Metabolic Abnormalities of Obesity Induced by Monosodium Glutamate and Their Effect on Male Sex Hormones in Rats

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Abstract

This study aimed to identify the potentially negative impacts of monosodium glutamate (MSG) on male rat sex hormones and several biochemical markers. There were two primary groups made up of thirty male Sprague Dawley rats. The first group (n=15) was given distilled water (serves as negative control). The other group (n=15) received 15 mg/kg B.W. of MSG orally throughout a three-month period. According to results the amount of total testosterone (TT) significantly dropped In addition, Triacylglycerol (TAG), total cholesterol (TC), glycated haemoglobin (HbA1c), insulin, leptin, tumour necrosis factor alpha (TNF-), interleukin-6 (IL-6), liver enzymes, renal function, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were significantly higher than before. prolactin (PRL) levels did not alter, though. It can be said that MSG has severe effects on the liver, kidneys, lipid profile, and may be a factor in male infertility.

Keywords: *obesity; sex hormones; monosodium glutamate*

INTRODUCTION

Obesity is a global problem which increases at an alarming rate in the world during the last three decades. It is a complex, multifactorial chronic disease involving environmental, genetic, physiological, metabolic, behavioral, and psychological components (1). Obesity is closely associated with the development of metabolic abnormalities including glucose intolerance, insulin resistance (IR), type 2 diabetes (T2D), cardiovascular diseases (CVD), metabolic syndrome, hyperlipidemia, chronic inflammation and male hypogonadism (2).An essential part of controlling inflammatory processes is played by fat tissue. Increased production of cytokines that cause a low-grade inflammatory response has been linked to increased visceral fat, and this could eventually lead to insulin resistance (3). Particularly, the establishment of insulin resistance in obesity and type 2 diabetes is stimulated by the production of numerous hormones and cytokines by adipose tissue which have side effects on skeletal muscle and the liver (4). In the regulation of insulin sensitivity, tumour necrosis factor type alpha (TNF- α) and adiponectin have shown an inverse association; whereas TNF- α contributes significantly to insulin resistance, adiponectin promotes insulin sensitivity. Other cytokines are also thought to be involved in this process (5). Interleukine-6 (IL-6) also rises with obesity and is strongly associated with endothelial dysfunction and sub-clinical

inflammation. Leptin has also been linked to disorders like insulin resistance syndrome (6) that include obesity, type 2 diabetes, dyslipidemia, and cardiovascular disease. Obesity and metabolic disorder in males are related to hypogonadism as a common feature, Thus, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are secreted from the pituitary as a result of the pulsatile release of hypothalamic gonadotropin-releasing hormone (GnRH) (7). The primary regulating hormones that affect the testicular cells are these gonadotropins. Inhibin synthesis is stimulated by FSH action on sertoli cells, which also indirectly controls spermatogenesis. On the other hand, inhibin works directly to downregulate pituitary FSH release through a negative feedback mechanism. LH encourages Leydig cells to increase testosterone production and steroidogenesis. Moreover Spermatogenesis is mediated by testosterone through its nuclear receptors in the sertoli cell (8).

Monosodium glutamate (MSG) (E621) is a common salt of glutamic acid widely used as a flavor enhancer at home as well as in food industry (9). Therefore, most canned food and fast food such as flavored flakes, ready meals, canned soups, mutton meat, bottled soy or Eastern sauces, tested and frozen tuna containing different concentrations of MSG (10).

MSG is harmful to both humans and test subjects' animals (11).it seems to have symptoms like headaches, flushing, numbness, dizziness, and weakness (12). High dosages of MSG have been linked to a number of diseases, including urticaria, cardiac arrhythmia, neuropathy, asthma, and atopic dermatitis (12). Additionally, it has neurotoxic effects that result in damage to brain cells, endocrine issues, retinal degeneration, and some pathological conditions like addiction, stroke, epilepsy, brain trauma, neuropathic pain, schizophrenia, anxiety, and depression, as well as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (13).

High doses of MSG administered to newborns or maternal are associated with obesity in animal models (14), probably through their effects on immature neurological mechanisms that control food intake and energy expenditure (15). Similarly, increased serum triglyceride, fasting glucose, and insulin levels are associated with increasing dietary MSG intake in rodent models, which are indicators of metabolic disorders (16).

The various mechanisms that MSG may cause male reproductive dysfunctions include spermatogenic alteration leading to low sperm count, high sperm abnormality, reduced live sperm, oxidative damage, histological alteration, and gonadotropin imbalance that ultimately results in male reproductive abnormalities (17).

Material and methods

From the Suez Canal University, Faculty of Veterinary Medicine's laboratory animal household, 30 healthy male Sprague-Dawley rats (weighing 120–150 g) were taken. Rats were housed in separate metal animal cages, five to a cage, with controlled humidity (55–60%), temperature (20–24° C), and dietary requirements. Rats had unlimited access to food and water (18). Two primary groups of rats were randomly assigned; the initial group, designated as Control one (group A) (n=15), distilled water was delivered orally once per day for three months. MSG is the second group (group B) (n=15), got MSG via stomach intubation once daily for three months at a dose of 15 mg/kg B.W. The weekly body weight was

used for adjust the MSG dosage. The study method's protocol was followed in accordance with the recommendations of the faculty of medicine's ethics committee at Suez Canal University in Egypt. The rats were slaughtered at the conclusion of the third month, and samples of blood were taken from the medial canthus of the eyes of the two groups.

Blood Samples

Blood was collected from two samples. There were two divisions of the samples. The first division was placed in chemically free tubes with anticoagulant (EDTA) for measuring glycated haemoglobin. While the second division was collected in centrifuge tubes without anticoagulant for serum separation, The blood samples were centrifuged at 3000 rpm for 15 minutes after clotting, and the clear serum was carefully aspirated into chemically free and clean tubes for the analysis of biochemical parameters.

Biochemical studies

Total cholesterol and triacylglycerol were determined using the procedures described by Allain et al. (19) and Siedel et al. (20), respectively. Fasting blood glucose (FBG), glycated hemoglobin (HbA1C) (%), and fasting blood insulin (FINS) according to Tietz (21), Zander et al. (22) and Sapin (23), respectively. HOMA-IR calculation in accordance with Simental-Mendía et al. (24). serum ALT and AST assay in accordance with ECCLS (25), and creatinine and urea assay in accordance with Jaffé (26) and Rock (27), respectively. Leptin, tumour necrosis factor alpha (TNF- α), and interleukin-6 (IL-6) levels were measured using the techniques described by Landt et al. (28), Feldmann and Maini (29), and Taga and Kishimoto (30), respectively.total testosterone was determined according to Thienpont et al (31). Follicle Stimulating Hormone (FSH), Luteinizing hormone (LH) and Prolactin hormone (PRL) were determined according to Bablok et al (32).

Statistical analysis

Independent sample t-test was used for statistical analysis using Windows SPSS, version 20. Results were showed as mean ± SE. $P< 0.001$ was regarded as statistically highly significant, and $P< 0.05$ as statistically significant.

Results and discussion

Obesity is associated with an array of illnesses, including T2D, IR, dyslipidemia, and cardiovascular disease (CVD). It is a major contributing factor to the emergence of metabolic disorders like insulin resistance, metabolic syndrome, glucose intolerance, low-grade inflammation, and male infertility (33). Obesity is described as having extra body fat or adipose tissue as a result of consuming too much food and/or using less energy (34). It is defined by an abnormal, excessive storage of energy in the form of fat in adipose tissue (35), which is caused by a malfunction of the brain's satiety centre, an imbalance between energy intake and usage, and hereditary differences (36).

Due to MSG's dual functions as a taste stimulation and a taste bud neuromodulator, use of the substance has expanded globally in recent years. MSG's use as a flavouring agent has been linked in numerous studies to the development of the metabolic syndrome and obesity in both humans and animals (37).

Table 1. Effects of MSG on body weight, total cholesterol, triacylglycerol and glucose homeostasis

Parameters	**Control group (group A)**	**MSG group (group B)**
Average body weight (BW/g)	$190^{b}\pm6.7$	$342^{a}\pm19.24^{**}$
Total Cholesterol (mg/dl)	$77.00^{b}\pm1.96$	$143.75^{a}\pm8.98^{**}$
Triacylglycerol (mg/dl)	$54.00^{b}\pm4.10$	$161.75^{a}\pm15.73^{**}$
Fasting blood glucose (mg/dl)	$76.25^{b}\pm5$	$139.25^{a}\pm3.48^{**}$
Glycated hemoglobin HbA1c (%)	$4.43^{b}\pm0.22$	$6.63^{a}\pm0.13^{**}$
Fasting blood insulin (ng /ml)	$6.25^{b}\pm0.32$	$19.25^{a}\pm0.48^{**}$
HOMA –IR	$1.00^{b}\pm0.08$	$5.85^{a}\pm0.25^{**}$

Represented data mean ± SEM. **Highly significant difference at $p<0.001$

The results in Table1 showed that group B exhibited significantly high increase ($p<0.001$) in body weight, total cholesterol, triacylglycerol, Fasting blood glucose, HbA1c, Fasting blood insulin and HOMA –IR when compared to the group A. MSG stimulated orosensory receptors, which led to an increase in body weight and also had a beneficial impact on the appetite centre, which led to an increase in weight due to an increase in food palatability (38).MSG may be neurotoxic by increasing energy intake, causing damage to the hypothalamic arcuate nucleus, which is essential for the control of metabolic balance and insulin secretion and action and impair leptin action by disrupting the hypothalamus signalling cascade, leading to leptin resistance associated with obesity (39). By making food more palatable and interfering with the leptin-mediated hypothalamic signalling flow, MSG use disrupts the body's sense of energy balance and ultimately results in obesity (40).

High significant increase in total cholesterol and triacylglycerol ($P< 0.001$) might be attributed to the lipid peroxidation of cell membranes, release of free fatty acids into the circulation from adipose tissue, a rise in acetyl CoA concentrations, which increases cholesterol synthesis (41).

Highly significant rise in the levels of insulin, HBA1C, and blood sugar in addition to HOMA-IR demonstrating that type 2 diabetes, obesity, hyperglycemia, hyperlipidemia, and insulin resistance are all caused in mice by parenteral MSG administration. The increase in blood sugar levels can be attributed to the liver's acceleration of glycogenolysis and gluconeogenesis as well as a temporary loss of the pancreas' endocrine functions (42).

The possibility of a worsening of glucose tolerance in rats after MSG administration has been raised. Even under the hyperinsulinemic conditions seen in mice treated with MSG, the altered glucose tolerance may be attributable to impaired cellular insulin sensitivity. Cells may

switch to pathways that promote gluconeogenesis in hyperinsulinemic circumstances to make up for the increased insulin secretion (43). Hugues et al. (44) also demonstrated the occurrence of hyperinsulinemia/hyperglycemia in MSG-treated rats. Despite the fact that insulin secretion increased to a higher degree, they discovered that glutamate did not lower blood glucose levels. They said glutamate was the cause of insulin resistance.

Table 2. Effects of MSG on kidney function tests and liver enzymes

Parameters	**Control group (group A)**	**MSG group (group B)**
Alanine transaminase (ALT) (U/L)	$38.75^{b}\pm1.11$	$71.25^{a}\pm3.12^{*}$
Aspartate transaminase (AST) (U/L)	$121.75^{b}\pm5.45$	$140.75^{a}\pm3.25^{*}$
Creatinine (mg/dl)	$0.50^{b}\pm0.06$	$0.62^{a}\pm0.06^{*}$
Urea (mg/dl)	$20.50^{b}\pm2.1$	$36.00^{a}\pm1.22^{*}$

Represented data mean ± SEM. * significant difference at $p<0.05$

The results in Table2 showed that group B exhibited a significant increase in serum ALT and AST activity than group A ($P<0.05$). This could be attributable to hepatocellular impairment and liver function alterations, which led to the release of more intracellular enzymes into the blood (45). Elevation level of creatinine and urea can be attributed to impairment of kidney function which may be brought on by the impact of MSG on kidney tissues (46). Additionally, blood levels of urea and creatinine elevated when the kidney's capacity to filter bodily fluid decreased (47).

Table 3. Effects of MSG on Leptin, TNF-α and Interleukin-6

Parameters	**Control group (group A)**	**MSG group (group B)**
Leptin (pg/ml)	$881.25^{b}\pm13.90$	$1435.00^{a}\pm25.33^{**}$
TNF-α (pg/ml)	$187.50^{b}\pm5.95$	$395.00^{a}\pm10.41^{**}$
Interleukin-6 (IL-6) (pg/ml)	$86.25^{b}\pm4.03$	$248.25^{a}\pm13.53^{**}$

Represented data mean ± SEM. **Highly significant difference at $p<0.001$

Table3. showed that MSG-obese rats had a high significant levels of leptin ($P<0.001$) than control rats (group A). This is in agreement with Perello et al. (48) who found that rodents given monosodium L-glutamate (MSG), which destroys between 80% and 90% of the neurons in the arcuate nucleus of the hypothalamus at neonatal age develop neuroendocrine and metabolic abnormalities, leading to a phenotype of adiposity characterised by GH deficiency, hyperinsulinemia, and hyperleptinemia because of leptin resistance.

Compared to rats in control groups, MSG-obese animals showed a highly significant rise in TNF- α and IL-6 levels ($P<0.001$). This is in

line with other studies that have demonstrated that persistent pro-inflammatory pathway activation in insulin target cells might result in obesity linked with IR. Therefore, it has been found that people with IR and diabetes have high levels of IL-6, TNF- α, and C-reactive protein, among other pro-inflammatory mediators (CRP). Additionally, obese, diabetic, and insulin resistant animals have higher levels of TNF- α in their blood and adipose tissue (49).

Table 4. Effects of MSG on sex hormones

Parameters	Control group (group A)	MSG group (group B)
Total Testosterone (ng/mL)	$3.38^{a}\pm0.18$	$1.58^{b}\pm0.25^{*}$
Follicle-Stimulating Hormones (FSH) (mIU/mL)	$2.93^{b}\pm0.17$	$6.38^{a}\pm0.44^{*}$
Luteinizing Hormones (LH) (mIU/mL)	$2.25^{b}\pm0.25$	$3.50^{a}\pm0.29^{*}$
Prolactin(PRL) (mIU/mL)	$4.90^{a}\pm0.47$	$4.18^{a}\pm0.34^{*}$

Represented data mean ± SEM. * significant difference at $p<0.05$

The results in Table4 illustrated that MSG obese rats exhibited a significant lowering in total Testosterone ($P<0.05$) levels comparative to rats in control. The decrease in total testosterone is brought on by the breakdown of the neurones in the hypothalamus gland as well as the ensuing disruption of the hypothalamic-pituitary-testicular axis (50). The hypothalamic-pituitary-testis regulatory axis, which controls testicular Leydig cells' steroidogenesis can be disrupted as a result of neuronal losses in the hypothalamus, according to a previous study that found that administering MSG to rats and mice could cause damage to their neurons (51). According to research by Fui et al. (52), overweight and moderate obesity are mostly linked to declines in total testosterone, especially in younger males. Total testosterone levels decline primarily as a result of decreased sex hormone binding globulin (SHBG) caused by obesity-related hyperinsulinemia. De Angelis et al. (53) reported that once obesity develops, in addition to insulin resistance, adiposity has been reported to have an impact on the hypothalamus-pituitary-gonadal axis, which may directly influence testosterone production. This suggests that the current decrease in plasma testosterone levels may be caused by insulin resistance.

Table 5. Pearson's correlation analysis of data

Correlations							
		HOMA-IR	HbA1c	FSH	LH	B_Weight	Testosterone
B_Weight	Pearson Correlation	$.989^{**}$	$.962^{**}$	$.935^{**}$	$.800^{*}$	1	$-.930^{**}$
	Sig. (2-tailed)	.000	.000	.001	.017		.001
	N	8	8	8	8	8	8
HOMA-IR	Pearson Correlation	1	$.965^{**}$	$.951^{**}$	$.860^{**}$	$.989^{**}$	-.927**
	Sig. (2-tailed)		.000	.000	.006	.000	0.001

	N	8	8	8	8	8	8

**Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

The current study demonstrated a significant rise in LH and FSH levels following MSG administration Table4. This could mean that MSG has disrupted or damaged the hypothalamus' hormonal secretion circuits (54). In response to hypothalamic gonadotropin releasing hormone, the pituitary releases both FSH and LH (GnRH). While FSH encourages Sertoli cells to assist spermatogenesis and inhibin B secretion, which inhibits FSH secretion, LH stimulates the secretion of testosterone from Leydig cells. In addition to promoting sperm production, testosterone acts as a feedback mechanism between the brain and pituitary to control GnRH secretion (55).

Because testosterone's negative feedback loop on the brain's and pituitary's secretory activities is reduced, higher levels of GnRH and FSH/LH secretion may be the cause of the high plasma concentrations of luteinizing hormone and follicle stimulating hormone after exposure to MSG in this study (56).

The observed increase in FSH level demonstrated that spermatogenesis is disrupted, resulting in an excess of signals to the brain to secrete FSH. Following MSG administration, both unstable levels of FSH and LH suggested that this substance may have damaged or disturbed the hormonal secretion pathways in the hypothalamus (54).

Table4 also showed that there is no significant change in circulating prolactin levels between MSG group and control group. These results correspond to the results obtained by Ernst et al. (57). They reported that prolactin directly promotes excess energy toward the visceral fat depot and found no evidence of a connection between the level of blood prolactin and the degree of obesity or its associated metabolic disturbances or any systematic changes in basal concentrations of the hormone after massive weight loss.

Conclusion

Obesity is a collection of connected metabolic features that directly raising the risk of type 2 diabetes, insulin resistance, dyslipidemia and male infertility. One of the most often utilised food additives consumed with commercially processed meals is MSG. In addition to having a negative impact on reproductive health, prolonged, excessive use of MSG can cause obesity, kidney damage, hepatotoxicity, and metabolic disorders.

Conflict of Interests

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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