % ($p<0.001$) relative to data in intact animals.

Keeping of animals of the 1st group on a high-fructose diet led to changes of carbohydrate and lipid metabolism (table 2).

Table 2.

Markers of carbohydrate and lipid metabolism in blood serum of intact animals, rats with insulin resistance under conditions of adequate iodine supply and iodine deficiency (M±m)

Indexes	Control, n=30	1st group, n=30	2nd group, n=30
Glucose, mmol/l	4.22±0.12	5.98±0.35****	6.89±0.48****
Insulin, mkU/l	13.31±0.21	17.66±0.34****	19.73±0.41**** $p_{1-2}<0.01$
HbA1c, μmol of fructose/g Hb	3.65±0.42	6.81±0.98*	7.58±1.22*
HOMA-IR index	2.63±0.11	4.42± 0.33****	5.48± 0.41****
Ghrelin, ng/ml	5.09±0.90	1.86±0.32***	1.08±0.10**** $p_{1-2}<0.05$
Leptin, ng/ml	0.95±0.14	1.68±0.18***	2.32±0.20**** $p_{1-2}<0.05$
TC, mmol/l	1.05±0.10	1.29±0.23***	1.78±0.38* $p_{1-2}<0.05$
LDL, mmol/l	0.20±0.02	0.31±0.06***	0.67±0.03*** $p_{1-2}<0.01$
HDL, mmol/l	0.96±0.21	0.72±0.12*	0.67±0.13*
TG, mmol/l	0.50±0.17	0.64±0.14*	0.62±0.06
AI, cu	0.45±0.8	0.85±0.9*	1.86±0.13**** $p_{1-2}<0.001$

In particular, in serum of rats with IR increased glucose by 42 % ($p<0.001$), insulin – by 33 % ($p<0.001$), HOMA-IR index by 68 % ($p<0.001$) relative to control was found. A criterion for impaired glucose tolerance was an increase of HbA1c level in rats of the 1st group by 87 % ($p<0.05$) relative to baseline values.

In animals that were on a high-fructose diet with proper iodine supply, signs of visceral obesity were observed, which was manifested by opposite changes in serum ghrelin and leptin levels. Thus, in rats of the 1st group, the level of ghrelin decreased by 64 % ($p<0.01$) with a simultaneous increase of leptin content by 77 % ($p<0.01$) compared to similar indexes of intact animals.

In animals with IR the violations of lipid metabolism were found. In rats of the 1st group, the level of TC, LDL and TG increased by 23 % ($p<0.01$), by 55 % ($p<0.01$) and by 28 % ($p<0.05$) respectively, against the background of a decrease of HDL content by 25 % ($p<0.05$) relative to the values of control group. AI in rats with IR increased almost twice ($p<0.05$) relative to baseline.

Under such conditions, changes of prooxidant-antioxidant homeostasis were observed. Thus, in animals of the 1st group, the intensity of free radical oxidation of lipids in most of the studied tissues increased (fig. 1).

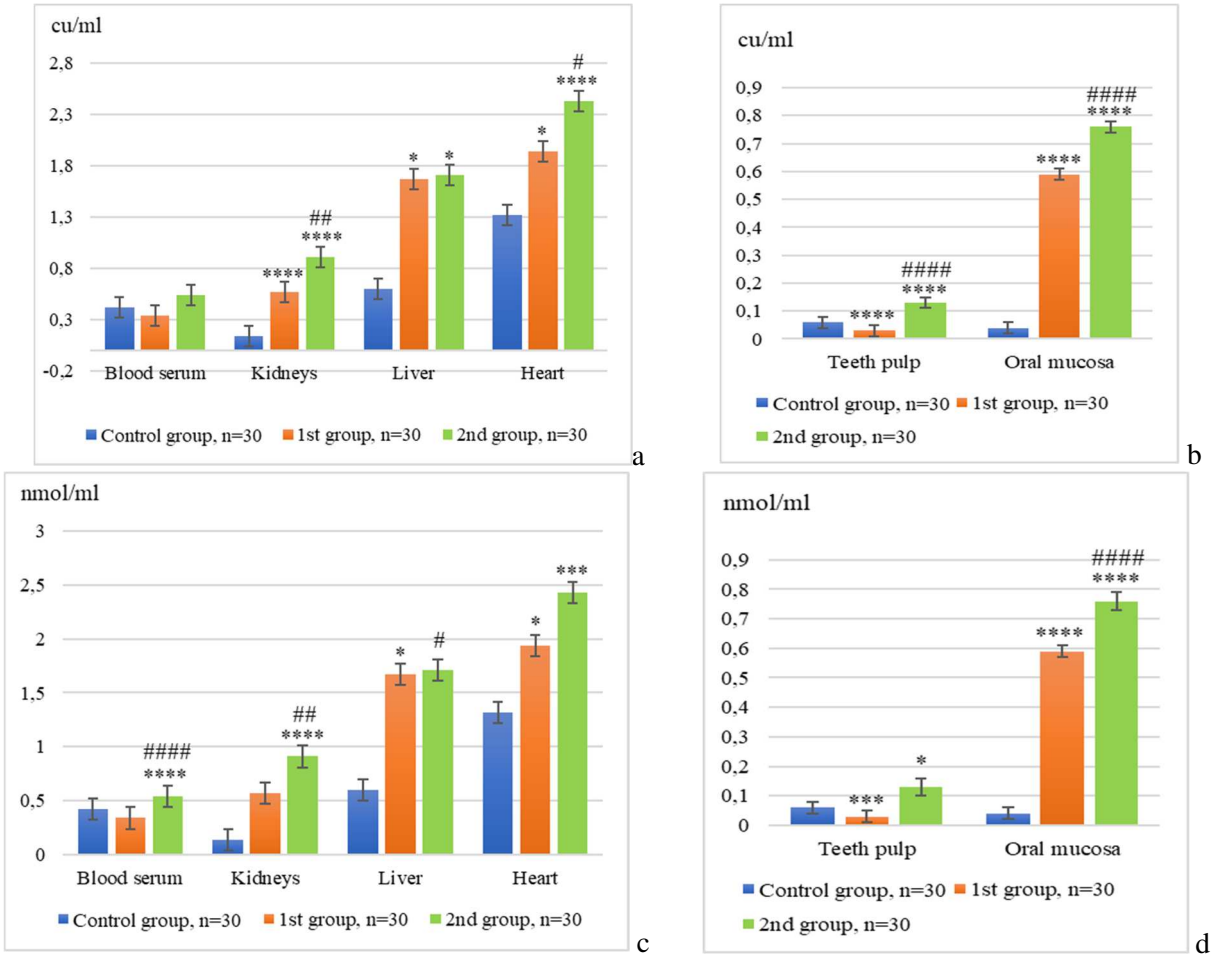

Fig. 1. The content of diene conjugates (a, b) and products responding to thiobarbituric acid (c, d) in the blood serum, kidneys, liver, teeth pulp and oral mucosa of intact animals, rats with insulin resistance under conditions of adequate iodine supply and iodine deficiency.

Note: Here and in the following figures: # – $p<0.05$; ## – $p<0.02$; ### – $p<0.01$; #### – $p<0.001$ – a reliable difference between the indexes in animals of research groups.

Atracts attention the accumulation of intermediate products of LP content in the homogenates of kidneys, liver, heart and OM, where the level of DC increased four times ($p<0.001$), almost three times ($p<0.05$), by 47 % ($p<0.05$) and fifteen times ($p<0.001$) respectively, relative to similar values of rats in the control group. However, in the teeth pulp the opposite changes of the DC content were observed, that was indicated by decreased level of intermediate product of LP in two times ($p<0.001$) compared with baseline. Herewith, in blood serum, homogenates of liver, heart, teeth pulp and OM, the concentration of LP final product increased by 72 % ($p<0.05$), by 31 % ($p<0.05$), twice ($p<0.05$), by 66 % ($p<0.001$) and by 2.5 times ($p<0.001$), respectively, relative to data in intact rats. Activation of oxygen-dependent processes was accompanied by a decrease of K activity by 68 % ($p<0.05$) against the background of GP activation by 50 % ($p<0.05$) relative to control (fig. 2).

Impaired glucose tolerance in rats with ID caused an imbalance of pituitary-thyroid axis, what was indicated by a decrease of fT_3 and fT_4 content by 47 % ($p<0.001$) and by 43 % ($p<0.001$), respectively, against the background of increasing TSH concentration by 15 % ($p<0.01$) in blood serum of animals of the 2nd group compared with baseline. The violation of conversion of T_4 to T_3 on the periphery was denoted by a decrease the fT_3/fT_4 index by 21 % ($p<0.01$).

In animals of 2nd group an increase the content of glucose by 63 % ($p<0.001$), insulin – by 48 % ($p<0.001$), the level of HbA1c and the HOMA-IR index – almost twice ($p<0.01$) relative to control was observed. The level of insulin was higher by 11 % ($p_{1-2}<0.01$) compared to data in animals with IR.

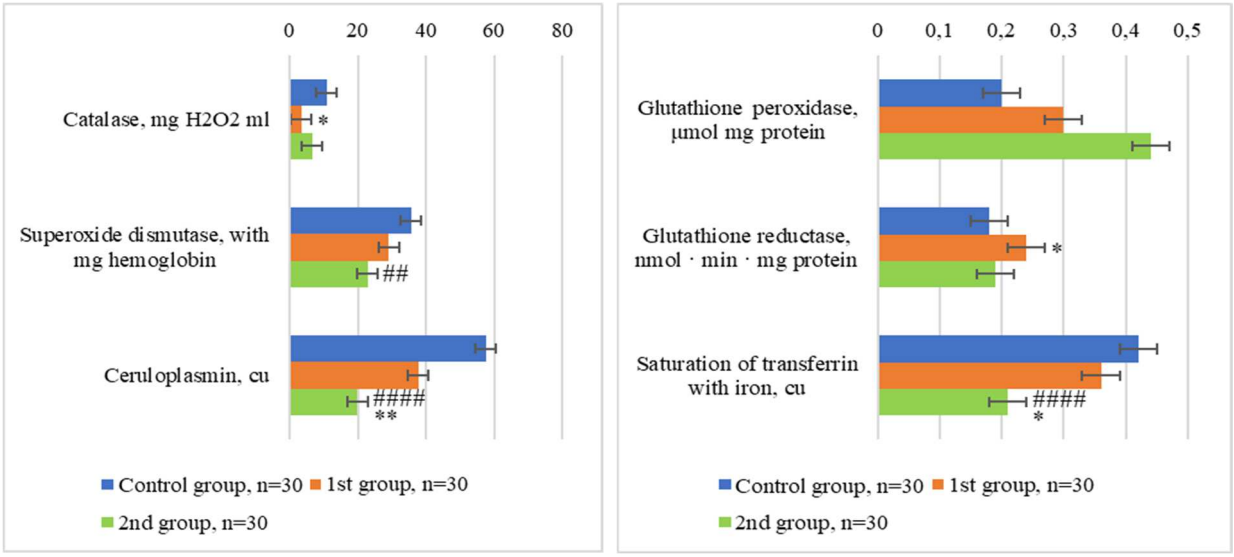

Fig. 2. Activity of antioxidant enzymes in the blood serum of intact animals, rats with insulin resistance under conditions of adequate iodine supply and iodine deficiency.

Insufficiency of insulin and thyroid hormones regulatory effect on target cells has led to multifactorial metabolic disorders. In particular, in blood serum of animals of the 2nd group, the level of leptin was higher more than twice ($p<0.001$) compared to control. The concentration of ghrelin under these conditions decreased by 80 % ($p<0.001$) relative to the baseline. Thus, in rats of 2nd group, the leptin content increased by 38 % ($p_{1-2}<0.05$) against the background of decreased ghrelin concentration by 42 % ($p_{1-2}<0.05$) in comperison with the correspondent indexes of animals with isolated endocrynopathy. The changes of lipid spectrum of blood were consistent with the biochemical signs of obesity of rats with IR on the background of ID. In particular, in animals of the 2nd group, the content of TC increased by 70 % ($p<0.05$), LDL more than three times ($p<0.01$) against the background of a decrease of HDL content by 30 % ($p<0.05$) relative to control. Such changes of lipid profile caused an increase of AI more than four times ($p<0.001$) relative to data in intact animals. It was found an increase of TC and LDL levels by 38 % ($p_{1-2}<0.05$) and more than twice ($p_{1-2}<0.01$) respectively compared to similar indices of rats with isolated IR. AI exceeded the value in animals of 1st group by more than twice ($p_{1-2}<0.001$).

Against the background of combined humoral disorders, manifestations of oxidative stress were observed. The content of DC significantly increased in all studied tissues relative to baseline. The content of LP final product in the blood serum, heart, teeth pulp and OM was two to seven times higher ($p<0.001$) against the background of a decrease of its level in kidney tissue by 86 % ($p<0.001$) compared to analogical indexes of control. The analysis of lipoperoxidation intensity in the tissues of rats of research groups found a predominant accumulation of DC content. Thus, in kidneys, heart, OM of animals of the 2nd group, the content of DC increased by 25–60 % ($p_{1-2}<0.05$), and in the teeth pulp – more than four times ($p_{1-2}<0.001$) relative to the correspondant values under IR conditions on the background of adequate iodine supply. An increase of TBA-AP level almost three times was observed only in the blood serum and homogenate of OM in rats of the 2nd group ($p_{1-2}<0.001$) compared to the values in animals with isolated IR. In the homogenates of kidneys and liver in rats of this group, the content of TBA-AP reliably decreased in comparison to indexes in animals of the 1st group. Under conditions of lipoperoxidation processes activation, the probability of free radicals aggression on lipid components of studied biostructures is high. Activation of peroxidation was accompanied by changes in the body's antioxidant defense system. Thus, the combined effect of IR and ID was manifested by a decrease of Tr and CP content in blood serum by 42 % ($p<0.05$) and by 65 % ($p<0.05$), respectively, relative to baseline. The activity of SOD, CP and Tr in rats with combined endocrine pathology was lower by 21 % ($p_{1-2}<0.01$), by 47 % ($p_{1-2}<0.001$) and by 42 % ($p_{1-2}<0.001$) respectively, than under conditions of isolated IR.

Considering that isoglycemia in living organisms is supported mainly by the insular apparatus of pancreas [13], the development of IR in experimental rats was accompanied by changes of glycemic profile and an increase of HOMA-IR index. It is known, that violations of carbohydrate metabolism lead to complex multiorgan disorders, as a result of interdependent metabolic processes in insulin-sensitive cells [9]. The results of our studies reflect the significant changes of prooxidant-antioxidant homeostasis, lipid profile, ghrelin and leptin blood levels in animals with IR on the background of ID. The physiological level of blood glucose is maintained due to the dynamic balance between the processes of its constant use by various tissues and organs and entry to the bloodstream from liver [1], so we can assume that the development of hepatopathy under

conditions of impaired glucose tolerance may increase the manifestations of IR. It is worth noting the insulin-sensitive action of adiponectins, which is associated with increased sensitivity of hepatocytes and myocytes to insulin, regulation of oxidation of free fatty acids, glucose utilization. It is believed that elevated levels of leptin inhibits the insulin synthesis and makes cells resistant to the hormone action, that contributes to the development of IR and obesity [2]. However, ghrelin has an antiatherogenic effect, is involved in the regulation of blood pressure, prevents inflammatory processes in the endothelium of blood vessels and the development of obesity [8]. The obtained results indicate an increase of leptin level on the background of a decrease the content of ghrelin in the blood, especially in rats with IR on the background of ID, that may exacerbate the manifestations of metabolic disorders, in particular from the cardiovascular system. In addition, it is known that epitheliocytes and fibroblasts of OM are able to synthesize ghrelin, which is locally involved in the immune response in case of infectious lesions of the oral cavity. Therefore, reducing its content along with the activation of peroxidation processes in OM may reduce the local resistance of the oral cavity [7].

Conclusions

1. Development of IR is accompanied by signs of obesity, manifested by a decrease of serum ghrelin level by 64 % against the background of an increase of leptin content by 77 % relative to baseline. An increase of AI almost twice relative to control reflects the possibility of atherogenic lesions of cardiovascular system under such conditions.

2. In rats which were on a high-fructose diet, the intensity of lipoperoxidation processes increases. In homogenates of kidneys, liver, heart and OM, the level of DC increases by 47 % – fifteen times, and TBA-AP content in most of tissues – by 31 % – by 2.5 times to control data. The manifestations of oxidative stress are accompanied by a decrease of K activity by 68 % on the background of GP activation by 50 % relative to control.

3. Impaired glucose tolerance on the background of ID causes more pronounced multifactorial metabolic disorders. The decrease of serum ghrelin content by 42 %, an increase of leptin level by 38 %, activation of lipoperoxidation in most of studied tissues (increase the content of LP products by 25 % – four times) against the background of systemic inhibition of antioxidant reserve (decrease of SOD and CP activity, and Tr level by 21–47 %), a significant increase of proatherogenic lipid fractions relative to the data in animals with isolated IR are found under such conditions.

4. The violation of carbohydrate metabolism potentiates the development of pathological changes in the internal organs, which can cause multiple organ failure, the risk of which increases under conditions of ID. A complex examination of metabolic disorders can promote the early diagnostics of not only endocrinopathies, but also possible complications against the background of their development by separate organs and systems.

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CORRECTION BY THE PREPARATION OF PLANT POLYPHENOLS OF METABOLIC CHANGES OF TISSUES OF RATS ORAL CAVITY UNDER CONDITIONS OF INTRAUTERINE HYPOXIA AND CARIOGENIC DIET

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The work is devoted to the study of the effect of the preparation of plant polyphenols on the dental status and the state of the tissues of the oral cavity of rats under conditions of intrauterine hypoxia and cariogenic diet. The experiment was carried out on 36 white rats of both sexes: 30 females and 6 males. A preparation of plant polyphenols had a caries-preventive and parodontoprotective effect in the offspring of rats under conditions of intrauterine hypoxia and a cariogenic diet. In the oral mucosa, the preparation showed anti-inflammatory and antioxidant effects. The preparation improved state of collagen in the intercellular matrix of the connective tissue of rat parodontal tissue as a result of normalization of the levels of general and free oxyproline in the oral mucosa, as well as general oxyproline in the alveolar bone of rats.

Key words: hypoxia, caries-prophylactic effect, metabolic markers, plant polyphenols, rats.

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КОРЕКЦІЯ ПРЕПАРАТОМ РОСЛИННИХ ПОЛІФЕНОЛІВ МЕТАБОЛІЧНИХ ЗМІН ТКАНИН РОТОВОЇ ПОРОЖНИНИ ЩУРІВ В УМОВАХ ДІЇ ВНУТРІШНЬОУТРОБНОЇ ГІПОКСІЇ ТА КАРІЄСОГЕННОГО РАЦІОНУ

Робота присвячена вивченню впливу препарату рослинних поліфенолів на стоматологічний статус і стан тканин ротової порожнини щурів в умовах дії внутрішньоутробної гіпоксії та карієсогенного раціону. Дослід проведено на 36 білих щурах обох статей: 30 самок і 6 самців. Препарат рослинних поліфенолів в умовах дії внутрішньоутробної гіпоксії і карієсогенний раціон у потомства цих щурів мав карієспрофілактичну і пародонтопротекторну дію. У слизовій оболонці порожнини рота препарат проявив протизапальну і антиоксидантну дію. Під дією препарату поліпшувався стан колагену міжклітинного матриксу сполучної тканини пародонту щурів в результаті нормалізації рівнів загального та вільного оксипроліну в слизовій оболонці порожнини рота, а також загального оксипроліну в кістці альвеолярного відростка щурів.

Ключові слова: гіпоксія, карієс-профілактична дія, метаболічні маркери, рослинні поліфеноли, щури.

The work is a fragment of the research project "Influence of hypoxia on the processes of collagen formation and mineralization on models of dental pathology and correction of the obtained disorders", state registration No. 0118U006963.

Hypoxia is a typical pathological process that occurs when there is insufficient oxygen supply to tissues or when its utilization is impaired. There are several types of hypoxic conditions, among which tissue or histotoxic hypoxia has been studied. This type of hypoxia develops as a result of a violation of the ability of cells to absorb oxygen (with its normal delivery to cells) or in conditions of a decrease in the effectiveness of biological oxidation as a result of the uncoupling of oxidation and phosphorylation processes.

Utilization of oxygen by tissues can be hampered by the action of various inhibitors of biological oxidation enzymes, changes in the physicochemical conditions of their action, disruption of the synthesis of tissue respiration enzymes.

One of the most important pathogenetic factors in the development of tissue hypoxia is the disintegration of the structure of mitochondrial membranes, which occurs under the influence of various etiological factors – bacterial, hormonal imbalance, during aging of the body [12].

Fetal hypoxia is a complex of changes in the fetus' body due to insufficient oxygen supply, which leads to fetal growth retardation, the appearance of developmental abnormalities. In children who have undergone hypoxia in the antenatal period, the incidence of developmental delays is significantly increased, and an increase in the incidence of caries is shown in comparison with healthy children. [3]. They develop