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# The Protective Effects of N-Carbamylglutamate on Changes in the Testicular Tissue Structure of Newborn Mice Induced by Monosodium Glutamate

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## ABSTRACT

**Background and Objective:** Monosodium glutamate (MSG) is widely used in convenience food and oxidative damage caused by the consumption of this compound has been proven. On the other hand, N-carbamylglutamate (NCG) plays a key role in protecting cells against thermal and oxidative stress. The aim of this study was to investigate the protective effects of NCG on the changes in the testicular tissue structure of baby mice caused by MSG consumption.

**Methods:** In this experimental study, 24 pregnant mice were randomly divided into four equal groups of six. The first group received 60 mg/kg MSG intraperitoneally, the second group received 500 mg/kg NCG by gavage, the third group received 500 mg/kg MSG and 60 mg/kg NCG simultaneously, and the fourth group received the same volume of normal saline as the other groups from the first day of pregnancy until delivery. On the 21st day of pregnancy and after the birth of the babies, the weight, head-to-tail length, and abdominal circumference of the newborns were examined, and then slides were prepared from the testicular tissue of the male babies and examined and compared under a light microscope.

**Findings:** The use of NCG increased the cephalo-caudal index (39.26±1.99) compared to the MSG group (34.05±0.67) (p=0.038). The use of MSG increased the mean thickness of the testicular capsule (13.35±0.75), which was statistically significant compared to the NCG group (11.85±0.9) (p=0.043). The use of NCG also significantly increased the diameter of the seminiferous tubules (56.57±5.17) compared to the MSG group (52.25±4.79) (p=0.031). The mean number of spermatogonial stem cells in the NCG group (25.13±3.29) was significantly higher compared to the MSG group (32.15±2.36) (p=0.021).

**Conclusion:** From the results of this study, it can be concluded that the use of NCG can reduce the negative effects of MSG on testicular tissue.

**Keywords:** *Monosodium Glutamate, N-Carbamylglutamate, Testis, Mouse*.

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## Introduction

Monosodium glutamate (MSG) is a very common amino acid in the natural environment. It is used as a food preservative, either in the form of hydrolyzed protein or as the purified monosodium salt. It can be found in frozen foods, tuna, broths, nutritional supplements, infant formula, and several other food products (1-5). Several studies have demonstrated the tissue toxicity of this compound on various human and animal tissues. Research on the effects of this substance has shown that MSG causes changes in cellular structure and function by producing compounds such as reactive oxygen species and subsequently causing oxidative stress (6-10). Various studies have indicated the effects of MSG on the male reproductive system, such as reduced fertility, reduced growth rate, reduced gonadal size, changes in the vascular system of testicular tissue, and impaired sperm production. Studies have shown that exposure to this substance during pregnancy causes adverse effects in the fetus, including brain lesions (11-14).

N-carbamylglutamate (NCG) is a synthetic analogue of N-acetylglutamate. It is an activator of the enzyme carbamyl phosphate synthase-1 (CPS-1). This enzyme plays an important role in the urea cycle and endogenous arginine synthesis (15, 16). It is currently used as an effective food additive to provide the amino acid arginine. The use of NCG in the diet promotes intestinal growth and the expression of heat shock protein 70 (Hsp70) (17, 18). The antioxidant effects of this compound have been confirmed in several studies. Dietary supplementation with NCG significantly improves total antioxidant capacity (T-AOC) and glutathione peroxidase (GSH-Px) activity in seminal plasma. In addition, this compound increases libido and improves protein quality in seminal plasma (19-24).

Various studies have investigated the antioxidant effects of NCG on various tissues of the adult animal body and male reproductive function, but so far, the effect of this substance on fetal indices and testicular tissue of newborns has not been investigated. Therefore, this study was conducted to investigate the role of NCG in improving MSG-induced testicular toxicity and reducing oxidative stress in testicular tissues.

## Methods

24 female mice weighing 30 to 35 g and aged 8 to 10 weeks were used in this experimental study. To familiarize them with the environment and reduce stress, the animals were kept for two weeks under standard conditions and free access to food and water in a room at a temperature of 22-25 °C and 12-hour light/12-hour dark cycle at the Faculty of Veterinary Medicine, Tabriz University. The ethics code of the article is FVMUT/2017/108. After two weeks, every two female mice were placed in the same cage with one adult male. The criterion for pregnancy of the mice was the observation of the vaginal plaque after mating. The pregnant mice were randomly divided into four groups of six. From the first day of pregnancy until delivery on day 21, the first group received MSG (L-Glutamic acid monosodium salt hydrate, Sigma-Aldrich, St Louis, MO 63178, USA) at a dose of 60 mg/kg intraperitoneally (6), the second group received NCG at a dose of 500 mg/kg by oral gavage (16), the third group simultaneously received NCG and MSG at doses of 60 and 500 mg/kg intraperitoneally and by oral gavage, respectively, and the fourth group, as the control group, received normal saline in the same volume as the other groups intraperitoneally and by oral gavage once daily.

At the end of the pregnancy and after delivery, the newborns were examined in terms of appearance and after recording the body weight at birth and determining the sex, embryological factors including crown-rump length and abdominal circumference were measured using a digital caliper (Guanglu, China). Then, 6 male newborns from each group were sacrificed and testicular tissue samples were placed in 10% buffered formalin solution for fixation for histomorphometric studies. The samples were subjected to tissue passage

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72 hours after fixation and after preparing paraffin blocks, 6 μm sections were prepared from the samples. Finally, the tissue sections were stained using hematoxylin-eosin and studied using a light microscope (LABOMED CxL, Labo America, Inc.) at different magnifications. Images obtained by a digital camera (Dino-Lite) were used with the help of image analysis software (DinoCapture, Ver. 2, A 1.5.28) to measure microscopic indices such as testicular capsule thickness (Figure 1, black arrow) and seminiferous tubule diameter. Morphometric results were obtained at 100x magnification and the results of the spermatogonial stem cells were obtained at 400x magnification. In each cross-section cut from the testis, 20 seminiferous tubules were examined.

Finally, the obtained data were analyzed using SPSS version 22. After confirming the assumption of normality using the Kolmogorov-Smirnov method, quantitative data were analyzed using one-way ANOVA and Tukey's post hoc test. Data were expressed as Mean±SD and $p<0.05$ was considered significant.

## Results

**Mean body weight and embryological indices:** The results of body weight measurements showed that the mean weight of newborns born to mice receiving MSG was lower compared to the control group, but this was not statistically significant. Also, the use of NCG alone or in combination with MSG increased the mean birth weight compared to the MSG group. The mean head-to-tail length index decreased in the treatment groups compared to the control group. This decrease was significant only in the MSG group compared to the other groups ($p<0.05$). Moreover, the use of NCG together with MSG led to an increase in the mean of the mentioned index. The abdominal circumference index also decreased in the MSG and NCG groups compared to the control group. This decrease was significant in the MSG group compared to the other groups ($p<0.05$) (Table 1).

**Table 1. Mean body weight, head-to-tail length index, and abdominal circumference index in baby mice on the first day of life**

| Variable \ Group | Control Mean±SD | MSG Mean±SD | NCG Mean±SD | MSG+NCG Mean±SD | p-value |
|---|---|---|---|---|---|
| Birth weight (g) | 4.88±0.41[a] | 3.93±0.23 a | 4.95±0.74[a] | 4.26±0.75[a] | 0.572 |
| head-to-tail length index (mm) | 40.32±0.87[a] | 34.05±0.67[b] | 39.26±1.99[a] | 38.39±2.25[a] | 0.038 |
| abdominal circumference index (mm) | 12.27±0.92[a] | 8.84±0.45[b] | 12.69±0.98[a] | 11.03±1.30[a] | 0.024 |

**a and b: indicate a significant difference compared to the other groups ($p<0.05$).**

**Results of histomorphometry study of testicular tissue:** MSG consumption increased the mean thickness of the testicular capsule compared to the control group. The highest increase was observed in the MSG group at 13.35±0.75, which was statistically significant compared to the control and NCG groups ($p<0.05$). In pregnant rats receiving MSG+NCG, the use of NCG caused a decrease in the thickness of the testicular capsule (12.73±0.88) compared to the MSG group, but it was not statistically significant (Table 2). The mean diameter of the seminiferous tubules decreased in all groups compared to the control group. The results of this index also showed that the simultaneous use of NCG and MSG significantly increased the diameter of the seminiferous tubules compared to the MSG group ($p<0.05$). Meanwhile, the use of MSG significantly decreased this index compared to the other groups ($p<0.05$). The use of NCG alone did not cause a significant change in the mean diameter of the seminiferous tubules compared to the control group. Furthermore, the simultaneous use of NCG and MSG significantly decreased the aforementioned index compared to the control group ($p<0.05$) (Table 2).

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**Table 2. Mean testicular capsule thickness and spermatogenic tubule diameter of baby mice**

| Group / Variable | Control Mean±SD | MSG Mean±SD | NCG Mean±SD | MSG+NCG Mean±SD | p-value |
|---|---|---|---|---|---|
| Testicular capsule thickness (μm) | 11.62±1.53[a] | 13.35±0.75[b] | 11.85±0.9[a] | 12.73±0.88[ab] | 0.043 |
| Diameter of the seminiferous tubules (μm) | 60.43±4.70[b] | 25.52±4.79[a] | 56.57±5.17[bc] | 45.51±5.64[c] | 0.031 |

**Different letters, a, b, c, indicate significant differences compared to other groups (p<0.05).**

The mean number of Sertoli cells in the treatment groups decreased compared to the control group. This decrease in the mean number of cells in the MSG group was significant compared to the control group (p<0.05). In addition, the mean cell population in the NCG receiving group and the group receiving the two aforementioned compounds simultaneously was significantly higher compared to the MSG group (p<0.05), which indicates the positive effect of this substance against the negative effects of MSG (Table 3). The average population of primary gonocyte cells in the treatment groups decreased compared to the control group. This population decrease was only significantly observed in the MSG receiving group compared to the control group (p<0.05). Meanwhile, the mean number of primary gonocyte cells in infants born in the NCG receiving group compared to the control group did not show a significant difference. However, the use of NCG alone or in combination with MSG significantly improved the aforementioned index compared to the MSG receiving group (Table 3).

**Table 3. Mean cell population of spermatogenic tubules of baby mice (number of cells in 20 tubes)**

| Group / Variable | Control Mean±SD | MSG Mean±SD | NCG Mean±SD | MSG+NCG Mean±SD | p-value |
|---|---|---|---|---|---|
| Number of Sertoli cells | 19.52±2.48[a] | 13.06±1.85[b] | 19.03±1.97[a] | 17.98±2.37[a] | 0.037 |
| Primary gonocyte cell population | 27.44±3.59[a] | 15.32±2.36[b] | 25.13±3.29[a] | 23.70±4.75[a] | 0.021 |

**a, b: indicate a significant difference compared to the other groups (p<0.05).**

**Results of histological study of the testis:** The results of tissue sections of the gonads showed that the testis was surrounded by a thin connective capsule and the spermatogenic tubules contained two types of cells; Sertoli cells in the peripheral part of the tubules with structural features including a large spherical nucleus and a prominent nucleolus, and primitive gonocyte cells with a bright nucleus with characteristics of dividing cells that occupied the middle part of the tube (Figure 1, a and d). In some sections of the seminiferous tubules, spermatogonia cells with spherical and dark nuclei were occasionally observed. The space between the spermatogenic tubules was occupied by thin connective tissue containing cells with endocrine characteristics and blood vessels. The histomorphological structure of the gonads in infants born in the NCG experimental group was similar to the control group (Figure 1, c). The results of histomorphological studies in the MSG receiving group showed that the testicular tissue in infants of this group had undergone some changes compared to the other groups. The most significant and obvious changes were in the cell population in the seminiferous tubules. Among them, the spermatogonia cell population decreased (Figure 1, b). In the group receiving NCG and MSG simultaneously, these changes were reduced (Figure 1, d).

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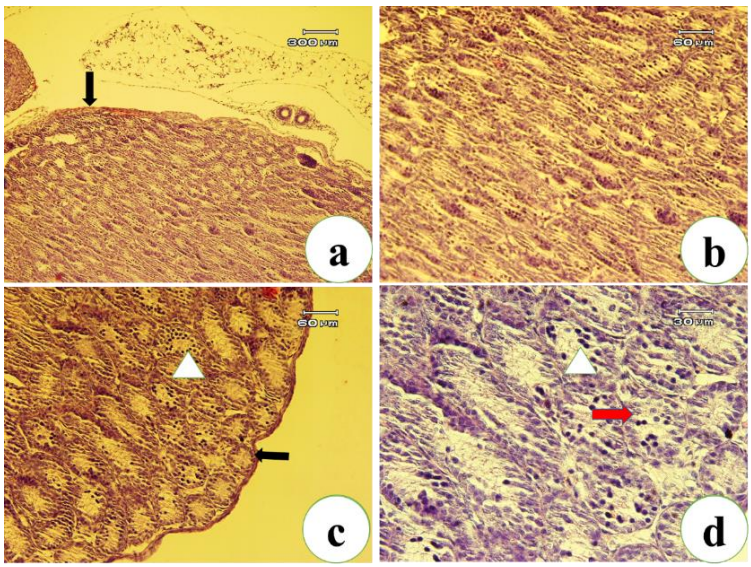


**Figure 1. Cross-section of testicular tissue of the study groups. Figure a: Testicular tissue of a one-day-old male mouse. Cross-section of spermatogenic tubules and primary gonocytes are visible. Figure b: Testicular tissue of a one-day-old male mouse born from a female receiving monosodium glutamate. Cross-section of spermatogenic tubules with reduced cell population is visible. Figure c: Cross-section of testicular tissue of the NCG receiving group. Structurally similar to the control group. Figure d: Group receiving N-carbamylglutamate and monosodium glutamate simultaneously. Reduced structural changes are visible. Black arrow= capsule, red arrow= Sertoli cells, white triangle= primary gonocytes. Hematoxylin and eosin staining, magnification 40x (Figure a), 200x (Figures b, c) and 400x (Figure d).**

## Discussion

The present study showed that the consumption of monosodium glutamate in pregnant female mice resulted in the birth of male infants that had lower body weight and showed a significant decrease in head-to-tail length and abdominal circumference compared to the control group. However, the simultaneous consumption of NCG with monosodium glutamate improved the aforementioned indicators in newborn male infants. Moreover, the use of MSG during pregnancy caused tissue damage to the testicles of infants, such as a decrease in the population of gonocytes and Sertoli cells, an increase in the thickness of the testicular capsule, and a decrease in the diameter of the spermatogenic tubules compared to the control group. However, the consumption of NCG during this period simultaneously with MSG was able to improve the destructive and undesirable effects of MSG.

The pleasant taste of MSG leads to its abundant use in foods, but excessive use of this substance causes it to be transferred to the blood and increase brain glutamate, and since MSG is a neurotransmitter, it causes dysfunction and damage to other organs of the body. On the other hand, dysfunction in brain performance can affect the hypothalamic-pituitary-gonadal axis (25). In the present study, the adverse effects observed in the testicular tissue of the MSG consuming groups may have been caused by affecting this axis. Previous studies show that oral consumption of MSG does not increase brain glutamate levels in rodents due to the blood-brain barrier (25). Therefore, intraperitoneal injection of MSG was used instead of oral consumption in this study.

Rat testicular tissue contains glutamate receptors (26). In developing rats, monosodium glutamate administration has resulted in structural changes such as resorption of the germinal tubules, swelling of spermatids and spermatocytes, observation of immature germ cells in the inner lumen of the tubules,

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condensation of nuclear chromatin, and hyperemia (27). In this regard, the results of a study have shown that short-term use of monosodium glutamate has caused vacuolation of the cytoplasm of spermatogonia, a decrease in the population of spermatids, and edema of the intertubular connective tissue (28). The presence of glutamate receptors in the cells of the walls of the seminiferous tubules can be considered as one of the possible ways in which structural disorders of testicular tissue occur under conditions of monosodium glutamate administration. Other mechanisms involved include the neurotoxic effects of monosodium glutamate on the activity of the hypothalamic-pituitary-gonadal axis (29). In this study, MSG consumption may also directly affect its receptors in testicular tissue and cause its adverse effects, which were ameliorated by NCG consumption.

The maternal placenta plays an important role in controlling the exchange of foreign substances and compounds with the fetus (30). In the present study, the testicular tissue of the neonates in the treatment group had a greater capsule thickness compared to the control group, which could be due to atrophy of the seminiferous tubules. Cytotoxic compounds such as monosodium glutamate can cause changes in the genetic material of the cells lining the seminiferous tubules through the process of oxidative stress, and subsequently reduce the population of these cells.

Testosterone plays an important role in the structure and function of testicular tissue. Although serum levels of hypothalamic-pituitary-gonadal axis hormones were not examined in this study, considering previous studies that emphasize the reduction in blood levels of hormones such as FSH, LH, and testosterone following monosodium glutamate consumption (31-34), it can be concluded that under monosodium glutamate consumption, the reduction in levels of gonadotropin hormones, especially testosterone, plays an important role in reducing the activity of cells lining the walls of the seminiferous tubules, especially Sertoli cells, which in this study was observed as a decrease in cell population and atrophy of testicular tissue.

Studies have shown that intraperitoneal administration of MSG increases lipid peroxidation and reduces the activity of antioxidant enzymes in testicular tissue, resulting in testicular tissue destruction in rats and mice (35, 36). The results of the present study also showed that MSG, by crossing the maternal blood barrier, causes destructive effects on the testicular tissue of male newborns.

Soltani et al. reported that MSG can induce autism in mouse offspring in a dose-dependent manner by increasing glutamate and decreasing GSH, and that MSG should not be used during pregnancy (37). Shosha et al. also reported that MSG administration during pregnancy significantly reduced fetal weight, head-to-tail length, and placenta weight, adversely affected fetal skeletal development, and caused several biochemical and histological changes in maternal and fetal liver and kidney tissues, indicating the toxic and teratogenic effects of MSG (38). In this study, MSG consumption in pregnant mice also caused adverse effects on neonatal testicular tissue and decreased neonatal weight, head-to-tail index, and abdominal circumference, which were ameliorated by NCG consumption. Furthermore, the recorded decrease in body weight and caudal head index in the MSG group was consistent with the findings of George et al., Tawfeeq et al., Abu Elnaga et al., Gad EL-Hak et al., Kondoh et al., and Tordoff et al. in mouse fetuses (39-44). Husarova et al. reported that MSG decreased the level of pituitary growth hormone, which is directly responsible for fetal growth (2). Zanfirescu et al. also suggested that the decrease in fetal body weight may be due to MSG-induced depression of the cellular differentiation process of fetal cells (45). Furthermore, Al-Ghamdi suggested that MSG may directly affect fetal cellular metabolism, as MSG can easily cross membranes and affect fetal growth (46). It can be stated that MSG consumption increases glutamate levels in the brain and disrupts its function. On the other hand, by affecting the pituitary gland and reducing growth hormone, it disrupts the hypothalamic-pituitary-gonadal axis and disrupts fetal development, which is consistent with the results obtained in this study.

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The use of NCG increases the synthesis of heat shock protein 70 in cells. This protein protects cells against various types of environmental stress and pressures, especially oxidative stress (47-49). Cao et al. reported that NCG can partially protect the liver and plasma from oxidative stress (50). Zhang et al. reported that NCG can protect infants from oxidative liver damage caused by experimental hemolysis by increasing the expression of antioxidant enzymes (including SOD, CAT, and GSH-Px), phase II metabolizing enzymes, and activating the NO pathway (51). In this study, NCG also reduced the negative effects of MSG on testicular tissue and fetal indices.

Ma et al. reported that NCG supplementation had positive effects on reproductive traits of roosters. NCG supplementation improved the development of reproductive traits of roosters by regulating gene expression in testicular tissues and thus improved the synthesis of reproductive hormones in the body (52). Another study showed that NCG supplementation improved egg production performance and quality in hens by regulating uterine function (22). Atiyah et al. reported that NCG supplementation in the routine diet of bulls can improve semen quality (53). Cai et al. reported that NCG supplementation increases plasma concentrations of arginine, nitric oxide, and progesterone by synthesizing endogenous arginine, which improves the intrauterine environment and provides nutrients for embryo implantation and pregnancy maintenance in ewes, resulting in an increase in the number of live embryos on day 38 of gestation in ewes (54). In this study, NCG also increased Sertoli cells and primary gonadotropins compared to the MSG group, indicating that it probably improved the conditions in the testicular tissue through the aforementioned mechanism.

Considering that in the present study, the groups receiving NCG improved the average histological and embryological factors compared to the group receiving MSG, it can be concluded that the use of NCG in food can be used to reduce the negative effects of MSG.

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