# Changes in the Structural Organization of Lymph Nodes and Biochemical Indicators of Blood Due to the Action of Sodium Glutamate

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**Abstract**

The objective of the research was to study the histological, morphometric and electron microscopic changes of the parenchyma of the lymph nodes and biochemical parameters of the blood of rats under the action of monosodium glutamate for eight weeks.

The paper presents and analyzes data from an experimental study conducted on 40 white rats in females and males of reproductive age.

After eight weeks of exposure to monosodium glutamate there is a significant decrease in the relative area of the cortical substance in the parenchyma of the lymph nodes and, accordingly, an increase in the relative area of the medullary substance compared with the intact group of animals. Histologically in the parenchyma of the lymph nodes the lumen of the marginal sinus, cortical and medullary intermediate lymphatic sinuses is expanded, the proportion of reticular connective tissue in it increases, and the proportion of lymphocytes decreases, all parts of the vascular bed undergo changes. Electron microscopically a large number of lymphocytes with signs of karyolysis and karyorrhexis, intercellular spaces are expanded, contain cellular detritus and osmophilic (fatty) inclusions, perivascular spaces are clarified, with signs of edema.

Mesenteric lymph nodes change under the influence of monosodium glutamate for eight weeks. Blood levels of glucose, cholesterol, LDL and HDL increase.

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## Introduction

One of the most common food additives in Ukraine and in the world is monosodium glutamate (MSG, C5H8NO4NaH2O).[1] The monosodium salt of glutamic acid (sodium glutamate), commonly known as the flavor enhancer, is used in most commercial foods. The definition of food additive has changed during time, being today defined as «any substance not normally consumed as a food by itself and not normally used as a typical ingredient of the food, whether or not it has nutritive value, the intentional addition of which to food for a technological purpose in the manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food results, or may be reasonably expected to result (directly or indirectly), in it or its by-products becoming a component of or otherwise affecting the characteristics of such foods».[2]

Through its stimulation of the orosensory receptors and by improving the palatability of meals, MSG influences the appetite positively, and induces weight gain.[3] That is why adding MSG to food simulates a high calorie diet (HCD). Despite its taste stimulation and improved appetite enhancement, reports indicate that MSG is toxic to human and experimental animals.[3,4,5]

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The systematic use of products with glutamate in humans violates the hormonal balance, problems with digestion, gastritis and gastric ulcer, obesity can develop. Animal studies show that sodium glutamate can cause hypothalamic lesions and resistance to leptin, possibly affecting energy balance, leading to overweight.[6] Excess body weight and obesity is a recognized risk factor for metabolic diseases[7], including insulin resistance[8,9], type 2 diabetes, hypertension[10], non-alcoholic fatty liver disease, splenomegaly[11], exacerbation of autoimmune diseases[12], polycystic ovaries and some cancers, etc.

The urgent issue for both morphologists and clinicians remains the question of the possibility of structural and functional changes in the internal organs, in particular organs of the immune system, due to the prolonged use of dietary supplements. Lymph nodes belong to the secondary lymphoid (immune) organs, are biological "filters" in the human body, provide protection of the body against genetically alien cells and substances coming exogenous or endo-pathways.[13, 14] Lymphocytes and macrophages are among the major cells involved in the immune response. [15,16,17]

The objective of the research was to study the histological, morphometric and electron microscopic changes of the parenchyma of the lymph nodes and biochemical parameters of the blood of rats under the action of monosodium glutamate for eight weeks.

## Materials and methods

The study was conducted on 40 white rats of male and female reproductive age (2.5-6.5 months) weighing 120-280 g.

Peculiarities of the structure of structural components and vascular bed of mesenteric lymph nodes of white rats under physiological norm were studied in 10 intact animals, 5 of which were male rats and 5 female rats. The experimental animals (20 animals) were on the HCD for eight weeks, of which 10 were male rats and 10 were female rats. HCD was achieved by adding to the diet of monosodium glutamate at a dose of 0.07 g/kg body weight of rats.

The control was 10 white rats, of which 5 male rats and 5 female rats. This group of animals received a standard diet of vivarium instead of a high-calorie diet for eight weeks to exclude age-related changes in the organ.

All experimental animals were kept in the vivarium of Lviv National Medical University named after Danylo Halytskyi. The studies were 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), Council of Europe Directives 86/609 / EEC (1986), Law of Ukraine No. 3447-IV «On the Protection of Animals from Cruelty behavior», the general ethical principles of animal experimentation, approved by the First National Congress of Ukraine on Bioethics (2001).

Before the material was taken, the animals were numbed with anesthesia. The fixation of the mesenteric lymph nodes was performed with a 1.5% solution of osmium tetroxide in 0.2 M sodium cacodylate solution at pH 7.2 for 2–2.5 hours in the cold. Dehydration in increasing concentrations of ethyl alcohol (50 °, 70 °, 90 ° and absolute) for 30 min each and propylene oxide for 10 min. The material was poured into a mixture of epoxy resins and polymerized for 24 h in a thermostat at 60 °C. The sections were made on a UMTP-6M ultramicrotome using a diamond knife (DIATOM) and double Reynolds and uranyl acetate were contrasted. Sections of lymph nodes were examined using a TEM - 100 transmission electron microscope. Photo material was documented using a SONY - H9 digital camera.
Morphometric studies were performed at specific times on histological specimens stained with hematoxylin and eosin using VideoTest-5.0, CAARA Image Base, Stepanizer, and Microsoft Excel on a personal computer.

Statistical processing of digital data was performed using Excel software and STATISTICA 6.0 using the parametric method. The numerical values of the parameters are represented by sample averages (M), standard deviation (σ), standard error of the mean (m), Student's t test (t). The results of the calculations were presented in graphical form in histograms using Microsoft Office, indicating confidence intervals at 95% confidence level (p = 0.95).

Blood levels of glucose, cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were determined by biochemical analysis of blood.

## Results

Histological and electron microscopic structure of mesenteric lymph nodes of white rats of males and females of intact and control groups corresponds to the species norm. Externally, the organ is covered with a connective tissue capsule, from which lead inside the parenchyma numerous septules or trabeculae. Vessels and nerves pass in trabeculae. The hilum is located on the concave part of the node. The parenchyma consists of the cortical substance of the node, which is located closer to the capsule and occupies the peripheral part of the node, and of the medullary substance, which is closer to the hilum and occupies the central part of the node. The cortical substance contains primary and secondary lymphoid follicles and cortical intermediate lymphatic sinuses. Lymphoid follicles separated from the capsule by the marginal sinus. The area of transition of the cortical substance to the medullary is called the paracortical zone, which contains mainly small subpopulations of T lymphocytes. The medullary substance consists of medullary cords and medullary intermediate lymphatic sinuses (Fig. 1).

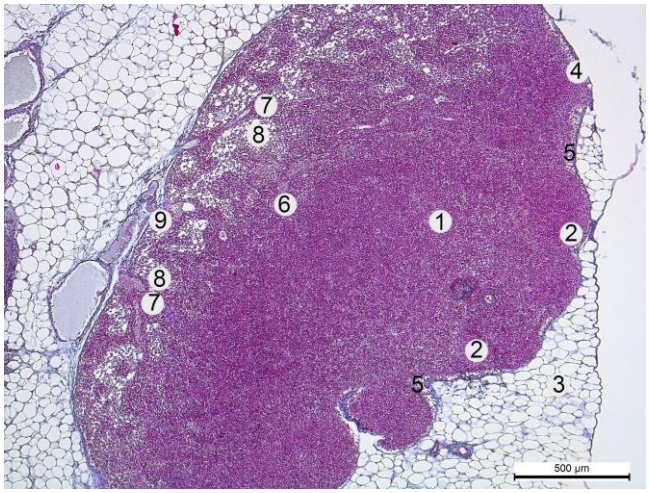


**Figure 1.** The structure of the mesenteric lymph node of an intact white rat male. Azane stained. Magnif: obj. × 5, ocul. × 10. Designation: cortical substance (1) contains lymphoid follicles (2); adipose tissue (3) surrounds the capsule (4); 5 - marginal sinus; 6 - paracortical zone; 7 - medullary cord; 8 - medullary intermediate lymphatic sinus; 9 - the hilum of the node.

Small, medium and large lymphocytes in the parenchyma of the node represent lymphoid tissue. With the help of reticular cells and tissue, the skeleton of the organ is formed. In addition to lymphocytes, the cellular component of the lymph node is represented by plasma cells and macrophages. Reticulo-endothelial cells line the walls of the intermediate lymphatic sinuses. The structure of lymphocytes is typical. Small lymphocytes 6-7 µm in diameter contain a relatively large nucleus, which is surrounded by a narrow area of the cytoplasm. Medium lymphocytes 7-9 µm in diameter have a rounded nucleus, which contains both heterochromatin and euchromatin, organelles are located in the cytoplasm (Fig. 2). Large lymphocytes (lymphoblasts) with a diameter of about 10 µm contain a nucleus, which is mainly euchromatin, so it is lighter than other lymphocytes, the nuclear membrane is smooth, the cytoplasm is light, contains organelles. Heterochromatin, located in the nucleus of plasma cells, resembles a "bycycle spokes", it is located eccentrically, separating the cytoplasm. Each lymph node is supplied with blood from 1 to 10 small branches departing from the nearest arteries. In the thickness of the organ, they pass as part of the trabeculae, branch to the capillaries and gather in postcapillary venules. The venules merge into the veins and leave the node in the area of the hilum.

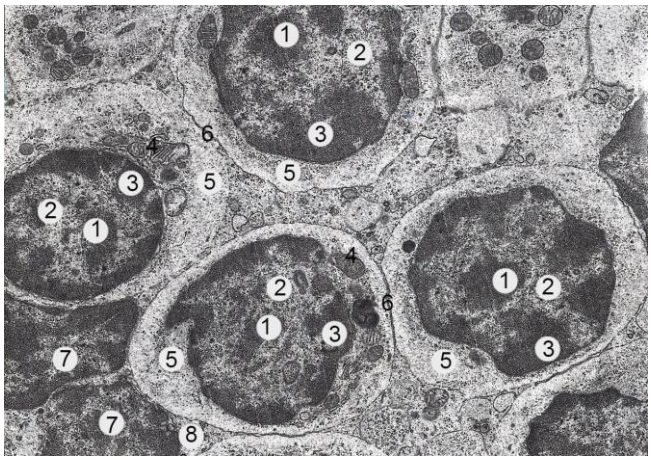

**Figure 2.** Electron microscopic structure of the germinal center of the secondary lymphoid follicles of the mesenteric lymph node of the white rat female intact group. Electronic micrograph. Approx. × 6000. Designation: nucleus of the middle lymphocyte contains the nucleolus (1), euchromatin (2) and heterochromatin (3); ribosomes (4) in the cytoplasm (5) of the middle lymphocyte; the intercellular space is not expanded (6); nucleus (7) and cytoplasm (8) of small lymphocyte.

The blood glucose level of white male and female rats after eight weeks of HCD increases to 7.55 ± 0.1 mmol/l and 7.36 ± 0.09 mmol/l, respectively, which is 27.97% and 22.67% more than intact animals. The level of cholesterol increases to 3.7 ± 0.01 mmol/l and 4.6 ± 0.05 mmol/l, respectively, which is 1.54 and 2.3 times higher than in the intact animals. The level of HDL in the blood of white male and female rats increased to 0.63 ± 0.01 mmol/l and 0.62 ± 0.01 mmol/l, 3.15 and 2.48 times, respectively exceeds intact animals. The level of LDL also increases and is equal to 1.09 ± 0.04 mmol/l and 0.87 ± 0.01 mmol/l, which is 2.79 and 2.18 times correspondingly higher than the rate of intact animals (Table 1).

| Biochemical index of blood | Group name | White male rats | White female rats |
|---|---|---|---|
| Glucose | Intact animals | 5.9±0.09 | 6.0±0.08 |
| | Experimental animals | 7.55±0.1* | 7.36±0.09* |
| Cholesterol | Intact animals | 2.4±0.07 | 2.0±0.05 |
| | Experimental animals | 3.7±0.01* | 4.6±0.05* |
| HDL | Intact animals | 0.2±0.02 | 0.25±0.01 |
| | Experimental animals | 0.63±0.01* | 0.62±0.01* |
| LDL | Intact animals | 0.39±0.02 | 0.4±0.01 |
| | Experimental animals | 1.09±0.04* | 0.87±0.01* |

**Table 1.** Changes of indicators in the biochemical analysis of blood of white rats of intact and experimental groups (mmol/l), (M ± m).
* - values that are statistically significantly different from those of the intact animal group (p <0.05).

| Morphometric index | Group name | White male rats | White female rats |
|---|---|---|---|
| $S_{cortic.subst.}$,% | Intact animals | 61.08±1.56 | 61.23±1.7 |
| | Experimental animals | 54.8±1.6* | 56.12±1.65* |
| $S_{medul.subst.}$,% | Intact animals | 38.92±0.78 | 38.77±0.76 |
| | Experimental animals | 45.2±0.87* | 43.88±0.78* |
| CMI | Intact animals | 1.57±0.11 | 1.58±0.11 |
| | Experimental animals | 1.21±0.2* | 1.28±0.1* |

**Table 2.** Changes in the relative area of cortical and medullary substances and cortical-medullar index (CMI) of lymph nodes of white rats of intact and experimental groups (M ± m).

After eight weeks of HCD there is a significant decrease in the relative area of the cortical substance in the parenchyma of the lymph nodes of white male and female rats to 54.8 ± 1.6% and 56.12 ± 1.65%, which is 10.3% and 8.3% less parameters of the intact group of animals (Table 2).Accordingly, the relative area of medullary substance increases to 45.2 ± 0.87% in male rats, and to 43.88 ± 0.78% in female rats. These figures are 16.1% and 13.2% higher than the parameters of the intact group of animals (Table 2). CMI decreases in both male and female rats by 22.9% and 19.0%, respectively.

After eight weeks of the experiment, in both male and female rats, the lumen of the marginal sinus, cortical and medullary intermediate lymphatic sinuses is expanded, the proportion of reticular connective tissue in it increases, and the proportion of lymphocytes decreases (Fig. 3).

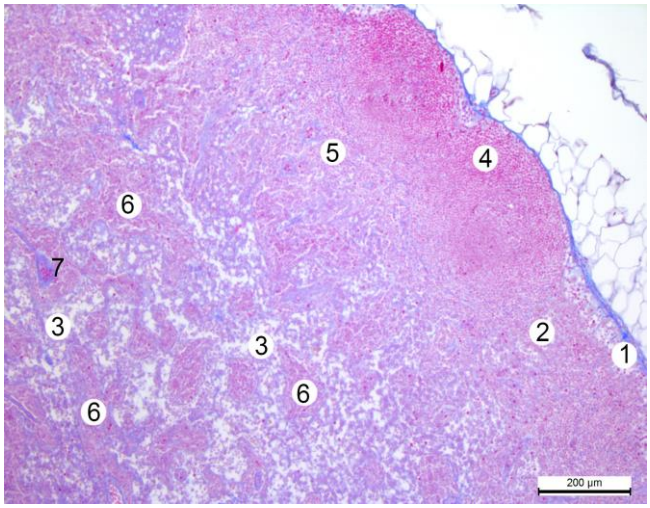


**Figure 3.** A fragment of a mesenteric lymph node of a white female rat after eight weeks of the experiment. Azane stained. Magnif: obj. × 10, ocul. × 10. Designation: enlarged marginal sinus (1), cortical (2) and medullary (3) lymphatic intermediate sinuses; 4 - secondary lymphoid follicles; 5 - paracortical zone; 6 - medullary cord; 7 - full-blooded venule.

Although the relative area of the cortical substance decreases, the number of secondary lymphoid follicles with dilated and enlightened germinal centers in it increases, which indicates the immune activity of the organ. The relative area of the paracortical zone decreases, the number of postcapillary venules with high endothelium in it increases significantly (Fig.4). It is known that this is where the lymphocytes are recirculated from the blood to the parenchyma of the organ. The increase in the number of postcapillary venules in this area indicates an

increase in lymphocyte migration, and hence the activity of this part of the immune defense. B-lymphocytes, plasma cells and macrophages are densely arranged in the medullary cords. Around the node significantly increases the content of adipose tissue compared to the control group of animals.

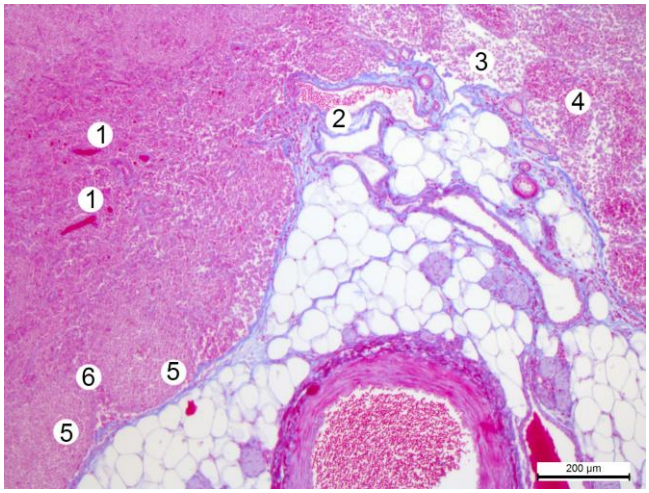


**Figure 4.** A fragment of a mesenteric lymph node of a white male rat after eight weeks of the experiment. Azane stained. Magnif: obj. × 10, ocul. × 10. Designation: full-blooded postcapillary venules (1) in paracortical zone; full-blooded and deformed vein (2) in the hilum of the node; 3 - medullary lymphatic intermediate sinuses; 4 - medullary cord; 5 - lymphoid follicles; 6 - cortical lymphatic intermediate sinuses.

All parts of the vascular bed undergo changes, namely the wall of arteries and arterioles is thickened, with signs of sclerosis, the lumen is filled with formed elements of blood. Veins and venules are dilated and deformed, especially in the area of the hilum of the node, in their lumen there are signs of adhesion and aggregation of platelets (fig. 4). Numerous hemocapillaries with a thickened swollen wall, with a reduced area of the lumen. Vessels with a damaged wall are observed, which leads to hemorrhages in the parenchyma of the organ.

Electron microscopically after eight weeks of action of monosodium glutamate in the parenchyma of the lymph nodes of both male and female rats, a large number of lymphocytes with signs of karyolysis and karyorrhexis, intercellular spaces are expanded, contain cellular detritus and osmophilic (fatty) inclusions, perivascular spaces are clarified, with signs of edema. The cytoplasm of lymphocytes, especially medium and large, is enlightened, contains organelles at different stages of decay. The number of macrophages has increased, in their cytoplasm a large number of cellular detritus and osmophilic (fat) inclusions. An increase in the proportion of collagen fibers and microfibrils is observed in the lumen of the sinuses and in Billroth's cords. The wall of the arterioles is thickened with signs of sclerosis. The nuclei of endothelial cells of irregular oval shape, increased in size. The lumenal surface of their cytolemma contains microvilli, which protrude into the lumen of the vessel, narrowing and deforming it, which complicates blood circulation, in particular in hemocapillaries. Some areas of lumen of blood capillaries are so narrow that they do not allow blood cells to pass (Fig. 5). A large number of lymphocytes in the wall and lumen of postcapillary venules in the paracortical zone may indicate an increase in the processes of recirculation of lymphocytes into the parenchyma of the lymph node from the blood. This explanation confirms the well-known opinion among morphologists that a high-calorie diet leads to the development of obesity, which is a chronic inflammatory process that leads to constant activity of the immune system.

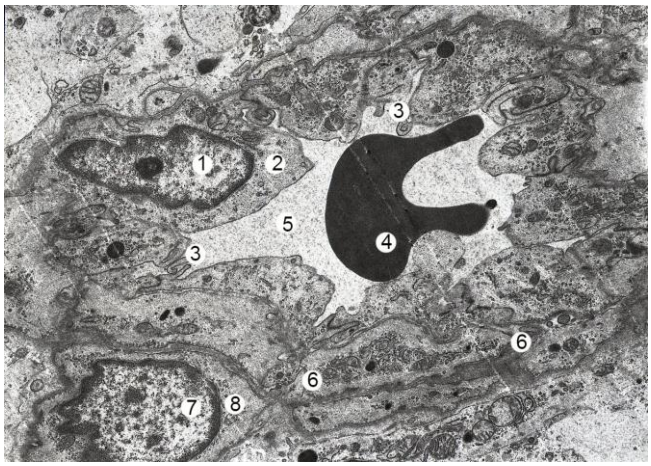


**Figure 5.** Electron microscopic organization of a fragment of the paracortical zone of the mesenteric lymph node of a white female rat of reproductive age after eight weeks of HCD. Electronic micrograph. Approx. × 6000. Designation: 1 - endothelial cell nucleus in the wall of the postcapillary venule; 2 - cytoplasm of endothelial cells; 3 - cytolemma processes on the lumenal surface of the endothelial cell; 4 - deformed erythrocyte in the lumen (5); 6 -

stratified and swollen basement membrane of the vessel; 7 - nucleus and cytoplasm (8) of a lymphocyte that migrates from the lumen of the postcapillary venule into the parenchyma of the node.

## Discussion

Similar changes were detected in blood vessels of the hemomicrocirculatory bed of the lymph nodes with nalbuphine administration during six weeks. Lumen of hemocapillaries was expanded, filled mainly with destructively altered erythrocytes, somewhere the integrity of the walls of hemocapillaries was violated with the release of the formed blood elements into the perivascular space; endothelial cells nuclei are increased, irregular, cytoplasm was edematous with damaged organelles; basal membrane is thickened; perivascular space is swollen and enlarged.[14]

The authors describe that obesity caused by a high-calorie diet leads to cell death and macrophage activation. Obesity-related inflammation induces fibrosis in the lymph nodes and probably contributes to the enlargement of the sinus lumen and subsequently to the reduction of immune cell interactions. The resulting effects of immune regulation are likely to contribute to the suppression of immunosuppression and dysfunction of lymphatic vessels during obesity.[18]

Obesity also resulted in significant changes in the macro and microscopic anatomy of lymph nodes as reflected by a marked decrease in size of inguinal lymph nodes (3.4-fold), decreased number of lymph node lymphatics (1.6-fold), loss of follicular pattern of B cells, and dysregulation of CCL21 expression gradients. Finally, obesity resulted in a significant decrease in the number of lymph node T cells and increased number of B cells and macrophages.[19]

Results of scientists indicated a shift of the markers of intoxication syndrome towards mainly catabolic substances. The results obtained after one week of the experiment correspond with phase of partial compensation, characterized by increased concentrations of low and middle molecular weight substances in red blood cells and plasma. After two weeks and up to one month of the experiment, the predominantly catabolic markers of endogenous intoxication continue to increase in erythrocytes and plasma, indicating a shift to the phase of partial decompensation to systems and organs of detoxification. In conclusions the administration of monosodium glutamate at a dose of 30 mg/kg body weight was associated with development of excessive contents of low and middle molecular weight substances with reduced ability of kidneys to excrete toxic products.[1]

Prospects for further development are related to the study of morphometric, histological and electron microscopic changes in the structural components of rats lymph nodes and biochemical indicators of blood under conditions of correction of the action of sodium glutamate.

## Conclusions

As a result of a study conducted on male and female rats, we found:

1. After eight weeks of exposure to monosodium glutamate there is a significant decrease in the relative area of the cortical substance in the parenchyma of the lymph nodes and, accordingly, an increase in the relative area of the medullary substance compared with the intact group of animals. Blood levels of glucose, cholesterol, LDL and HDL increase.
2. Histologically in the parenchyma of the lymph nodes the lumen of the marginal sinus, cortical and medullary intermediate lymphatic sinuses is expanded, the proportion of reticular connective tissue in it increases, and the proportion of lymphocytes decreases, all parts of the vascular bed undergo changes.
3. Electron microscopically a large number of lymphocytes with signs of karyolysis and karyorrhexis, intercellular spaces are expanded, contain cellular detritus and osmophilic (fatty) inclusions, perivascular spaces are clarified, with signs of edema.

## Declaration of Interest

The authors report no conflict of interest and the article is not funded or supported by any research grant.

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