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Ingestion of monosodium glutamate (MSG) in adult male rats reduces sperm count, testosterone, and disrupts testicular histology

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ABSTRACT

Objective: Monosodium glutamate (MSG) is a widely used food additive with controversial side effects. Though neonatal administration of MSG has been shown to affect fertility via arcuate nucleus ablation, the body of work involving the effects of adult MSG administration on male rat fertility has yet to be collectively assessed.

Design: Systematic review.

Methods: A PubMed search using terms “monosodium glutamate” in addition to “male fertility” or “male reproduction” or “sperm” or “testes” was performed. Inclusion criteria included: English language, adult administration of MSG, male reproductive outcomes, and control groups. Additional studies were identified via reference lists of relevant articles.

Results: Of 167 records originally identified, six studies remained after removal of duplicates and studies not meeting inclusion criteria. Data ranges included: cohort sizes of 24 – 32 animals, dosing from 0 to 4 g/kg, MSG administration duration of 10 – 56 days, and weight 75 – 200g. In MSG fed rats compared to controls: Sperm count was lower in three of four studies, serum testosterone concentration was lower in two of two studies, testicular component weights or size was decreased in two of three studies, and abnormal testicular and sperm histology was observed in five of six studies.

Conclusion: Adult intake of MSG can negatively impact sperm count and serum testosterone concentrations as well as testicular morphology and histology in rats. Further investigation of this effect should be evaluated in humans for such a popular flavor enhancer.

Keywords: Monosodium glutamate, MSG, fertility, male, rats, sperm, sperm count, testosterone, seminiferous tubules, testicles,

INTRODUCTION

The flavor enhancer monosodium L – glutamate (MSG) is widely utilized across the globe and in different types of food preparations.¹ Daily intake of added MSG varies from 0.55 grams per day in the United States to 1.57 grams per day in Korea, though a highly seasoned meal can contain five grams of MSG in itself.^{2,3} Yet, glutamate ingestion from common and natural foods far exceeds the flavor enhancing doses utilized in cuisines; with 5.6 grams of glutamate per 100 grams of peas as well as 9.6 grams of glutamate per 100 grams of parmesan cheese.² Though some still report anecdotes of “Chinese Restaurant Syndrome”, double-blinded placebo controlled crossover studies have failed to demonstrate a reproducible link between MSG intake and symptoms.^{1,4}

When administered at high doses parenterally or very high doses via bolus gavage to rats and rabbits, MSG has been shown to cause damage to neurons in the hypothalamus, however primates appeared to have much less damage.^{1,5-7} Hepatotoxic and nephrotoxic effects have also been demonstrated in rats upon excess administration of MSG (8 grams MSG per kilogram of body weight via intravenous injection).⁸ The reproductive system can also be affected as a number of rat studies have shown hypothalamic-pituitary-gonadal axis dysregulation via ablation of the hypothalamic arcuate nucleus following high-dose, or more than 1.0 grams of MSG per kilogram of bodyweight, MSG bolus administration during neonatal development.⁹⁻¹³ These doses remain far below the oral dosage that is lethal to 50% of rats and mice, which is 15 – 18 grams MSG per kilogram of bodyweight, respectively.¹

Since MSG usage in milk and baby foods is highly limited, it is more relevant to evaluate studies of adult MSG administration in order to assess present dietary consumption patterns.¹⁴ This review summarizes the findings of adult MSG intake of rat subjects, mainly through oral ingestion, and the resulting effects on parameters of male fertility such as sperm count, serum testosterone levels, as well as testicular morphology and histology.

METHODS

A Pubmed search was conducted in October 2014 using search terms “monosodium glutamate” in combination with either “male reproduction”, “sperm”, or “testes”. Specific search MeSH terms are detailed in **Table 1**. Search records were compiled and duplicates removed automatically using EndNote X7 software (Thomson Reuters). Remaining records underwent abstract and text screening for inclusion criteria of English language, adult MSG administration, outcomes as parameters of male fertility, and having a control group. Reference lists of remaining articles were then screened for additional relevant studies. The following information was extracted from studies: author, year of publication, country, rat species, study subject characteristics (weight as a proxy of maturation and development, MSG dose and frequency, duration of MSG administration, and route of MSG administration), and outcomes (sperm count, serum testosterone concentration, testicular gross morphology or weight, and histological assessment of testicular tissues).

Table 1. Search term details

PubMed Search Terms	MeSH Search Terms
Monosodium glutamate male fertility	((("sodium glutamate"[MeSH Terms] OR ("sodium"[All Fields] AND "glutamate"[All Fields]) OR "sodium glutamate"[All Fields] OR ("monosodium"[All Fields] AND "glutamate"[All Fields]) OR "monosodium glutamate"[All Fields]) AND ("male"[MeSH Terms] OR "male"[All Fields]) AND ("fertility"[MeSH Terms] OR "fertility"[All Fields])) AND English[lang]
Monosodium glutamate male reproduction	((("sodium glutamate"[MeSH Terms] OR ("sodium"[All Fields] AND "glutamate"[All Fields]) OR "sodium glutamate"[All Fields] OR ("monosodium"[All Fields] AND "glutamate"[All Fields]) OR "monosodium glutamate"[All Fields]) AND ("male"[MeSH Terms] OR "male"[All Fields]) AND ("reproduction"[MeSH Terms] OR "reproduction"[All Fields])) AND English[lang]
Monosodium glutamate sperm	((("sodium glutamate"[MeSH Terms] OR ("sodium"[All Fields] AND "glutamate"[All Fields]) OR "sodium glutamate"[All Fields] OR ("monosodium"[All Fields] AND "glutamate"[All Fields]) OR "monosodium glutamate"[All Fields]) AND ("spermatozoa"[MeSH Terms] OR "spermatozoa"[All Fields] OR "sperm"[All Fields])) AND English[lang]
Monosodium glutamate testes	((("sodium glutamate"[MeSH Terms] OR ("sodium"[All Fields] AND "glutamate"[All Fields]) OR "sodium glutamate"[All Fields] OR ("monosodium"[All Fields] AND "glutamate"[All Fields]) OR "monosodium glutamate"[All Fields]) AND ("testis"[MeSH Terms] OR "testis"[All Fields] OR "testes"[All Fields] OR "inferior colliculi"[MeSH Terms] OR ("inferior"[All Fields] AND "colliculi"[All Fields]) OR "inferior colliculi"[All Fields])) AND English[lang]

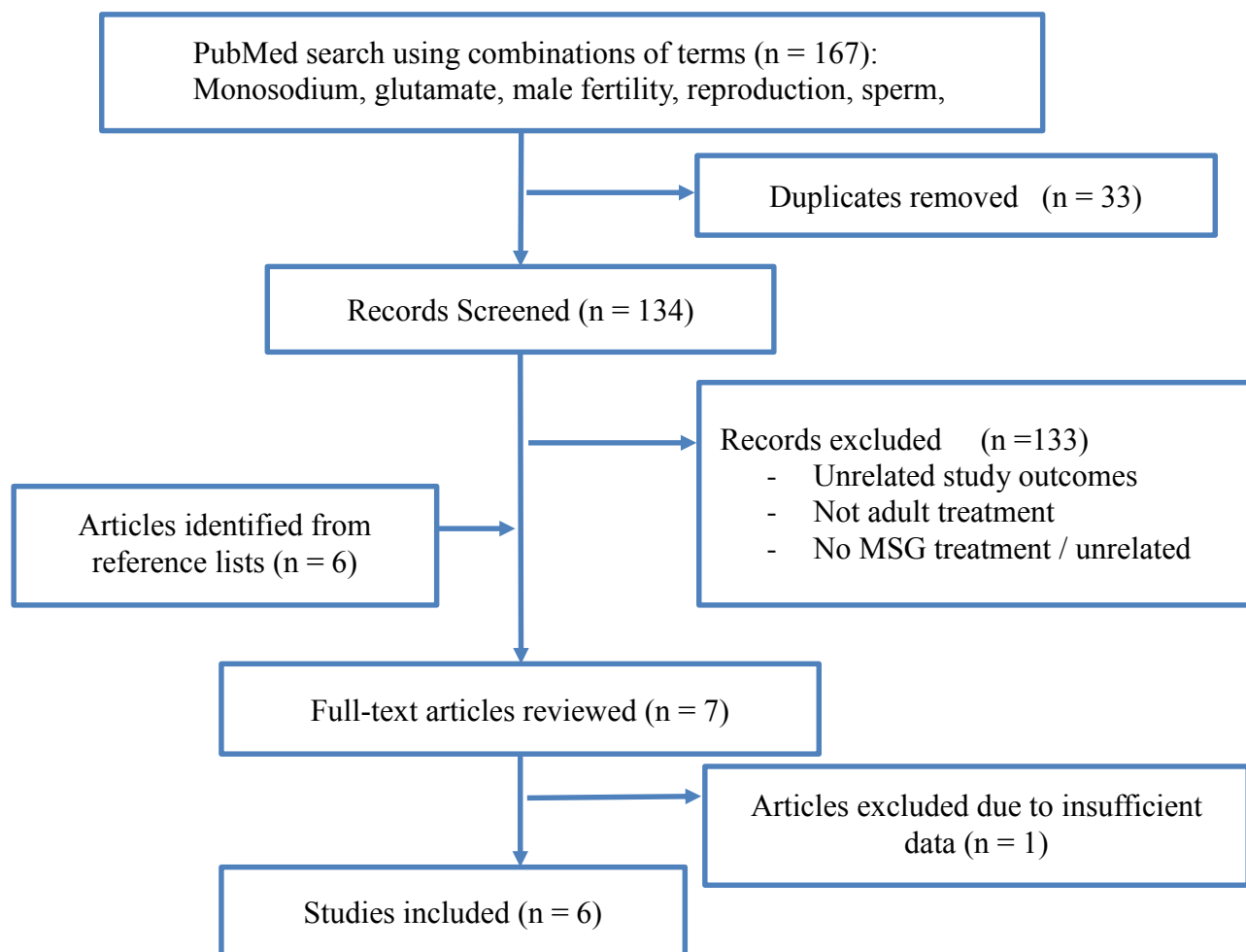
RESULTS

Selection of studies

A total of 167 records were obtained from original PubMed searches in October 2014, and 33 were identified as duplicates. Of the remaining 134 records that were screened via abstract or full text, 133 were excluded due to

lack of related outcomes or were identified as studies not involving adult rats. An additional six studies were identified from reference lists of screened articles. One more record was then excluded due to insufficient data for outcomes, leaving six publications to be included in this review. This search for relevant studies is summarized in **Figure 1**.

Figure 1. Flow diagram of search algorithm



Study Characteristics

Study characteristics are summarized in **Table 2**. Study publication dates were recent (2008 – 2014). Though not shown on Table 2, there were two studies from Nigeria, and one study each from Saudi Arabia, Thailand, Egypt, and India. Rat species were different as three studies used Wistar rats, two used Sprague-Dawley rats, and one used *Rattus norvegicus*. Total study sizes were similar (n=24 to n=32) with dosing groups ranging from four to 10 rats per group. Weights of rats

were used as a proxy of maturation, which ranged from 75 grams to 200 grams. One study did not provide rat weights but indicated study initiation at eight weeks of life.¹⁵ MSG dosing ranged from 0g/kg for controls up to an estimated 12.27g/kg, and frequency was every 24 hours except for one study in which the MSG was administered every 48 hours. Duration of administration also ranged widely from 10 days to 56 days. MSG was administered orally in four studies and via intraperitoneal (IP) injection in two studies. Some study characteristics were

provided via additional communication with authors.¹⁶

Sperm Count

Of the four studies that reported sperm count measured in either total sperm count ($\times 10^6$) or in concentration ($\times 10^6/\text{ml}$), three studies showed significant reductions in sperm. The study that did not observe significant reductions in sperm count had duration of MSG oral administration for 14 days,¹⁷ whereas the other two studies of oral administration for 28 and 42 days saw significant reductions ($p < 0.05$) of sperm count comparing high MSG dose group to control group.^{15,18} One study that reported sperm count used IP injections as administration route for the MSG and observed significant ($P < 0.0001$) reductions in sperm count at both 15 days and 30 days.¹⁶ Control sperm count levels varied widely when measured in total sperm count (216.31×10^6 , 925.56×10^6) and varied less with sperm concentration values ($36.88 \times 10^6/\text{ml}$, $49.90 \times 10^6/\text{ml}$).

Serum Testosterone

Two studies reported serum testosterone concentrations in ng/ml. *Iamsaard et al.* observed a reported dose dependent relationship for reductions in serum testosterone with $P > 0.05$, $P < 0.05$, and $P < 0.01$ compared to the control group for oral doses of 0.25 g/kg, 3g/kg, and, 6g/kg respectively.¹⁵ *Igwebuike et al.* also observed depression of serum testosterone among MSG administered groups in an incomplete dose-dependent fashion, with low (1g/kg) and medium (2g/kg) MSG dose groups showing similar reductions compared to controls ($P < 0.05$) and the high (4g/kg) MSG group had significant reductions ($P < 0.05$) below the low and medium dose groups.¹⁸

Testicular Gross Morphology and Weight

Two of three studies observed gross testicular morphological changes, though studies did not measure the same parameters. One study found significant reductions in seminal vesicle weight ($P < 0.01$) and epididymal weight ($P < 0.05$);¹⁵ another study observed significant reductions in overall testicular weight ($P < 0.05$).¹⁶ One study found no microscopic or macroscopic changes to testicular tissues.¹⁸

Testicular Histology

Five of six studies described histological changes, such as spermatogonia loss,^{15,17,19,20} cell vacuolization,^{15,19,20} interstitial loss or hyalination,^{15,17,19} leydig cell loss,^{17,19} atrophied seminiferous tubules,¹⁹ irregular seminiferous tubules,¹⁷ dilated blood vessels,¹⁹ loss of late spermatids,²⁰ and decreased sperm morphology ($P < 0.0001$).¹⁶ One study, which observed reductions sperm count and serum testosterone, did not detect any histological lesions or changes in seminiferous tissue or interstitial epithelia nor changes in gross morphology.¹⁸

Table 2. Summary of study characteristics and outcomes

Author (Year)	Species	N (total)	N (groups)	Weight (g)	MSG Dose (g/kg) [frequency]	MSG Duration (days)	MSG admin	Results		
								Sperm (x10 ⁶)	[T] (ng/ml)	Testicular Morphology/ Histology of increasing MSG dosage
Alalwani (2013)	Wistar Rats	30	10 10 10	75-85	0 3 6 [24 hours]	56	Intra-peritoneal injection	--	--	Atrophied seminiferous tubules Necrotic spermatogonia Germ cell vacuolization Leydig cell necrosis Interstitial tissue loss, hyalinated Dilated blood vessels
Iamsaard (2014)	Sprague-dawley rats	32	8 8 8 8	-- 8 weeks of age	0 0.25 3 6 [24 hours]	28	Oral	36.9 ^c 34.3 37.0 24.7* (per ml)	0.45 ^c 0.44 0.27* 0.14**	Decreased seminal vesicle weight** Decreased Epididymis weight* Germ cell vacuolization Interstitial tissue loss Sloughing of spermatogenic cells
Igwebuikwe (2011)	Sprague-dawley rats	28	7 7 7 7	160 - 180	0 1 2 4 [48 hours]	42	Oral	216.3 ^c 137.5* 96.1* 47.6*	3.40 ^c 1.18* 1.24* 0.33****	No pathological lesions in seminiferous or interstitial epithelia No gross morphological changes
Kadir (2011)	Wistar rats	20	4 4 4 4 4	126 - 200	0 1.53 ^o 3.07 ^o 6.13 ^o 12.27 ^o [24 hours]	14	Oral	49.9 ^c 46.1 49.2 52.5 51.0 (per ml)	--	Decreased sperm motility* Decreased normal sperm morphology* Reduction in spermatogenic cells Reduction in interstitial tissue Reduction in leydig cells Irregular seminiferous tubules
Mohamed (2012)	Rattus norvegicus	24	6 6 6 6 6 6	180 - 190	0 g/kg 2 g/kg 4 g/kg [24 hours]	10 30	Oral	--	--	Decreased primary spermatocytes Necrotic spermatogenic cells Sertolli cell vacuolization Loss of late spermatids
Nayanatara (2008)	Wistar Rats	24	6 6 6 6	120 – 130 [†]	0 g/kg 4 g/kg [24 hours] [†]	15 30	Intra-peritoneal injection	925.6 ^c 132.0 ^{***} 137.8 ^{***}	--	Decreased testicular weight* Decreased testicular ascorbic acid levels ^{***} Decreased normal sperm morphology ^{***} (head, tail, microcephaly, cephalocaudal junction abnormalities)

^c control group^o Dosing estimated from average of rat inclusion weight limits and MSG dilution dataReported significance compared to control group: * P<0.05 **P<0.01 [†] P<0.001 ^{***} P<0.0001

*** P<0.05 significant reduction as compared to low dose group as well

[†] information retrieved from communication with author (unpublished)

DISCUSSION

Adult administration of MSG in male rats, whether oral or intraperitoneal, appears to cause significant reductions in sperm count and serum testosterone levels in addition to morphological and histological changes to testicular tissue.

However, not all studies agree on all effects. Though *Kadir et al.* observed significant reductions in sperm motility and morphology among other histological changes, there were no detected changes in sperm cell count.¹⁷ One major difference in their MSG administration compared to other groups was duration of the oral administration, which was 14 days, compared to 28, 30, 42, 56 days of other studies that administered MSG orally. This could potentially indicate that the more acute effect of oral MSG ingestion is related to spermatid maturation or quality of spermatogenic cells rather than the quantity of spermatids present. Interestingly, *Nayanatara et al.*, also had a short course of 15 days, and showed marked change in sperm concentration ($P < 0.0001$).¹⁶ Yet, this comparison may not be as valid because *Nayanatara et al.* administered the MSG via intraperitoneal injection.

Additionally, *Igwebuike et al.* observed significant reductions in sperm cell count and serum testosterone concentration but no pathological changes to testicular tissue on gross or histological evaluation.¹⁸ The notable factor in this study was the dosing frequency of MSG, which was every 48 hours, compared to the dosing frequency of 24 hours implemented by the rest of the studies. Perhaps this indicates the temporal duration in which cells of the testicular interstitium and seminiferous tubules are able to repair any modifications caused by the MSG influx before the following insult. Even

though the cytoarchitecture appears normal, a significant reduction of sperm cell count and serum testosterone was still detected.¹⁸

This data shows important implications on male fertility for the oral, and peritoneal, intake of MSG. Even so, it is challenging to assess if these changes are enough to truly affect the ability of the rat to produce progeny as breeding was not assessed in the reviewed studies. Furthermore, the correlations to human ingestion are still unknown, but it appears that the effects of MSG on parameters of fertility can be reversible, at least during short courses of MSG administration.²¹ Additionally, the dosing utilized in these rat studies are far greater than the normal dosages of human consumption, especially because excess MSG use can actually decrease palatability.¹ This dose of optimal palatability is observed at 60mg/kg compared to the large doses, such as three g/kg, used in the rat studies.¹

The addition of MSG in food preparation continues worldwide and appears to not have profound broad reaching acute symptoms, however the question of whether sperm count, testosterone, and testicular changes are present in chronic consumption of optimally palatable MSG doses (~60mg/kg) remains. Thus further investigation into the mechanisms of these effects, especially in humans, should be considered.

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