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Impact Of Excitatory Amino Acid Neurotransmitters As Clinical Probe To Assess Gonadotropin Releasing-Hormone Neuronal Function

Jaleel Kamran[1], Syed Salman Faris Bukhari[2], Sania Basharat[3], Jawairia Amjad[4], Fahad Qadeer[5], Hira Ehsan Khattak[6]

[1]Associate Professor, Department of Physiology, Watim Medical and dental College, Rawat
[2]Demonstrator, Department of Physiology, Watim Medical and dental College, Rawat
[3]Demonstrator, Department of Physiology, Watim Medical and dental College, Rawat
[4]Demonstrator, Department of Physiology, Watim Medical and dental College, Rawat
[5]Postgraduate Resident, Respiratory Medicine, Pakistan Institute of Medical Sciences (PIMS), Islamabad.
[6]Senior Demonstrator, Department of Physiology, Watim Medical and dental College, Rawat

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Abstract

Objective: To evaluate how peripheral glutamate injection affects human gonadotropins and testosterone production

Methodology:

During 6th October to 30th December 2023, an experimental investigation was conducted. Intravenous doses of 0, 5, 10, or 20 mg/kg BW of monosodium glutamate (MSG) were given at random to adult healthy men (n = 4 each dose). Sequential blood samples were taken at 30-minute intervals for one hour prior to and three hours following the administration of MSG. Specific enzyme immunoassays (EIA) or immunoenzymatic assays (IEMA) were used to assess testosterone, follicle stimulating hormone (FSH), and luteinizing hormone (LH) levels in serum. By using a t-test to compare the mean hormone concentrations recorded before and after the medication delivery times, the effectiveness of MSG was assessed.

Results:

When 5 mg and 10 mg doses of MSG were administered along with saline (0 mg MSG), the post-MSG LH concentration increased ($P<0.05$) in comparison to the mean pre-MSG levels of LH in the serum. The levels of the serum LH was not impacted by the 20 mg dose of MSG. All MSG injection dosages resulted in a notable rise in mean levels of serum FSH. FSH levels remained unchanged in those who received 0 mg of MSG. Serum testosterone levels remained unchanged by MSG dosages of 0, 5, and 10 mg. However, blood testosterone levels decreased ($P < 0.05$) in response to a 20 mg dosage of MSG.

Conclusion:

The current findings show for the first time that gonadotropin secretion is stimulated by peripheral MSG treatment. These results suggest that glutamate is involved in the regulation of gonadotropin release.

MeSH Terms:

Glutamate, Human, Gonadotropins, Testosterone, N----P---Y---

INTRODUCTION

Glutamate is one of the most significant major excitatory amino acids (EAA) and a key mediator in brain functions, neurotransmission in the central nervous system[1] and, hormonal release[2]. A wide range of different neurotransmitters seem to be involved in altering the behaviour, which includes both activation and inhibition of the GnRH neurons, the most prominent ones being GABA, NPY, glutamate, and, more recently, kisspeptin have also emerged[3, 4, 5] The excitatory amino acids are majorly found in presynaptic boutons of several important hypothalamic structures, such as the preoptic area (POA), supraoptic, suprachiasmatic, paraventricular and, arcuate nuclei, and organum vasculosa of the lamina terminalis (OVLT). Moreover, it is proved that the anterior, middle, and posterior lobes pituitary contain non-NMDA (kainate) and ionotropic N-methyl-D-aspartate (NMDA) receptors simultaneously. The OVLT/ preoptic area, which is home to GnRH cell bodies, appears to be the primary location of NMDA action, whereas AMPA and kainate may primarily act at the arcuate nucleus/ median eminence, which is home to GnRH nerve terminals[6].

All significant regions of hypothalamus are vital to reproduction containing glutamate and its receptors. It functions mainly by causing Nitric oxide (NO), a gaseous neurotransmitter to be released, triggering the Guanylate cyclase, a heme-containing enzyme, increases the synthesis of cGMP and ultimately releases GnRH[7]. Finding the anchoring or clustering proteins that connect the glutamate-NO neurotransmission pathway and target glutamate receptors to the synapse, has been the focus of recent research[8]. The transition of childhood into adulthood, a process also known as puberty is regulated by the hormones specifically GnRH activation. Both neurotransmitter and glial cell regulatory pathways have been implicated in the stimulation of GnRH neurones to initiate puberty[9, 10]. To control pituitary gonadotropin secretion, in the pituitary portal circulation, GnRH is released via axons that originate from the hypothalamic GnRH neurones and go to the median eminence. Gonadotropins like LH and FSH are also released in pulsatile manner in response to the pulsatile production of GnRH critical for the proper functioning of the gonads[11, 12, 13]. finally releasing testosterone[14]. Recent studies suggest the stimulation of GnRH neurons during puberty is a major function of direct glutamate transmission at these neurons.

EAAs' impact on pulsatile LH and FSH production has also been demonstrated in animals specifically mice, but no efforts have been made to test it on man[13,15, 16,17,18.]

This review focuses on MSG's impact on gonadotropin secretion when administered intravenously and their target hormones in adult healthy male individuals.

MATERIALS AND METHODS:

During 6th October to 30th December 2023, an experimental study was conducted in the Medicine Department of Watim General Hospital Rawat Rawalpindi. Following approved by the Clinical Research Ethics Committee of the institute, the study was initiated.

Inclusion criteria:

A total of sixteen (16) adult males in good health, aged 20 to 37 (mean ± SEM: 27.4 ± 1.5 years) having a body weight of 49–80 kg (mean ±SEM: 62.1 ± 2.1 kg) participated in the study.

Exclusion criteria:

Abnormal clinical and biochemical reproductive function, significant comorbidity or systemic disease, as well as medical or recreational drug use.

The patient's informed written consent was obtained following a thorough description of the study's purpose, length, and procedures in their native tongue. Following a comprehensive examination of the patient's medical history, four (4) patients per group were chosen at random to get a single intravenous bolus of MSG at the dosages of Zero, Five, Ten, or

Twenty mg/kg BW, as indicated in Table 1.

Teflon cannulas were used to create two intravenous lines in the radial veins: one for the drug delivery and blood collection, and the other for saline infusion (0.9% NaCl). For 60 minutes prior to and 180 minutes following the MSG injection, blood samples were taken at 30-minute intervals. An extra sample was taken 15 minutes after the injection. Throughout, physiological indicators like body temperature, pulse, and blood pressure were tracked.

Following follow-up exams 24 and 48 hours after administration, subjects were monitored for any negative reactions while being permitted to eat and drink accordingly. EIA and IEMA were used to determine the levels of testosterone, FSH, and LH, as indicated in Table 2.

Data Analysis:

SPSS version 23 was applied to analyse the data. Changes in hormone concentrations in response to MSG were statistically analyzed using a t-test; results were displayed as mean ±SEM, and a P-value <0.05 was considered significant.

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 ± 2 3.9	63.7 ± 2.9

Table 2: Characteristics of Performance for Various Assays

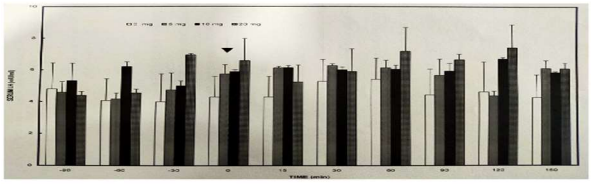
Hormone	Assay type	Intra-assay Co-efficient of Variation	Sensitivity
FSH	IEMA	< 5%	1.0 mI U/ml
LH	IEMA	< 6%	1.0 mI U/ml
Testosterone	EIA	< 6%	0.5 ng/ml

Results:

Figure 1 displays the effects of varying MSG dosages on serum LH concentrations. When saline (0 mg MSG) was administered, the serum levels of LH remained unchanged. Every participant who received dosages of 5 and 10 mg of MSG exhibited an increase in LH secretion. In response to 5 and 10 mg ($P < 0.05$) dosages of MSG, mean post-MSG LH levels were higher than pre-MSG values (Figure 2). Although the rise was not statistically significant, mean LH concentrations in the post-20 mg MSG period similarly raised in comparison to pre-MSG levels.

It was clear that all MSG dosages significantly raised blood FSH levels (Figure 3). Figure 4 compares the mean FSH concentrations before and after MSG. The FSH concentration in the saline-treated patients remained unchanged. The administration of 5 mg ($P <0.005$), 10 mg (0.0005), and 20 mg ($P < 0.01$) dosages of MSG resulted in a substantial increase in mean FSH levels.

Figure 5 illustrates how intravenous MSG challenges affect testosterone levels in the blood. Figure 6 compares the



mean testosterone serum concentrations before and after injections of various MSG dosages. Following the administration of dosages of 0, 5, and 10 mg of MSG, the mean serum testosterone levels remained unchanged. In comparison with the pre-MSG testosterone concentrations, the mean testosterone levels that were present following the injection of 20 mg MSG were lower ($P < 0.05$).

Figure 1.

Variations in the mean ± SEM serum levels of LH following intravenous injection of various MSG dosages (n = 4 per dose). The MSG injection time is shown by an arrow.

Figure 2.

Mean ± SEM LH concentrations before and after MSG at different MSG dosages (n = 4 per dose). A substantial rise ($P < 0.005$) in the post-MSG hormone concentrations is shown by an asterisk.

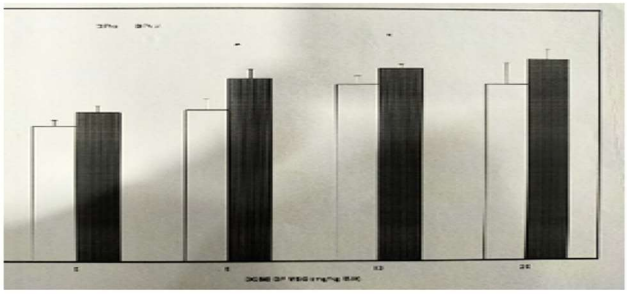


Figure 3.
Variations in the mean ± SEM blood levels of FSH following intravenous injection of various MSG dosages (n = 4 per treatment). The MSG injection time is shown by an arrow.

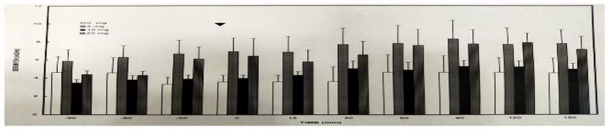


Figure 4.
Mean ± SEM FSH concentrations before and after MSG at different MSG dosages (n = 4 per dose). A substantial (P < 0.005) change in the post-MSG hormone concentrations is shown by an asterisk

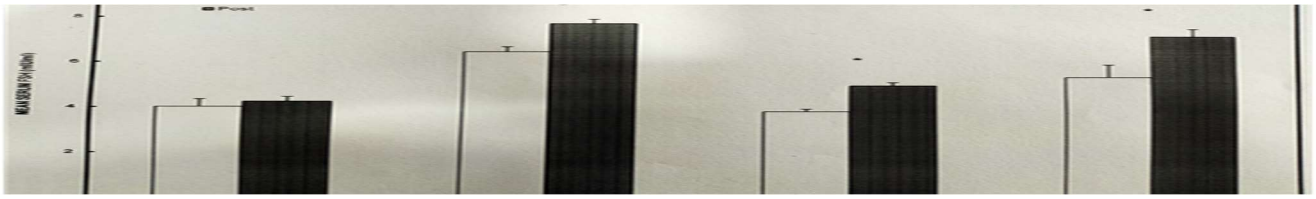


Figure 5.
Variations in the mean ± SEM Testosterone blood concentrations following intravenous injection of various MSG dosages (n = 4 per treatment). The MSG injection time is shown by an arrow.

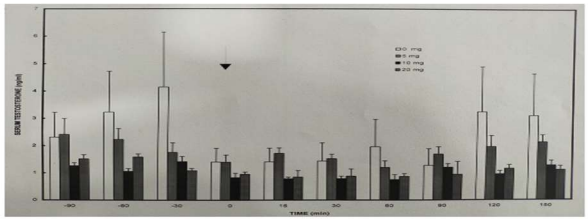
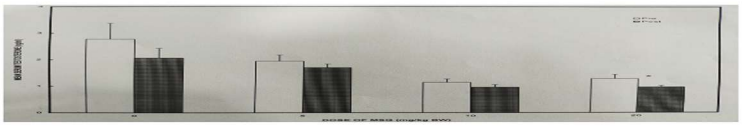


Figure 6.
Mean ± SEM Testosterone concentrations before and after MSG at different MSG dosages (n = 4 per dose). A substantial drop (P < 0.005) in the post-MSG hormone concentrations is shown by an asterisk.



Discussion:

Glutamate is typically found in the diet as a free amino acid and as a part of protein [19]. MSG a common dietary addition in the food industry, is present in trace amounts to enhance flavour but typically goes unlabelled, can be found in our meals [20]. Generally speaking, MSG creates free radicals that lead to oxidative stress, which is the pathophysiology of numerous illnesses[21, 22]. Testicular tissue damage is caused by oxidative stress through DNA damage and elevated lipid peroxidation in the tissue's long-chain polyunsaturated fatty acids. Considering the findings of Koohpema et. al. 2022 [23] following six months of MSG (3 g/kg bw), the MSG group's LH, FSH, and testosterone levels in the blood sharply decreased. The influence of MSG on the pituitary-gonadal-hypothalamic axis may be the primary cause of this reduction. It has been demonstrated that MSG destroys nerve cells in the pituitary and hypothalamic regions of the central nervous system (CNS), which can impact GnRH (gonadotropin-releasing hormone) release. Kayode et al. 2020 [24] conducted another study that supports the MSG's neurotoxic effects interfere with the hypothalamic-pituitary-axis (HPA) circuit to cause excitotoxicity in the brain. As an excitatory neurotransmitter, glutamate can generate a large intracellular calcium influx in neurons, which can result in neuronal death. Among the sex hormones are testosterone, luteinizing hormone, and follicle-stimulating hormone, whose levels may be lowered by HPA disturbance. Ultimately, this causes changes in the quality of sperm.

Serum levels of testosterone, FSH, and LH were significantly decreased in another study by Alrashidi et al. 2023 [25] following intraperitoneal delivery of MSG at a daily dose of 4 g/kg for about 28 days.

According to a different study by Oluwole et al. 2024 [26] giving Wistar rats 4 mg/kg of MSG for 120 days had a negative impact on the production of testosterone, sperm parameters, serum enzymatic activities, GnRH, LH, and FSH, as well

as serum cholesterol levels.

Rats were given MSG via gastric tube at a dose of 60 mg/kg body weight per day in another study by Taha et al. 2024[27] as injection of MSG had a negative impact on sperm parameters, testosterone production, and hormone levels.

Following the injection of 5 and 10 mg doses of MSG, blood levels of both LH and FSH increased slightly but statistically substantially in the current investigation. The secretion of gonadotropins was found to be affected differently by the 20 mg dose of MSG. A slight increase in blood LH levels was identified with a 20 mg dose of MSG, however there was a considerable increase in serum FSH concentrations. The study's surprising conclusion was that after taking a 20 mg dose of MSG, blood testosterone levels seemed to be decreased. Although the exact causes of this discovery are unknown, it may be related to differences in endogenous testosterone secretion in those who received a 20 mg dosage of MSG.

In a study done by Mondal et. al 2018[28], the Charles Foster strain's female virgin rats (about 120 gm) showed a significant elevation in serum levels of LH, FSH, and estradiol during 30 and 40 days when administered MSG orally, by gavage at doses of 0.8, 1.6, and 2.4 gm/kgBW/day, respectively.

However, Jubaidi et al. 2019 [29] observed a rise in FSH and a decrease in LH and testosterone levels, indicating a disruption in spermatogenesis that results in an overabundance of signals to the brain to release FSH following MSG supplementation at 120 mg/kg body weight.

Conclusion:

The current study offers the first, however early, proof that systemic MSG treatment can increase gonadotropin production in healthy adult men. It is yet unknown, though, if MSG or other EAAs have a physiological role in controlling human gonadotropin secretion. The current findings also raise the prospect of employing EAA as clinical probes to evaluate the GnRH neurons' functional integrity under diseased and pathogenic circumstances. There aren't many researchs that look at how MSG affects the release of gonadotropins. To confirm or deny MSG's effects on the hormonal profile, more experimental research is required.

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