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# The Physiological Effects of Excitatory Amino Acid Neurotransmitters as A Clinical Probe to Evaluate Thyroid Stimulating Hormone as Well as Thyroid Hormones Production

**Hira Ehsan Khattak[1], Jaleel Kamran[2], Nadia Latif[3], Muhammad Sameer Hanif[4], Wardah Naseer Khan[5], Insha Fatima[6]**

[1]Assistant Professor, Department of Physiology, Watim Medical and Dental College Islamabad.
Email ID: hira88khattak@gmail.com
[2]Associate Professor, Department of Physiology, Watim Medical and Dental College Islamabad.
Email ID: drjaleelkamran@ymail.com
[3]Associate Professor, Department of Physiology, Fazaia Medical College, Air University Islamabad
Email ID: nnadiaamc@hotmail.com
[4]Assistant Professor, Department of Physiology, Poonch Medical College Rawalakot
Email ID: dctrsameer@gmail.com
[5]Demonstrator, Department of Physiology, Watim Medical and Dental College Islamabad.
Email ID: wardah34.255@gmail.com
[6]Demonstrator, Department of Physiology, Watim Medical and Dental College Islamabad.
Email ID: inshafatima749@gmail.com

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**ABSTRACT**

**Objective:** To evaluate how peripheral glutamate injection affects human thyroid stimulating hormone and thyroid hormones production.

**Methodology:** In 2023, an exploratory inquiry was carried out from October 6 to December 30. Adult healthy men were randomly assigned to receive intravenous Monosodium Glutamate dosages of 0, 5, 10, or 20 mg/kg BW (n = 4 per dose). For one hour before and three hours after the injection of MSG, sequential blood samples were obtained at 30-minute intervals. Serum concentrations of thyroxine (T4), triiodothyronine (T3), and thyroid stimulating hormone (TSH) were assessed using specific enzyme immunoassays (EIA) or immunoenzymatic assays (IEMA). The effectiveness of MSG was evaluated by comparing the mean hormone concentrations measured before and after the pharmaceutical delivery timings using a t-test.

**Results:** With the exception of the 0 mg dose, all MSG dosages raised the serum TSH values ($P < 0.05$-0.005). Serum T4 concentrations were only shown to increase ($P < 0.05$) at the highest dose of MSG (20 mg). The mean blood T3 levels significantly decreased (P < (1.01-0.005)) following injections of 0 mg, 5 mg, and 10 mg dosages of MSG. However, after receiving a 20 mg dosage of MSG by injection, no similar drop in T3 levels was seen.

**Conclusion:** For the first time, the current findings show that in case of adult males, the peripheral injection of MSG increases their secretion of thyroxine and TSH. These findings imply that glutamate plays a role in controlling a man's output of thyroid hormones and TSH

**Key Words:** *Glutamate, Human, Thyroid stimulating hormone, Thyroid hormones*

## 1. INTRODUCTION

The white crystal salt of glutamic acid known as monosodium glutamate (MSG) is composed of 78% glutamate, 20% sodium, and 2% water[1] . The primary excitatory mammalian central nervous system neurotransmitter is glutamate[2,3]. Numerous principle neurons use it, including pyramidal cells in the hippocampus and cerebral cortex, thalamic projecting neurons, and granule cell neurons in the hippocampus and cerebellum[4]. Memory, learning and cognition[5,6] ,metabolism[7] including astrocyte fatty acid homeostasis regulation[8] and control of sleep wake cycle management[9] are all implicated by glutamate. Prefrontal glutamate deficiency is closely linked to working memory system malfunctions, sleep disorders and poor decision-making in older adults[10]. It has been evident during the past two decades that glutamate has a role in neuroendocrine control[11]. It has also been demonstrated that glutamate agonists increase the release of thyroid-stimulating hormones[12] and other anterior pituitary hormones[13,14] in a variety of mammals, including primates that are not humans. There is very little information about how glutamate functions in humans. Even though the Food and Drug Administration (FDA) maintains that MSG is safe, long-term MSG use has been linked to deleterious effects in animal studies. Numerous diseases, including asthma, hypertension, obesity, headaches, neurotoxicity harmful to the reproductive organs, have been linked to these adverse consequences. The liver, pancreas, thymus, brain, testes, and kidneys are among the organs where these effects have been noted[15].

Hypothalamic thyrotropin-releasing hormone (TRH) and thyroid hormones (FT3 and FT4) regulate thyroid-stimulating hormone (TSH), released by the pituitary gland. Thyroid dysfunction can be indicated by variations in TSH levels, and even slight changes can have a big impact on a number of clinical outcomes, such as depression, cardiovascular disease, bone mineral density, and metabolic syndrome.

Reduced pituitary gland secretion of thyroid stimulating hormone (TSH) might result excessive glutamate's damage to thyrotropin-releasing hormone (TRH) neurons in the hypothalamus. Reduced production of triiodothyronine (T3) and thyroxine (T4) hormones can result from damaged and deconstructed thyroid follicular cells as well as decreased TSH secretion[16]. This results in abnormal functioning of thyroid tissue[17].

## 2. MATERIALS AND METHODS

An experimental study was carried out at the Medicine Department of Watim General Hospital Rawat Rawalpindi from October 6, 2023, until December 30, 2023. The study was started after being authorised by the institute's Clinical Research Ethics Committee.

**Inclusion criteria**: Participants in the study included sixteen (16) healthy adult males between the ages of 20 and 37 (mean ± SEM: 27.4 ± 1.5 years) weighing between 49 and 80 kg (mean ± SEM: 62.1 ± 2.1 kg).

**Exclusion criteria:** Significant comorbidity or systemic disease, abnormal clinical and biochemical reproductive function, and drug usage for medical or recreational purposes.

After providing a comprehensive explanation of the study's objectives, duration, and methods in their mother tongue, the patient gave their informed written consent. Four (4) patients per group were randomly selected to receive a single intravenous bolus of MSG at dosages of zero, five, ten, or twenty mg/kg BW after a thorough review of the patient's medical history, as shown in Table 1.

Two intravenous lines were made in the radial veins using Teflon cannulas: one for saline infusion (0.9% NaCl) and the other for drug delivery and blood collection. Blood samples were collected at 30-minute intervals for 60 minutes before and 180 minutes after the MSG injection. Fifteen minutes following the injection, a second sample was collected. Physiological markers such as blood pressure, pulse, and body temperature were monitored throughout. Subjects were allowed to eat and drink as they pleased while being watched for any adverse responses 24 and 48 hours after administration, with follow-up exams. TSH, T3, and T4 levels were measured by EIA and IEMA, as shown in Table 2.

**Data Analysis:**

The data was analyzed using SPSS version 24. A t-test was used to statistically analyze changes in hormone concentrations in response to MSG; findings were shown as mean ±SEM, and a significant P-value was defined as <0.05.

**Table 1: Shows the mean ± SEM ages and body weights of subjects administered with various MSG dosage**

| Dose of MSG (mg/kg BW) | N | Age (years) | Body Weight (Kg) |
|---|---|---|---|
| 0 | 4 | 28.2 ± 3.3 | 64.7 ± 4.5 |
| 5 | 4 | 25.2 ± 3.0 | 56.0 ± 2.6 |
| 10 | 4 | 27.2 ± 3.0 | 63.7 ± 5.9 |
| 20 | 4 | 26.5 ± 23.9 | 63.7 ± 2.9 |

**Table 2: Characteristics of Performance for Various Assays**

| Hormone | Assay Type | Intra-assay Co-efficient of Variation | Sensitivity |
|---|---|---|---|
| TSH | IEMA | < 3% | 0.15 µI U/ml |
| T3 | EIA | < 4% | 0.5 ng/ml |
| T4 | EIA | < 5% | 20.0 ng/ml |

## 3. RESULTS

**Figure 1** shows the variations in TSH serum concentrations brought on by various intravenous bolus dosages of MSG. The mean TSH levels before and after the 0 mg dose of MSG did not differ from one another. On the other hand, MSG dosages of 5, 10, and 20 mg markedly increased TSH secretion.

**Figure 2** displays the mean TSH concentrations before and after MSG. Following the injections of 5 mg ($p < 0.05$), 10 mg, and 20 mg ($P < 0.005$) dosages of MSG, there was a substantial increase in TSH concentration.

**Figure 3** illustrates how MSG treatment affects T4 secretion.

**Figure 4** shows that the mean serum concentrations of T4 were unaffected by MSG dosages of 0, 5, and 10 mg. However, following the administration of a 20 mg dose of MSG, serum T4 concentrations rose noticeably ($P < 0.05$).

**Figure 5** illustrates the alterations in T3 secretion in response to MSG ingestion. Following the administration of 0 mg ($P < 0.01$), 5 mg ($P < 0.01$), and 10 mg ($P < 0.005$) dosages of MSG, the mean T3 concentrations in the serum decreased (Figure 6). Nonetheless, the average T3 levels before and after a 20 mg MSG dosage were similar.

**Figure 1:**

**Changes in mean ± SEM serum concentrations of TSH in response to intravenous administration of different doses of MSG (n=4 per doses). Arrow indicates the time of injection of MSG.**

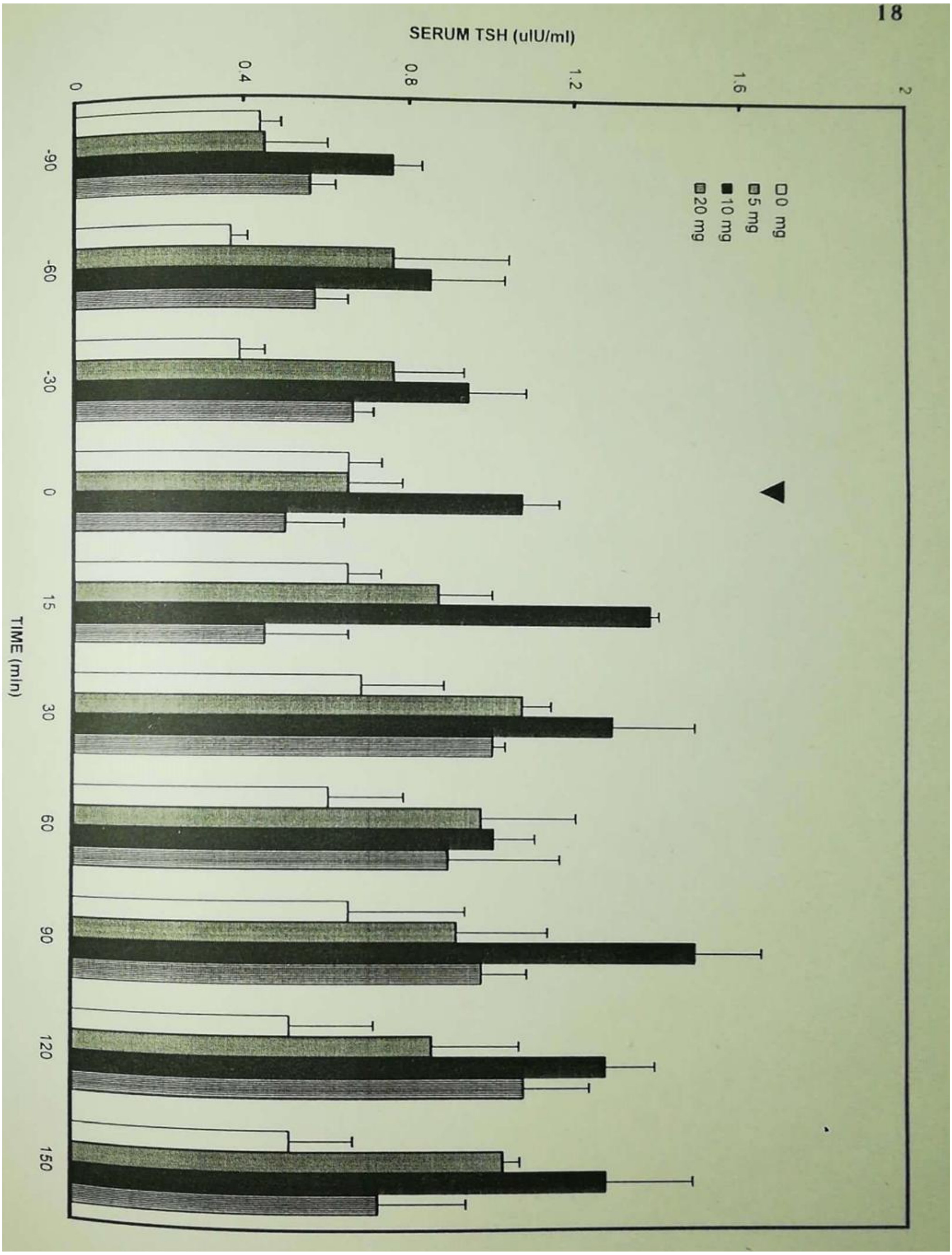


**Figure 2:**

**Mean ± SEM pre- and post-MSG concentrations of TSH at various doses of MSG (n = 4 per dose). Asterisk (*) indicates a noteworthy rise (P < 0.05) in the post-MSG hormone concentrations.**

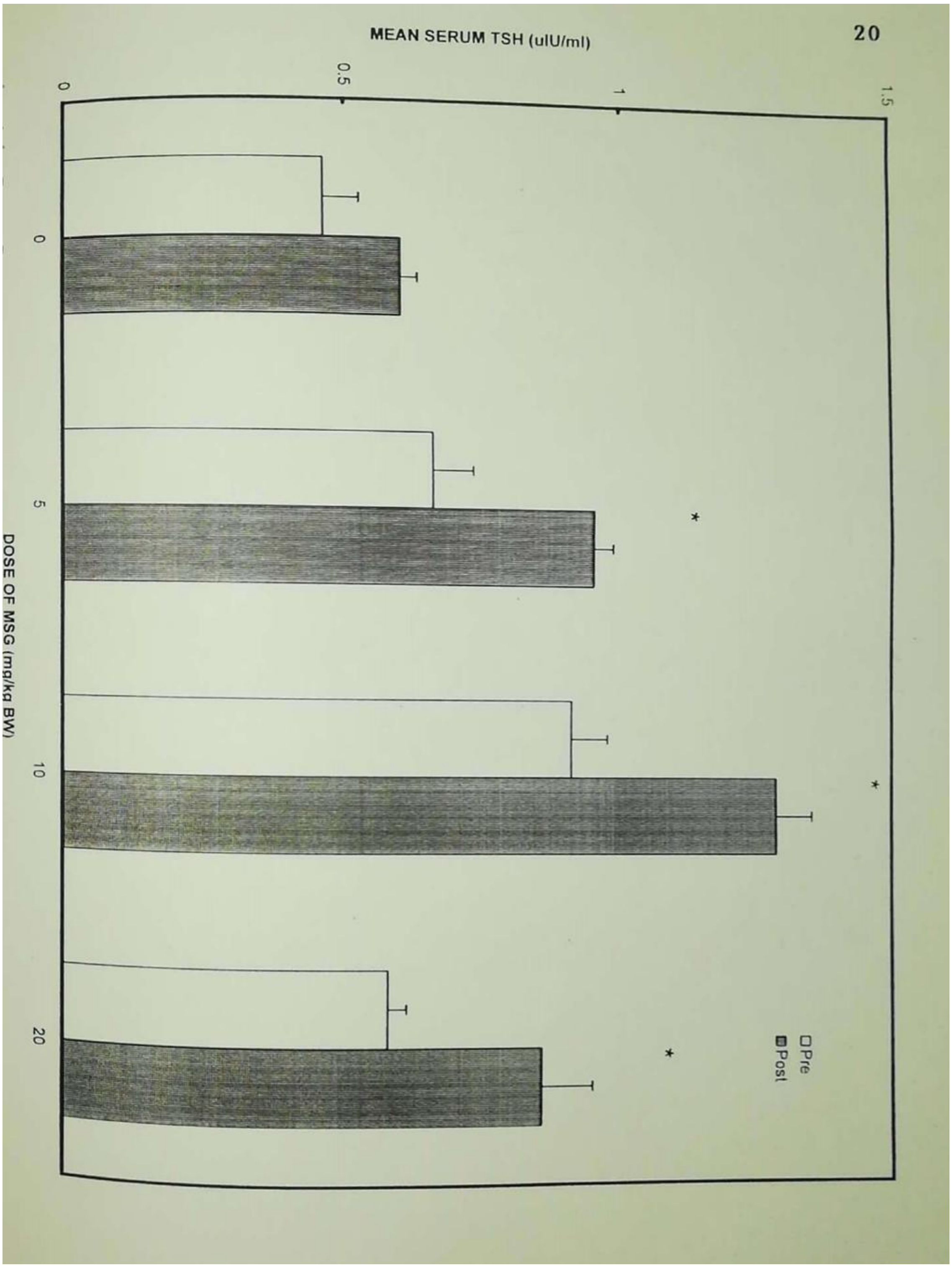


**Figure 3:**

**Changes in mean ± SEM serum concentration of T4 in response to intravenous administration of different doses of MSG (n = 4 per doses). Arrow indicates the time of injection of MSG.**

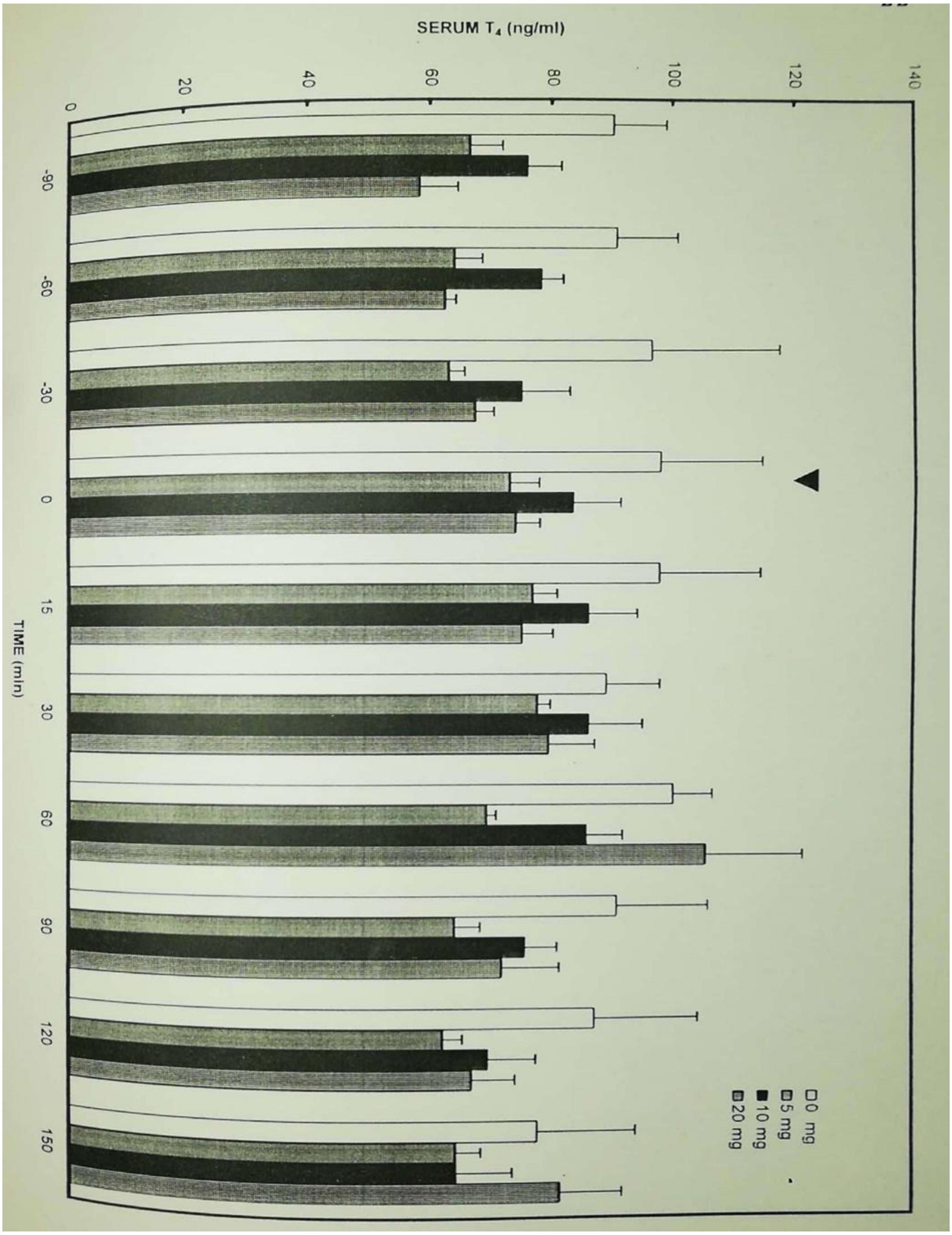


**Figure 4:**

**Mean ± SEM pre and post-MSG concentrations of T4 at various doses of MSG (n = per dose). Asterisk (*) indicates a noteworthy rise (P < 0.05) in the post-MSG hormone concentrations**

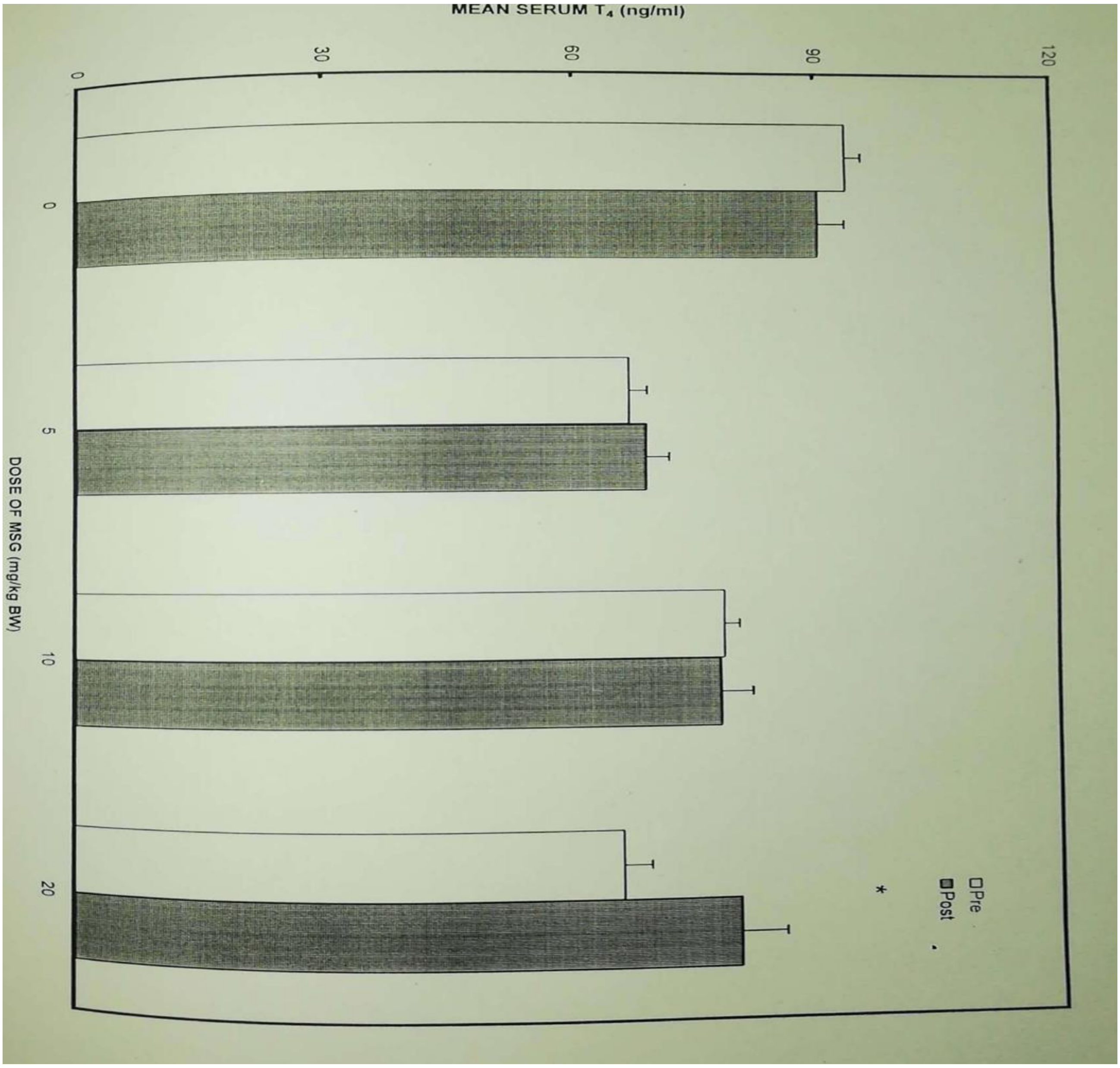
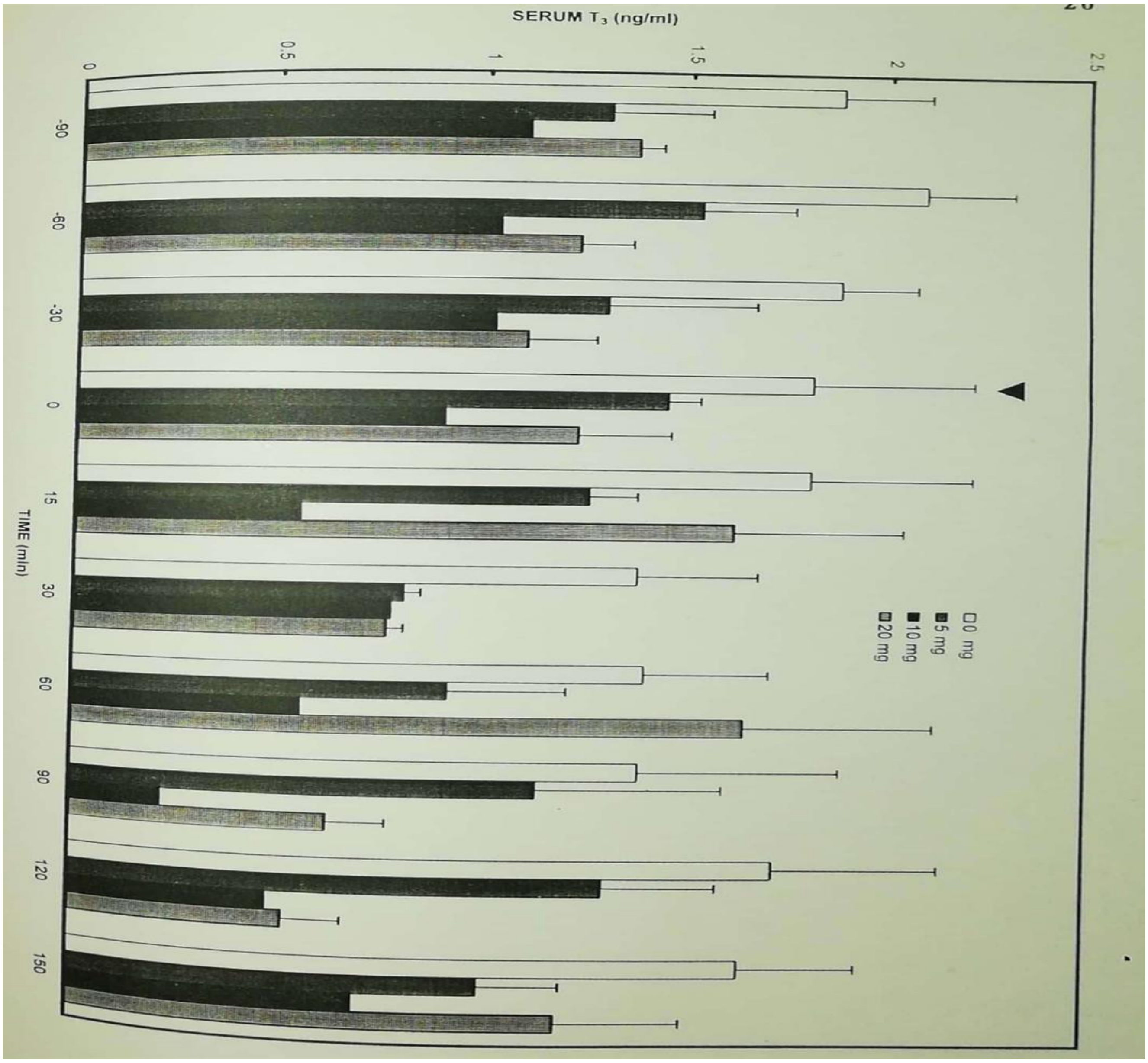


**Figure 5:**

**Changes in mean ± SEM serum concentrations of T3 in response to intravenous administration of different doses of MSG (n = 4 per doses). Arrow indicates the time of injection of MSG**



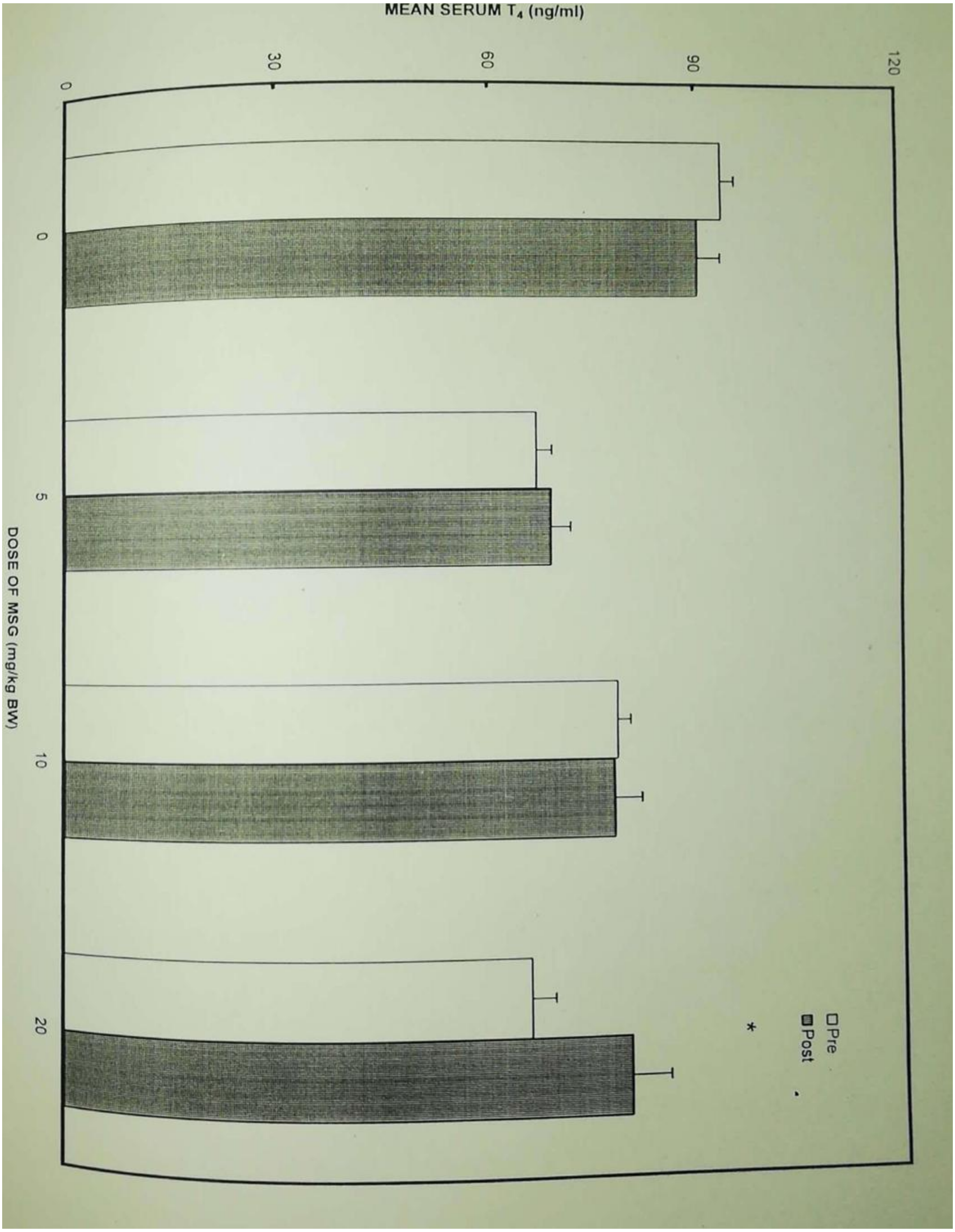
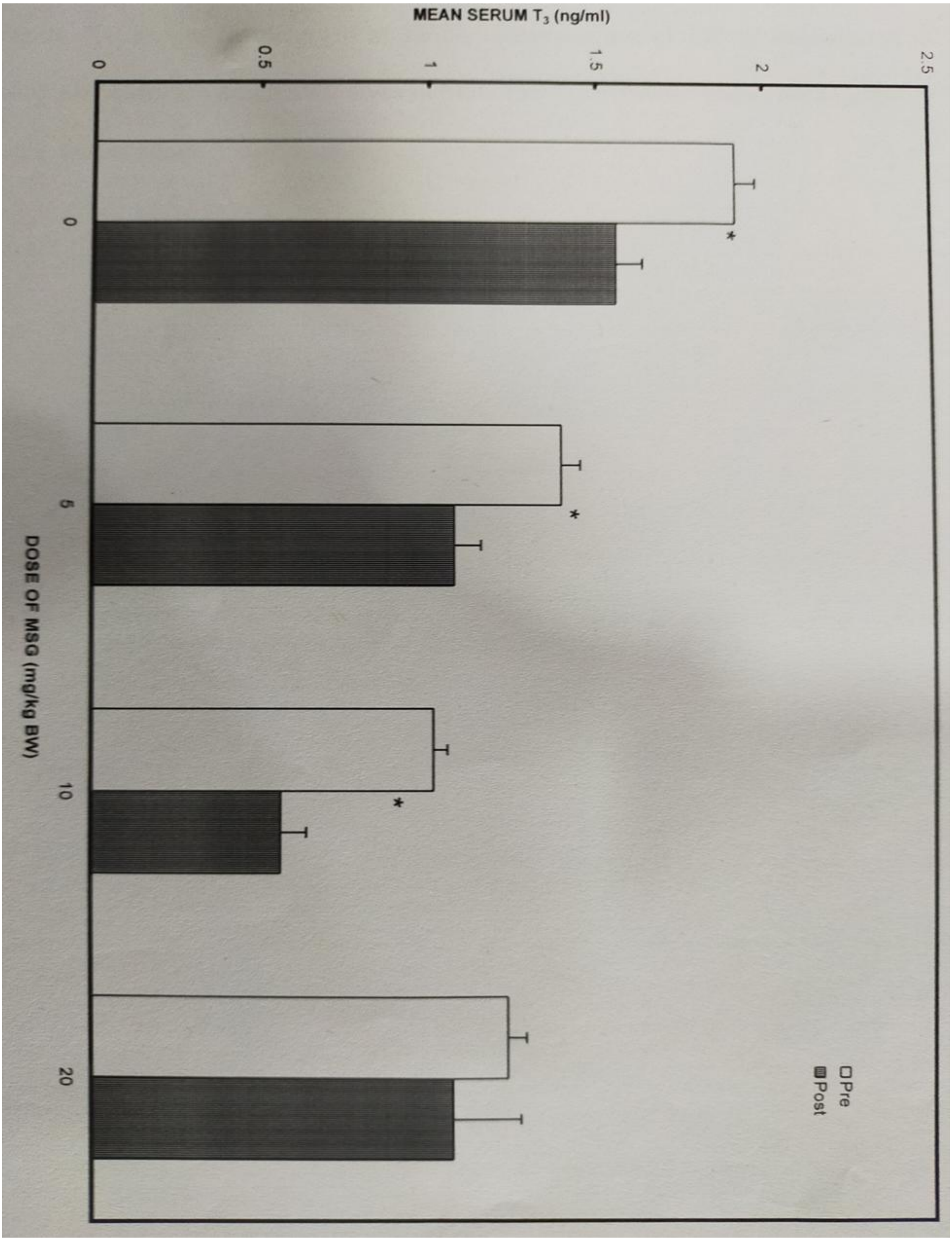



**Figure 6. Mean ± SEM pre- and post-MSG concentrations of T3 at various doses of MSG (n = 4 dose). Asterisk (*) indicates a significant decrease (P<0.005) in the post-MSG hormone concentrations.**




## 4. DISCUSSION

Glutamate, one of the most prevalent amino acids in the central nervous system, is the main ingredient in MSG(18). Monosodium glutamate (MSG) is one of the most widely used flavorings in modern times. It can be found in a lot of home and restaurant recipes as well as in many commercially packaged goods (such chips, crackers, bouillon, sauces, etc.). MSG gives processed foods a pronounced umami flavor, which is Japanese for "savoury taste." After sweet, sour, salty, and bitter, umami is the fifth fundamental taste. MSG's umami flavor enhances the flavor of low-salt foods, making up for their lower salt content and making even low-salt items more palatable[19]. Eman G.E. Helal found that monosodium glutamate raises both T3 and T4 levels in a study involving 40 male albino rats[20]. Thirty male albino rats weighing 170 ±10 g were given MSG (60 mg/k g b.wt./day) for 28 days, which raised TSH levels and decreased T3 and T4 levels, according to a study by Amira L. Abd Allah[21]. According to a study by Manal N. Al Hayder For 30 days, rats received oral gavage of 0.25 cc of monosodium glutamate (20 mg/KgBW). Triiodothyronine (T3) significantly dropped ($P<0.05$) and tetraiodothyronine (T4) significantly rose ($p<0.05$), although there were no a noteworthy variations in the concentrations of thyroxin stimulating hormone (TSH)[22] Nonetheless, TSH levels rose, T3 levels fell, and T4 levels rose in the current study. In a different experiment, done by Mekkawy AM rats in the group treated with MSG (6 mg/gmbodyweight/day) for 60 days showed significantly reduced levels of serum fT3 and fT4, and elevated levels of serum TSH[23]. According to a study by Khalaf and Arafat, the blood levels of T3 and T4 were significantly higher in the groups treated with high and hazardous doses of MSG than in the control group, whereas they were not significantly higher in the group treated with medium doses[24]. In a study by Dalia Abd Elrazik Noya, the mean blood levels of T3, T4, and TSH were substantially lower in the group (P value<0.001) that received MSG at a dose of 6 mg/g./day[25]. Samah A. El-Hashash reports that for six weeks, twenty mature female albino rats were given MSG dosage of 6 mg/kg body weight every day. The TSH levels were significantly higher ($0.08\pm0.01$ compared to $0.00 \pm 0.00$ uI U/ml in the healthy control) ($P<0.05$), while the T4 and T3 levels were lower $2.76 \pm 0.36$ as opposed to the healthy control's $3.4 \pm 0.43$ ng/dl ($P<0.05$)[26]

## 5. CONCLUSION

Taken together, the current study's findings offer the pioneer but preliminary evidence that systemic administration of MSG can stimulate the secretion of TSH and T4 in the adult healthy men. It might be mentioned here that the dose of MSG utilized in the current study did not induce any behavioral effects in the subjects suggesting that the doses were not in toxic amounts. Therefore, whatever neuroendocrine perturbations were elicited by MSG, were not a reflection of neurotoxic influence of the drug. Nevertheless, present data extend the neuroexcitatory actions of EAA to humans and furnish a strong rationale to undertake further studies for characterizing the role of EAA neurotransmission in regulating the pituitary hormone secretion in the men

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