

ORIGINAL ARTICLE

MORPHOLOGICAL PECULIARITIES OF THE PANCREAS OF MALE RATS AFTER PROLONGED ADMINISTRATION OF MONOSODIUM GLUTAMATE DURING THE RECOVERY PERIOD

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ABSTRACT

The aim: To study changes in the exocrine and endocrine parts of the pancreas of rats after abolition of monosodium glutamate (MSG) administered in the diet.

Materials and methods: White male laboratory rats with a baseline weight of 120 ± 5 g were randomized into 3 groups: 1 – control, 2 – animals with daily feeding of 70 mg/kg MSG for 8 weeks, 3 – abolition of MSG with transfer of animals to a standard diet and pancreatic examination after 8 weeks. We used histological studies with morphometric analysis and statistical processing of acini and acinar cell areas, Langerhans islets, connective tissue (according to Stolte M.) and adipose tissue. Preparations of pancreas were stained with hematoxylin and eosin and azan.

Results: The animals of groups 2 and 3 showed atrophic, degenerative and inflammatory disturbances in the exocrine and endocrine parts of the pancreas, which worsened after 8 weeks of MSG withdrawal (3rd group). In the preparations, the Langerhans islets were of different shapes and sizes. Small islets predominated, as well as islets with low density of α- and β-cells, different capillary filling with blood and overgrowth of connective tissue in the capillary areas. The acinar cells and acini were reduced, and degenerative abnormalities were detected in the structures.

Conclusions: After daily administration of 70 mg/kg MSG for 8 weeks, atrophic and degenerative changes in the exocrine and endocrine parts of the pancreas were revealed. No recovery of pancreatic structures was observed 8 weeks after MSG withdrawal.

KEY WORDS: monosodium glutamate, pancreas, experiment, rats

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INTRODUCTION

To date, more than 2500 additives are added to food products to preserve their properties and extend their shelf life. One of the most widely used additives both in Ukraine and around the world is monosodium glutamate (MSG) [1]. Despite the widespread use of MSG in the food industry, some questions about its effects on the body are in the field of debate [2, 3]. The metabolic effects of MSG have been demonstrated in animal studies using different concentrations from 2 mg/kg to 6 g/kg weight [3, 4]. It has been shown that MSG even in low concentrations has a toxic effect on the central nervous system, causes disorders in the liver, kidneys, lymph nodes, spleen, pancreas and reproductive system [2, 5-9].

MSG is of great importance for pancreatic function. According to the data of various studies (molecular-biological, electrophysiological and immunohistochemical) it is established that the cells of islets of Langerhans express functional receptors of MSG [10] and glutamate transporters [11]. These data indicate that glutamate can function as a signal intercellular mediator, modeling glucagon and insulin secretion in Langerhans islets. In addition, glutamate transporters and an antiporter are present in the pancreas. Glutamine entering the pancreas through the bloodstream is metabolized to glutamate in islet cells. Relative to pancreatic cells, glutamate can enter the acinus cells through the islet-acinus ductus axis, but the transporters of this pathway are under investigation. In addition, acini cells can absorb glutamine from their environment and excrete it as glutamate into pancreatic juice [12]. Thus, as defined by the authors, the dynamics of pancreatic glutamate can potentially play a significant physiological role in the homeostasis of the entire body, as well as reflect the endocrine function of the pancreas [12]. In this regard, the administration of exogenous MSG in different concentrations can affect the state of the pancreas. However, while there are fundamental studies on the state of the body's metabolic systems after administration of MSG, studies that would address the possibility of determining the state of the body's organs and systems after its long-term action with subsequent withdrawal of use are limited.

THE AIM

To study changes in the exocrine and endocrine parts of the pancreas of rats after abolition of monosodium glutamate (MSG) administered in the diet.

MATERIALS AND METHODS

The experimental study was performed on 20 white male laboratory rats with an initial weight of 120±5 g. Animals were randomized into three groups: Group 1 (n=5) - control rats; Group 2 (n=5) - experimental animals given MSG for 8 weeks, were removed from the experiment and served as a control for Group 3, in which 5 animals received MSG for 8 weeks and were then transferred to a standard diet, and after 8 weeks these animals were removed from the experiment to evaluate the recovery process in the pancreas. The animals were housed in individual well ventilated cages in the vivarium of the Daniel Galitsky Lviv National Medical University. The experiment was conducted in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986) [13] and was guided by the protocol of the Bioethics Commission of the Daniel Galitsky Lviv National Medical University.

ADMINISTRATION OF MSG

The rats were weighed before the experiment and at its stages. To assess the condition of the pancreas, the rats of the experimental group were given daily food with supplement MSG in a dose of 70 mg/kg for 8 weeks [14.]. MSG was administered orally. In conversion, our chosen dose of 70 mg/kg for the rat is equivalent to 700 or 816 mg for humans weighing 60 or 70 kg, respectively [15, 16]. The control group of animals received a standard diet without the addition of MSG. After 8 weeks, MSG was abolished and the animals were switched to a standard diet. After 8 weeks the animals were removed from the experiment under anesthesia by decapitation, which was necessary to collect blood for further biochemical studies.

HISTOLOGICAL INVESTIGATION

Rat pancreas was fixed in a 10% solution of neutral formalin, dehydrated in ascending alcohols (ethanol), cleared in xylene, and embedded in paraffin. Serial sections of 7-10 μm thickness were obtained on a Reichert microtome (Austria). Dewaxed sections were stained with hematoxylin and eosin (combination) and azan. Morphometric studies were performed using Test-5, Stepanizer, KAAPA Image, Base, and Microsoft Excel programs on a personal computer using a visual analysis system. Images of histological preparations were displayed on a computer monitor using an SEO SCAN microscope and a Vision CCD Camera.

Exocrine and endocrine parts of the pancreas were examined. The exocrine part of the pancreas was analyzed by evaluating the area of acini and acinar cells. Appearance of fibrous disorders was estimated according to Stolte M. [17]. The author classified 4 degrees of fibrotic changes depending on the location of the connective tissue in the organ (diffuse or segmental fibrosis). Grade I was defined as predominantly perilobular fibrosis with mild atrophy or without atrophy of exocrine parenchyma, i.e. mild fibrosis. If fibrosis has spread into pancreatic portions with moderate atrophy of exocrine parenchyma, is regarded as moderate fibrosis (grade II). In case of wide areas of fibrosis in intralobular sections accompanied by atrophy of exocrine parenchyma, they are defined as degree III, i.e. high degree of fibrosis. Under fibrous reconstruction of pancreas accompanied by destruction of exocrine parenchyma was defined as IV degree of fibrosis. Fat tissue was assessed according to a scoring system: 0 – single islets of adipocytes in the areas of vascular triads, 1 point –single foci of adipose tissue between lobules, 2 points – about 30% between lobule septa, 3 points – overgrowth in interlobular septa and interacinar spaces. We assessed larger diameter of Langerhans islets (μm), as well as the percentage of Langerhans islets with connective tissue overgrowth to islets without fibrosis.

STATISTICAL ANALYSIS

Two hypotheses were tested as a result of the statistical analysis of the experimental series: H_0 - indicating no difference between the averages in the compared groups and H_1 an alternative hypothesis based on the assumption that the averages in these groups are not equal. The level of statistical significance was assumed to be $p < 0.05$. Data were presented as M±m, where M is the mean value, m is the standard arithmetic deviation. Comparative analysis of the experimental data including normally distributed (diameter of Langerhans islets, acinar cell area and acini area) was performed using One Way Anova analysis of variance with the addition of Tukey's honestly significant difference test (Tukey's HSD), which is based on a studentized range distribution (Q) (this distribution is similar to the t-test). Dispersion analysis ANOVA shows the presence or absence of statistically significant differences (p) between compared variables using the F-criterion (ratio of between-group (factor) variance to within-group (residual) variance). However, ANOVA is not sufficient to decide how exactly the groups differ from each other. Tukey's HSD test provides a test of the differences between the paired means of a sample for significance, controlling for the probability of committing One Way Anova error, and also shows which means of particular groups (when compared with each other) differ in magnitude.

The non-parametric Mann-Whitney U-test was used to assess differences between two independent samples (islets with fibrotic changes). If Ukr > Uemp (Ukr is the value from the Mann-Whitney table; Uemp is the estimated value), the hypothesis of a significant difference in the compared experimental groups (H_1) was accepted; If Ucr < Ump, there is no effect (H0). (H_0).

RESULTS

After 8 weeks of feeding rats with food including MSG, degenerative and destructive disorders were found in the exocrine and exocrine parts of the pancreas. Marked edema of the organ was observed. Reduction of acini size, their delimitation from each other by layers of loose connective

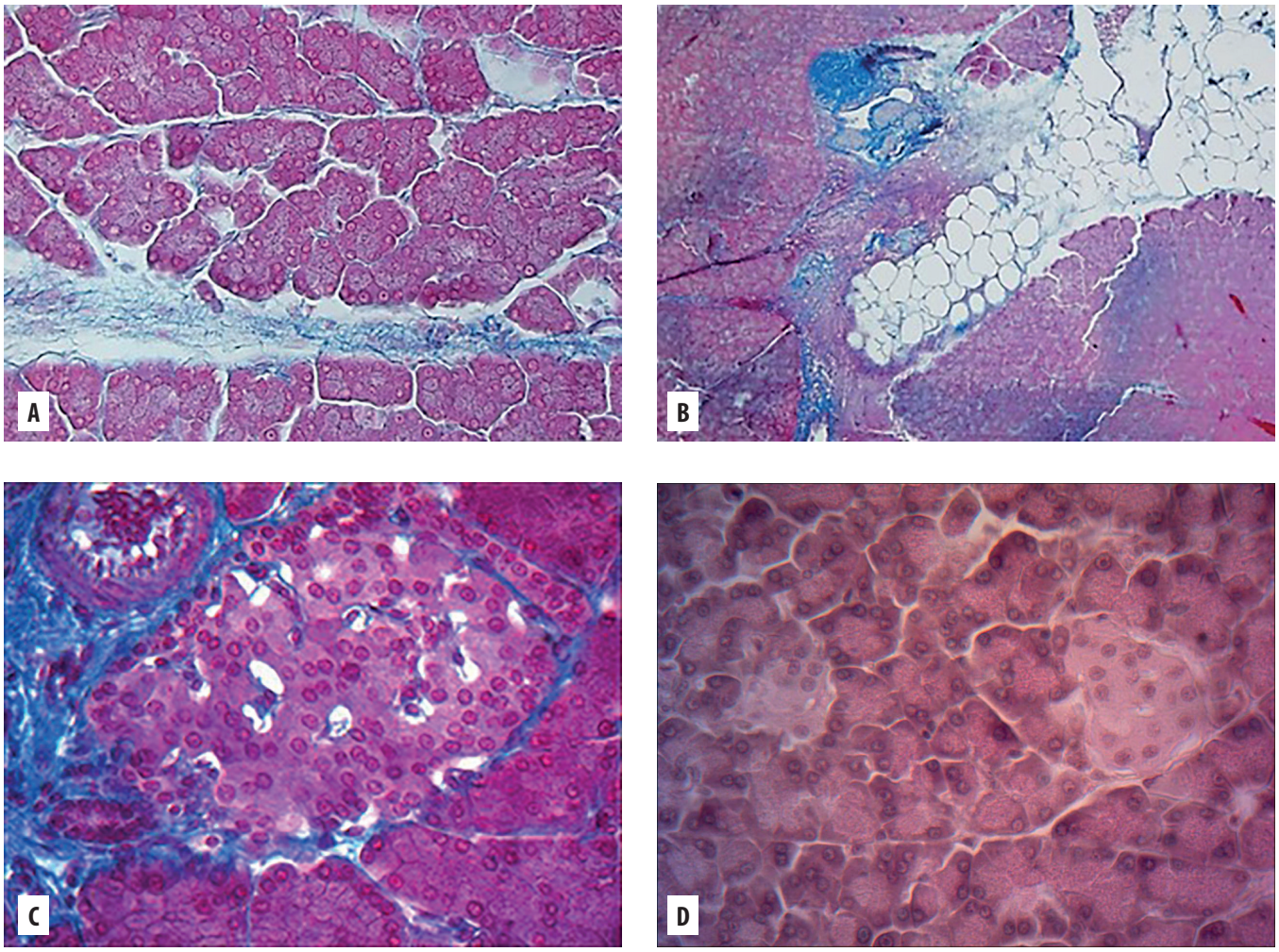

Fig. 1. 8 weeks of MSG administration. Fragments of rat pancreas. A. Acini of reduced size, overgrowth of loose connective tissue. Azan. X 200. B. Replacement of lobules with fatty tissue, edema, overgrowth of connective tissue. Azan. X 200. C. Langerhans islet. Connective tissue in capillary spaces. Adjoining acini crowded with zymogenic granules. Azan. X 400. D. Langerhans islet. Single β-cells. Hematoxylin and eosin. X400.

tissue was noted (Fig.1 A). Connective tissue overgrew between acini and in the spaces between lobules that resulted in acini deformity. According to Stolte M. [17], at 8 weeks after cessation of feeding animals with sodium glutamate a grade II fibrosis was noted.

Areas of lymphocytic infiltration located between acini and lobules were detected. Some acini and even lobules were replaced by adipose tissue, marked borders of adipose tissue, which was localized in triads, and around ducts (Fig. 1. B). The ducts, both interstitial and acini, were dilated and filled with vacuolized fluid; edematous fluid was present between the acini, leading to their separation and destruction. Vessels were sharply dilated, full of blood, small extravasations were formed.

Acini were of different shapes and sizes, but small acini prevailed. There was revealed pycnosis of exocrinocytes, more such cells were located in marginal parts of the gland and in the areas of edematous fluid accumulation. Exocrinocytes were irregularly filled with zymogenic granules, nuclei were characterized by heteromorphism, from small hyperchromic with dense chromatin to large hypochromic with diffuse chromatin distribution.

Langerhans islets in the preparations were of different shapes and sizes. Small islets prevailed, as well as islets with low density of α- and β-cells (Fig. 1. C). A peculiarity was different capillary filling with blood and overgrowth of connective tissue in the capillary sections (Fig. 1.D).

After cancellation of MSG and feeding rats with standard food for 8 weeks of the study were revealed: an increase in atrophic, degenerative and inflammatory manifestations. Signs of edema were preserved and increased degenerative changes were detected in both exocrine and endocrine parts of the pancreas. Overgrowth of loose connective and fatty tissues was revealed. The acini in most areas of the pancreas were disconnected due to oedema, small acini predominated, some with destructive changes. A pairwise comparison (One-Way ANOVA test) of the acinus area values of the experimental series yielded statistically significant results: 1:2 ($p = .00013$), 1:3 ($p = .00000$) and 2:3 ($p = .02940$) (Table I). A pairwise comparison of the series with a further validation by The Tukey's HSD test confirmed the validity of the One-Way ANOVA test, showing that the direction of destructive changes of the acini was highly significant in

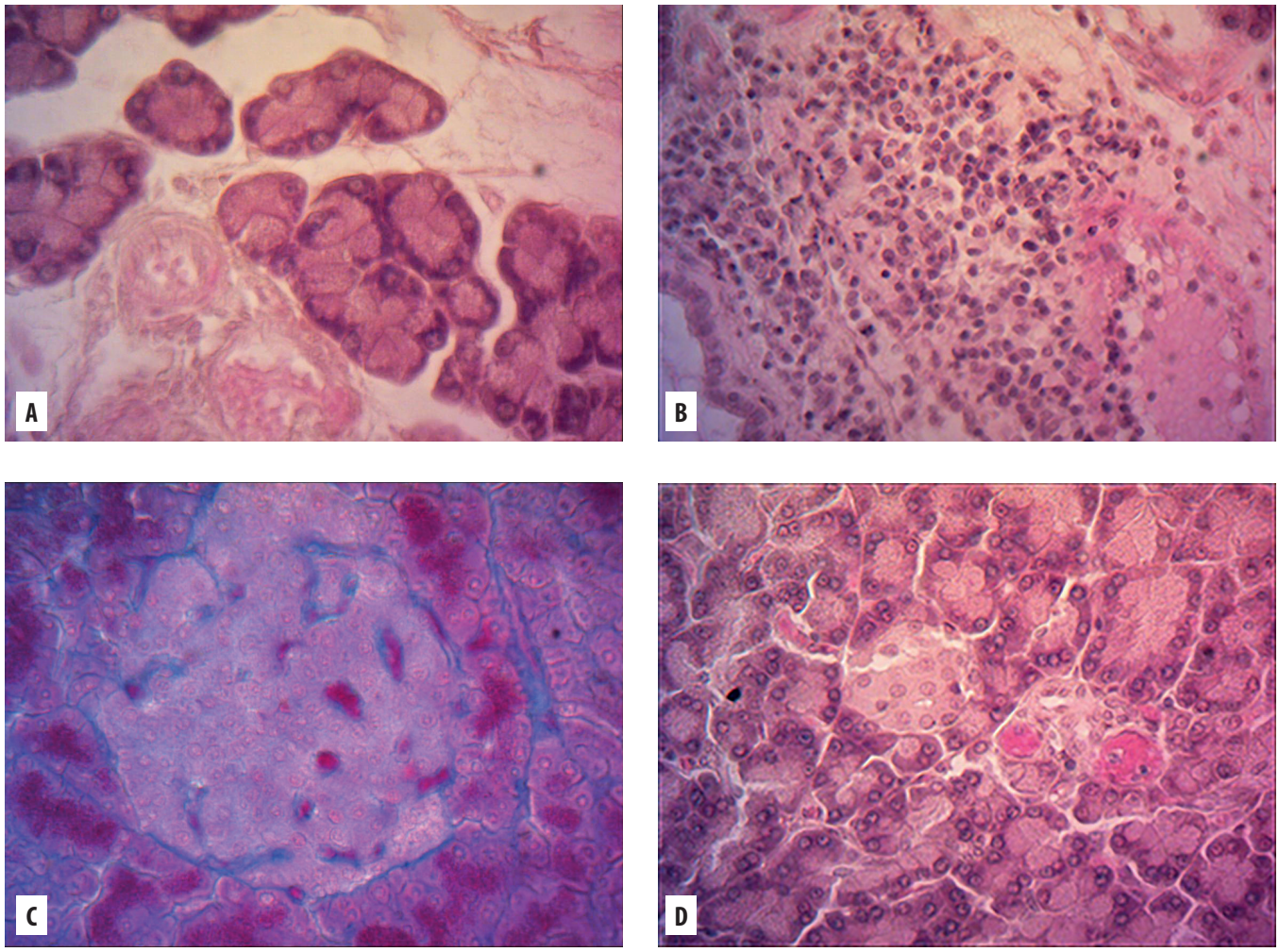

Fig. 2. 8 weeks after MSG withdrawal. Fragments of rat pancreas. A. Edema. Detachment of acini. Destruction. Remains of ductal system. Destruction of vessels. Hematoxylin and eosin. X 400. B. Lymphoplasmacytic infiltration. Edema. Disturbance of duct wall. Ductal epithelium flattened, desquamated in places. Hematoxylin and eosin. X 400. C. Langerhans islet with overgrowth of connective tissue. Azan. X 400. D. Small islets of Langerhans. Low density of α- and β-cells. Dilated vessels with stasis in and near the islet. Hematoxylin and eosin. X400.

the compared series 1:3, less so in 1:2, the lowest values were recorded in the 2:3 series, but the validity of the difference indicated a progression of the abnormalities after withdrawal of the MSG. A pairwise comparison (One-Way ANOVA test) in the experimental groups (1:2, 1:3, 2:3) showed statistically significant results for the acinar cell area in the pancreas (Table II). The Tukey's HSD test revealed that the highest rates of destruction were seen in the 1:3 series (Table II).

Areas of pancreatic ductal permeability were present, leading to oedema and accompanied by destructive changes of the acini, which were placed among plasmatic eosinophilic substance (Figure 2 A).

Areas with permeable ducts were present, resulting in edema and accompanied by destructive changes in the acini, which were placed among the plasmatic eosinophilic substance (Fig. 2 A). Some were without cells. Diffuse focal infiltration with lymphoid and plasmocytic elements was present for all terms of the study (Fig. 2 B). There was no significant difference between the index of adipose tissue in the pancreas in three series of the experiment.

A decrease in the number, size and shape of Langerhans islets was recorded. Blood supply disorders were noted due to edema and overgrowth of connective tissue in spaces between capillaries (Fig. 2 C), as well as in some islets dilated capillaries were overfilled with blood or empty (Fig. 2 D). Decreased density of **α**- and **β**-cells and their apoptosis were noted. By the end of the experiment, signs of chronic inflammatory process persisted. The count of Langerhans islets with connective tissue overgrowth showed that while this index at the end of MSG feeding (series 2) was (39.1 ± 4.09)%, 8 weeks after cancellation (series 3) it was increased (57.948 ± 3.285)% (p= 0.01208, Mann-Whitney U test).

The assessment of islets of Langerhans with connective tissue overgrowth after 8 weeks of feeding and after 8 weeks of withdrawal showed that while this index at the end of MSG feeding (2^{nd} series) was (39.1 ± 4.09) %, after 8 weeks of withdrawal (3^{rd} series) it was increased (57.95 ± 3.285)%. Assessment of series statistical significance using the Mann-Whitney U test revealed that Ukr 4 > Uemp 1; (p = 0.01208), i.e., hypothesis H1 was accepted, that is, connective tissue overgrowth in islets of

Table I. Comparative analysis of acini area in the series of experiments

Pairwise Comparisons* of the indicators of the experimental series		$HSD_{.05}$ = 93.9938 $HSD_{.01}$ = 119.1378	$Q_{.05}$ = 3.4358 $Q_{.01}$ = 4.3549
1:2	1 = 925.07 2 = 748.73	176.33	Q = 6.45 (*p* = .00013)
1:3	1= 925.07 3= 646.00	279.07	Q = 10.20 (*p* = .00000)
2:3	2 = 748.73 3 = 646.00	102.73	Q = 3.76 (*p* = .02940)

* One-Way ANOVA test used; The Tukey's HSD – honestl significant difference

Table II. Comparative analysis of acinar cell area in the series of experiments

Pairwise Comparisons* of the indicators of the experimental series		$HSD_{.05}$ = 9.5619 $HSD_{.01}$ = 12.1198	$Q_{.05}$ = 3.4358 $Q_{.01}$ = 4.3549
1:2	1= 84.59 2= 73.51	11.07	Q = 3.98 (*p* = .01989)
1:3	1= 84.59 3= 62.62	21.97	Q = 7.89 (*p* = .00000)
2:3	2= 73.51 3= 62.62	10.89	Q = 3.91 (*p* = .02231)

* One-Way ANOVA test used; The Tukey's HSD – honestl significant difference

Table III. Comparative analysis of changes in the diameter of Langerhans islets in the series of experiments

Pairwise Comparisons* of the indicators of the experimental series		$HSD_{.05}$ = 9.5619 $HSD_{.01}$ = 12.1198	$Q_{.05}$ = 3.4358 $Q_{.01}$ = 4.3549
1:2	1= 133.67 2= 104.78	28.89	Q = 4.87 (*p* = .00365)
1:3	1= 133.67 3= 79.93	53.75	Q = 9.07 (*p* = .00000)
2:3	2= 104.78 3= 79.93	24.85	Q = 4.19 (*p* = .01350)

* One-Way ANOVA test used; The Tukey's HSD – honestl significant difference

Langerhans was increased 8 weeks after discontinuation of MSG feeding.

Use of a One-Way ANOVA test showed statistical significance in pairwise comparisons of islet Langerhans diameter of experimental series 1:2 (p = .00365), 1:3 (p = .00000), 2:3 (p = .01350) (Table III). The Tukey's HSD paired series comparison analysis with additional validation confirmed the statistical significance of the increase in small islets in the pancreas of the paired series with a high value in the 1:3 series. After discontinuation of the MSG, by the end of the study (2:3), an increase in the pancreas of small-diameter islets of Langerhans was recorded in the pancreas of rats.

DISCUSSION

The use of nutritional supplements is of great interest to researchers to evaluate their various side effects on the body. A large number of experimental studies have shown negative effects of MSG (E 621) on organs and body systems [3, 6, 18,19]. In our study, the effect of MSG on the pancreas of rats at a dose of 70 mg/kg weight was evaluated using histological methods. The data obtained indicate that MSG after 8 weeks of use has an inhibitory effect on the endocrine and exocrine parts of the pancreas, and after cancellation of MSG there is no restoration of its structural organization. After MSG action there is pancreatic edema, which persists during the stages of MSG withdrawal, which leads to separation of acinar structures and their death. A decrease in the area of acini, a change in their shape and a decrease in the area of acinar cells, which is reflected in their metabolism, are noted. The revealed changes under the conditions of histological and morphometric study reflect the toxic effect of MSG, which should be considered in combination with other negative effects on other systems of the body. Thus, adipose tissue formation under the influence of MSG promotes the biosynthesis of proinflammatory cytokines by adipocytes, these molecular factors activate apoptosis, disrupt intercellular interactions and adaptive reserves of phagocytes [2, 20]. In addition, the progression of structural disorders of the pancreas after withdrawal of MSG may be associated with imbalances in the immune system, increased cytotoxic function of immunocompetent cells. In addition, potential triggers of the inflammatory process can be cellular hypoxia, mechanical stress of adipocytes, excess of free fatty acids and lipopolysaccharides [21]. It has been proved that even low doses of MSG, namely,

the administration of MSG to rats at a dose of 30 mg/kg for a short period of 4 weeks leads to an increase in the serum content of total and tyrosine-containing peptides, affects the content of low and medium molecular weight substances, and also leads to an increase in the index of intoxication factor, which indirectly indicates a violation of the detoxification of endogenous metabolites in the liver of animals [22]. It can be assumed that the toxic effect of MSG on AA transporter (EAAC), identified only in acinar cells, leads to early atrophic and destructive changes in the acini. Combined with the literature data that in the pancreas identified glutamate receptors and transporters, namely in Langerhans islets AA type L (LAT1), glutamate 1 (GLT1), glutamate-aspartate (GLAST), cystine-glutamate antiporter (xCT), the latter also identified in duct cells [23]. We can speculate that the toxic effect of MSG 70 mg/kg leads to damage to transporters in Langerhans islets and acini.

CONCLUSIONS

The nature and degree of expression of changes in histomorphometric parameters of rat pancreas after prolonged action of MSG and in 8 weeks after its cancellation indicate the presence of morphological signs of decrease in its exo- and endocrine activity. In the rat pancreas we detected progression of degenerative changes in comparison with the control series and after cancellation of MSG: enlargement of connective tissue, edema of organ parenchyma, disorders of vessels and ducts walls with fluid going out into interacinaric spaces, enlargement of diffuse-focal inflammatory infiltration area. When assessing statistical significance, a decrease in the area of acini and acinar cells, reduced diameter of Langerhans islets and increased islets with overgrowth of connective tissue were revealed. Immediately after drug withdrawal, there were no cells in some acini, acinar cells had small nuclei with dense chromatin. The data presented suggest a toxic effect of MSG on the pancreas during the intake phase and progression of degenerative changes after withdrawal.

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