

EFFECT OF LONG-TERM ADMINISTRATION OF MONOSODIUM GLUTAMATE ON THE HISTOLOGICAL STRUCTURE OF THE THYROID GLAND IN ADULT MALE ALBINO RATS

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ABSTRACT

This study focuses on the effect of long-term intake of monosodium glutamate (MSG) as feed additives on the histological picture of the thyroid gland in adult male albino rats. For this purpose, forty adult male rats were divided into four groups. Control groups (C1 and C2) were orally administered only distilled water for 30 and 75 days, respectively. The treated groups (G1 and G2) were orally administered 15mg/kg B.W. MSG for 30 and 75 days, respectively. At the end of the experiment, all specimens were sacrificed, and samples were fixed in 10% neutral buffered formalin (NBF). Hematoxylin-eosin (H&E) stain was used for staining. Tissues were examined under the light microscope. As the treatment time of the experiment progressed. The results indicated hyperthyroidism, characterized by significant hypertrophy of thyroid follicles and hyperplasia of thyroid follicular cells, alongside a low height of the follicular epithelium. This epithelium ranged mostly between high squamous and low cuboidal. High cuboidal to columnar follicular cells were not observed. Some follicles were engorged with thin, homogenous colloids, others contained thick, coagulated colloids. Long-term treatment groups exhibited the fusion of smaller or medium-sized follicles, creating larger ones. It was recorded that the prolonged intake of MSG induces an exaggerated functional overload on the thyroid gland. Continuous pressure on the free surface of the follicular cells may lead to increased mitotic activity. Despite their limited activity, squamous cells may exhibit the highest activity when their numbers increase on account of their limited function. This study introduces, firstly, a fourth type of thyroid activity, termed "extra hyperactivity," to the existing traditional three classifications of thyroid functions.

Key words: Food additive, Hyperthyroidism, Monosodium glutamate, Thyroid gland.

INTRODUCTION

One of the public food additives is monosodium glutamate (MSG). A Japanese

professor has used it as a taste enhancer since 1907 (Al-Otaibi *et al.*, 2022). The thyroid is an important gland in the endocrine system that produces hormones, regulates metabolism, and supports the functions of various organ systems throughout the body. Follicles represent the structure and secretory units of the thyroid.

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The follicular lumen of these units is occupied by a colloidal material that contains the important hormones thyroxine (T₄) and triiodothyronine (T₃) (Rykova *et al.*, 2019). Unfortunately, literature investigating MSG's effect on the morphology and function of the thyroid gland is very controversial. Other investigators reported slight morphological changes in the thyroid following chronic exposure to MSG in rats (Zayed *et al.*, 2023). In contrast, there is an increase in the height of follicular epithelium and a decrease in the diameter of the follicles, with irregularity in their outlines. Moreover, follicular hyperplasia was observed in some follicles; these had pyknotic nuclei both in follicular and interfollicular cells, in addition to many exfoliated cells within the colloid lumen (Khalaf & Arafat, 2015).

The follicular epithelium shows significant compression, indicating a stress response, while the follicles themselves are enlarged due to the accumulation of colloids, highlighting noteworthy changes in thyroid functionality. Importantly, the histological appearance of the thyroid gland remains consistent across animals sacrificed after both short-term and long-term exposure, underscoring the reliability of these observations (Lee *et al.*, 2016). Some authors reported that MSG induces marked hypothyroidism in mice (Rani *et al.*, 2013). Other authors recorded endocrine disorders after the administration of MSG, represented by an increase in the diameter of thyroid follicles and height and area of follicular cells and a decrease in the number of colloids within the follicles (Miskowiak & Partyka, 1999). The current study aims to investigate the effect of long-term MSG consumption on the histological picture of the thyroid gland. Besides, the study warns food consumers against exposure to MSG-containing food additives for long periods.

MATERIALS AND METHODS

Ethical Approval:

The study was carried out according to the Institutional Ethics Committee (IEC) approval and guidelines of the College of Veterinary Medicine, University of Fallujah NO.1 on 30 Jan 2025

Experimental procedure

This study involved forty adult male albino rats, each weighing between 190 and 250 grams, to ensure reliable and relevant results. They were housed separately in cages under similar environmental conditions, providing food and water. Animals were divided into four groups, each group consisting of ten rats. The animals of the first and second groups (C1 and C2) were orally administered with distilled water for 30 and 75 days, respectively, as control groups. Treated groups (G1 & G2) were administered 15mg/kg B.W. MSG (Sigma Chemical Co. USA) dissolved in distilled water orally via a gavage tube for 30 and 75 days, respectively (Keshewani *et al.*, 2024). At the end of each period for each group, the animals were euthanized, the thyroid gland was collected and irrigated with normal saline, fixed with 10% Neutral-Buffered Formalin (NBF) for 72 hours, and then dried out using sequence concentrations of ethyl alcohol (70%, 80%, 90%, and 100%) after they cleared in xylene, then embedded in paraffin wax, and sliced to the thickness of 4-5 micrometers by using the microtome. Hematoxylin-Eosin (H&E) stains were used to stain the slides (Suvarna *et al.*, 2018; Hammoodi *et al.*, 2024), and after that were examined under a light microscope. Measurement was done using Optical View Seven image analysis software.

Statistical analysis

The data were analyzed by analysis of variance (ANOVA) one-way using SPSS (version 25), and the least significant differences (LSD) test was used to determine the differences between treatment or time (Hammoodi *et al.*, 2024).

RESULTS

The histological examination of the specimen from the control group on the 30th day after the administration of distilled water (C1) revealed a normal thyroid gland architecture. The thyroid gland exhibited typical follicles with normal follicular cells. Some of the follicles were devoid of colloid, while others were partially filled, indicating the gland's normal activity, as illustrated in (Table 1) and (Figure 1).

On the 75th day after the administration of distilled water, the histological section of the control group (C2) exhibited high epithelium, a large number of smaller size follicles were devoid of colloid, and the presence of the large follicles lay at the periphery (Table 1 and Figure 2).

The histological section of the thyroid gland from the treated group with MSG after 30th days (G1) showed some follicles engorged with colloid, while others lack colloid. Also, an adhesion line between two follicles was noticed, which forms a larger follicle (Table 1 and Figure 3).

On the 75th day after the administration of MSG (G2), the histological section of the thyroid specimen showed low compressed epithelium. Some follicles were filled with homogeneous colloids, and others with coagulated thick colloids. An irregularity of the shape of the follicles, with a reduction in the height of follicular cells and a rise in the diameter of thyroid follicles (Table 1 and Figure 4).

Table 1: Parameters of thyroid glands in control and MSG treated groups at different experimental periods (Mean $\pm$ SE)

Parameters	Control group (C1)	MSG treatment group (G1)	Control group (C2)	MSG treatment group (G2)
	30 days		75 days	
Thickness of follicular cells	17.97 $\pm$ 0.93 B	17.36 $\pm$ 1.44 B	20.48 $\pm$ 1.52 A	13.549 $\pm$ 0.77 C
Follicular cell number	12.96 $\pm$ 0.48 B	13.87 $\pm$ 0.46 AB	11.66 $\pm$ 0.33 B	21.885 $\pm$ 2.14 A
Follicular diameter	108.89 $\pm$ 3.77 B	115.36 $\pm$ 4.61B	104.781 $\pm$ 4.40 B	187.552 $\pm$ 10.29A

Capital letters denotes differences between groups at different times ($P \geq 0.05$).



Figure 1. A histological section of the thyroid gland (control group) after 30 days (C1) shows normal architectures, normal follicles with normal follicular cells (black arrow), some follicles were empty (black star), others were nearly-filled with colloid (blue star). (H & E stain), 400X.

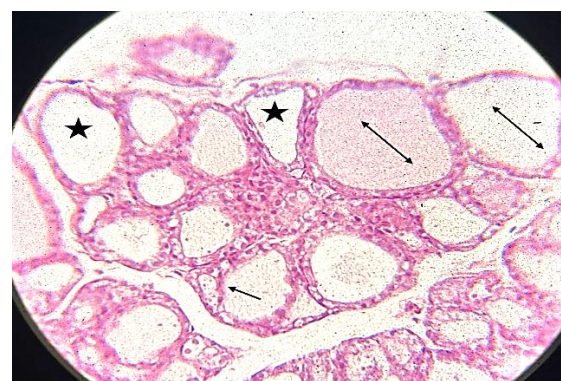


Figure 2. A histological section of the thyroid gland (control group) after 75 days (C2) shows high epithelium (black arrow), many smaller size follicles, and most follicles were devoid of colloid (stars). Notice the large follicles lie at the periphery (double-head arrows). (H & E stain), 400X.

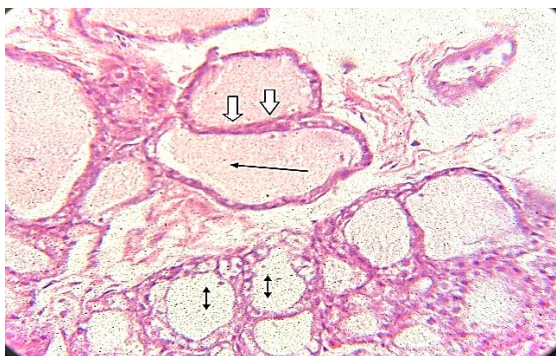


Figure 3. A histological section of the thyroid gland (treated group) (MSG) after 30 days (G1) shows some follicles were engorged with colloid (black arrow), and others lacked colloid (double-headed arrows). Note the adhesion line between two follicles yielding a larger one (white arrows). (H&E stain), 400X.



Figure 4. A histological section of the thyroid gland (treated group) with MSG after 75th days (G2) shows low compressed epithelium (black arrow). Some follicles were filled with homogeneous colloids (black stars), others were filled with coagulated thick colloids (double stars). Notice the irregularity of the shape of the follicles. (H&E stain), 400X

DISCUSSION

The present results revealed that excessive administration of MSG induces a continuous high production of colloid that fills the follicles and presses on the apical surfaces of the follicular cells, creating low-height epithelium. This pressure prevents the epithelium reaching a higher height. The functional overload can't be controlled by the traditional biological mechanisms of the body. So the follicular cells are triggered toward the mitotic direction. Two pathways were observed in the treatment group at 75th days. The first was the fusion between small or medium-sized follicles yielding larger ones, and the second was the increased number of follicular cells by mitosis. This explains why the thyroid follicles were increased in size. This was in agreement with Bereda (2022), who referred to the significant cellular follicular hyperplasia after MSG administration. This was created by hypertrophy of the thyroid follicles and hyperplasia of follicular thyroid cells, leading to hyperthyroidism. Also, these findings align with the results reported by Hussin *et al.* (2021), who demonstrated that long-term intake of MSG leads to the enlargement of the mesangium in the kidney glomeruli. This is to meet the

functional compensatory need for the follicular cells. The present finding was partially at variance with the result of Dhindsa *et al.* (1981), who hypothesized that hypothyroidism is caused by the effect of the drug on the hypothalamus-pituitary axis activity and the hormone secretion that regulates thyroid metabolic activity. Besides, the current study was different from the findings of Rani *et al.* (2013), who referred to the presence of endocrine disorders. The present result hypothesized that the low height of follicular cells was due to the pressure of the profuse, continuous production of colloids that occupies the follicles, which can't give these follicles the chance to drain their secretion.

Hussin and Khudhayer (2016) classified the thyroid activity into three types, namely; the hypoactive, active, and hyperactive, represented by the squamous, cuboidal, and columnar follicular cells respectively. So the present study agreed with the study by Hussin and Khudhayer (2016) and added a new type of thyroid activity classification, the extra hyperactivity. The study first nominated this type as extra-hyperthyroidism.

CONCLUSION

It was concluded that long-term consumption of the feed additive appetizer MSG salt causes an exaggerated functional overload on the thyroid tissue. The study first classified and nominated this state as extra-hyperthyroidism, because in spite of the presence of low-height follicular cells, there was a significant increase in the number of these cells and finally the activity of the thyroid gland. Moreover, the study indicates the risk of long-term intake of monosodium glutamate.

Despite its low activity, the squamous type of cell can play a very high activity when its number increases. This study adds a new type of thyroid activity classification: extra hyperactivity.

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أثر تناول الجلوتامات أحادية الصوديوم لفترات طويلة على التركيب النسيجي للغدة الدرقية في ذكور فئران الألبينو البالغة

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تركز هذه الدراسة على تأثير تناول مضافات غذائية من غلوتامات أحادية الصوديوم (MSG) على المدى الطويل على الصورة النسيجية للغدة الدرقية لدى ذكور الجرذان البيضاء البالغة. لهذا الغرض، قُسم أربعون جرّداً ذكراً بالغاً إلى أربع مجموعات. أعطيت المجموعتان الضابطتان (C1 , C2) ماءً مقطرًا فقط عن طريق الفم لمدة ٣٠ و ٧٥ يومًا على التوالي. أما مجموعتا المعالجة (G1, G2) فقد أُعطيتا ١٥ ملغ/وزن الجسم من غلوتامات أحادية الصوديوم عن طريق الفم لمدة ٣٠ و ٧٥ يومًا على التوالي. في نهاية التجربة، قُطعت جميع العينات، وثبّتت في فورمالين مُنظّم محايد بنسبة ١٠% (NBF) واستُخدمت صبغة الهيماتوكسيلين-إيوزين (H&E) للتلوين. وفُحصت الأنسجة تحت المجهر الضوئي. مع تقدم وقت العلاج للتجربة، أشارت النتائج إلى وجود فرط نشاط الغدة الدرقية، والذي يتميز بتضخم كبير في بصيلات الغدة الدرقية وفرط تنسج خلايا الجريبية الدرقية، إلى جانب ارتفاع منخفض للظهارة الجريبية. تراوحت هذه الظهارة في الغالب بين الخلايا الحشوية العالية والمنخفضة المكعبة. لم يتم ملاحظة الخلايا الجريبية عالية المكعبة إلى العمودية. كانت بعض الجريبيات محتقنة بغرويات رقيقة ومتجانسة، بينما احتوى البعض الآخر على غرويات سميكة ومتخثرة. أظهرت مجموعات العلاج طويلة الأمد اندماج بصيلات أصغر أو متوسطة الحجم، مما أدى إلى تكوين بصيلات أكبر. وقد تم تسجيل أن تناول MSG لفترات طويلة يسبب حالة من التحميل الوظيفي المبالغ فيه على الغدة الدرقية. قد يؤدي الضغط المستمر على السطح الحر للخلايا الجريبية إلى زيادة النشاط الانقسامي ويمكن أن يؤدي إلى ذلك. على الرغم من نشاطها المحدود، قد تُظهر الخلايا الحشوية أعلى نشاط عندما تزداد أعدادها بسبب وظيفتها المحدودة. تقدم هذه الدراسة، أولاً، نوعاً رابعاً من نشاط الغدة الدرقية، ويسمى "فرط النشاط الإضافي"، إلى التصنيفات الثلاثة التقليدية الموجودة لوظائف الغدة الدرقية.