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RESEARCH ARTICLE

# Monosodium Glutamate Affects Metabolic Syndrome Risk Factors on Obese Adult Rats: A Preliminary Study

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## Abstract

Monosodium glutamate (MSG) is one of the most widely employed food taste enhancers and there is a safety concern on glutamate with respect to the obesity epidemics. The reported effects are attributed to the actions of MSG in the brain, which would affect food intake, body weight and lipid metabolism. The aim of this study was to evaluate the effects of the addition of MSG to the rat chow on body weight, food intake, plasma glucose and aminotransferases and plasma and liver lipids in adult obese and diabetic IIMb/Beta rats. Twelve male, 70-days-old rats randomly divided in two groups -Control and MSG (with 1 mg MSG/g of feed)- were housed in individual cages and allowed food and water *ad libitum* during 40 days. At day forty glycemia, total cholesterol and fractions, triacylglycerols (TAG), aspartate amino transferase (AST), alanine amino transferase (ALT) were quantified. Animals were euthanized, and abdominal fat pads and livers were excised and weighed. Liver lipids were extracted and quantified. There were no significant differences in feed intake, final body weight, perigonadal fat depots, plasmatic glucose and lipids, AST and ALT between groups. Retroperitoneal fat depots and liver relative weights as well as liver total lipid content were significantly higher in the MSG group. A relevant effect of MSG intake on abdominal fat and liver weight as well as liver lipid content was demonstrated in this study.

## Keywords

Monosodium glutamate, Obesity, Metabolic syndrome, Liver steatosis, Beta rats

## Introduction

Food taste enhancers and flavouring agents are additives of particular importance as they can improve palatability of nutritionally important foods that lack appeal. Free amino acids and protein hydrolysates have been employed as natural flavouring agents in cooking for many centuries and in different cultures. The fifth widely accepted taste -umami- is produced in protein rich foods, seafood, meats, stews and soups when they are cooked for a long time.

In 1908 Professor Kikunae Ikeda, working at the Imperial Tokio University identified glutamic acid salts as the chemical compounds responsible for the umami taste; later he isolated MSG from the kombu seaweed.

When MSG is added to foods it provides a flavour similar to the naturally occurring free glutamate. It is used to enhance the natural flavour of meat, seafood, poultry, snacks, soups and stews [1]. Food additives that provide umami taste, are categorized by Codex Alimentarius as flavour enhancers [2]. MSG is one of the most widely employed food taste enhancers, as it is added to a diversity of products in a concentration that goes from 0.1-0.8% of weight; a level similar to the concentration of native free glutamate in tomatoes and parmesan cheese [3].

Worldwide MSG consumption has increased in re-

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cent decades due to its action as both a taste stimulus and as a neuromodulator in taste buds [4]. It has also been proposed and evaluated as a substitute for sodium chloride, as an initiative to reduce the sodium content, particularly in industrialized foods, due to the association of excess plasmatic sodium and the development of several chronic non-communicable diseases [5].

There has been a safety concern of MSG with respect to the overweight and obesity epidemics [6]. Several studies, in both humans and animals, have associated the use of MSG as a flavour enhancer with the onset of obesity and the metabolic syndrome [7,8]. The reported effects are generally attributed to the direct actions of MSG in the brain, which would affect food intake, body weight and lipid metabolism. MSG has also been related to the glycolytic process, particularly when it is ingested with carbohydrates, but its effects on glucose metabolism are poorly characterized [9].

One of the most controversial aspects of MSG consumption is appetite; while some authors argue that by increasing palatability and altering the signaling cascade of leptin at the hypothalamic level, consumers become voracious, others describe a biphasic effect: the addition of MSG would stimulate appetite during ingestion but would improve post-symptomatic satiety [8,10,11]. Concern about MSG has been expressed as a risk factor, but epidemiological studies that have tried to prove linkage have yielded conflicting results [12,13]. Finally, the role of MSG, as a food additive, in the global obesity epidemic is still unclear.

The safety of glutamic acid-glutamates (E 620-625) has been re-evaluated by the European Food Safety Agency (EFSA) Panel on Food Additives and Nutrient Sources added to Food (ANS) on July, 2017. A level of 3.200 mg MSG/kg body weight as NOAEL (no observed adverse effect level) could be established from a neurodevelopmental toxicity study. Based on this NOAEL the Panel derived a group acceptable daily intake (ADI) of 30 mg/kg body weight per day, expressed as glutamic acid, for glutamic acid and glutamates. The Panel noted that, for some population groups, the exposure to these additives exceeded not only the proposed ADI, but also doses associated to adverse effects in humans [14].

The aim of this study was to evaluate the effects of the addition of MSG to the commercial rat chow on body weight, food intake, plasma glucose and aminotransferases and plasma and liver lipids on 70-days-old adult IIMb/Beta rats.

## Materials and Methods

### Animals and diets

For this study 12 male, 70-days-old IIMb/Beta rats, raised in the Biology department of the School of Medicine of the National University of Rosario (República Argentina), were used. This obese line of rats was obtained by a high degree of inbreeding and upward selection of body weight; it has been internationally recognized as a murine model for the study of metabolic syndrome [15].

The rodents, with an average weight of 246.9 ± 34.9 g (mean ± SD), were randomly divided in two groups. Animals were housed in individual cages for 40 days and kept in standard lighting (12 h light/12 h dark) and room temperature (22 ± 2 °C).

Initial levels of glucose, total cholesterol and TAG determined in fasting blood samples from tail puncture were (mean ± SD): blood glucose 108.9 ± 34.9 mg/dl; total cholesterol 124.0 ± 12.4 mg/dl; TAG 193.6 ± 40.4 mg/dl.

Throughout the experimental period, rats were allowed food (Rata/ratón laboratorio; GEPSA Feeds; Grupo Pilar S.A., Ruta Provincial 13 KM 2,5 Córdoba, Argentina) and water *ad libitum*. Feed composition was: protein 24 g/100 g; ether extract 6 g/100 g; fibre 7 g/100 g; moisture 13 g/100 g; ash 8 g/100 g. The animals were maintained in keeping with the National Institute of Health Guide for the Care and Use of Laboratory Animals and the protocol was approved by the Bioethics Committee of the National University of Rosario.

### MSG addition and daily intake

A water solution of 1 g MSG/100 ml was prepared. This solution was sprayed on the rat chow in a proportion of 100 mg MSG/100 g of the rat chow. Considering an average daily food intake of 30 ± 2 g, the MSG daily intake was 30 ± 2 mg.

### Measurements

Body weight and food intake were measured every other day. Food conversion efficiency was calculated according to the following equation:

Food conversion efficiency: (Body weight increase (g)/Food intake (g) × 100).

At day forty of the experiment, fasting cardiac blood samples were collected under anesthesia (ketamine hydrochloride 0.1 mg/100 g body weight and acetopromazine maleate 0.1 mg/100 g/body weight). Glycemia, total cholesterol, HDL and LDL cholesterol, TAG, AST, ALT were quantified, with enzymatic spectrophotometrical methods using Wiener Laboratories kits (Wiener Laboratorios SAIC; Rosario, Argentina). Animals were euthanized with 18% sodium pentobarbital overdose (10/12 mg/body weight) injected intraperitoneally [16]. Abdominal fat pads (retroperitoneal and epididymal) and livers were excised, rinsed in physiological solution, dried with filter paper and weighed. Relative fat depots and liver weights were calculated as the relation between organ weight and total body weight: (Organ weight/total body weight × 100).

Livers were stored at -18 °C until analyses.

### Liver analyses

Liver samples were homogenized in a Potter-Elve-

jahn homogenator and lipids were extracted with chloroform/methanol according to Folch [17]. Total lipids were quantified gravimetrically after evaporation of the solvents. Liver TAG and total cholesterol were determined with the same analytical procedures used for plasma.

### Statistics

All data are presented as mean values with their standard deviations. Statistical analyses were carried out using Graph Pad Prism 3.02 version program. Data were analyzed using Student's t test. A value of P below 0.05 ($p < 0.05$) was considered significant.

## Results

During the experimental period there was a significant increase in blood glucose and TAG levels, in both Control and MSG groups; total cholesterol remained in normal levels.

At the end of the experiment there were no significant differences between MSG and the control group in feed intake, final body weight nor in body weight increase (Table 1).

Final plasmatic glucose, total cholesterol and fractions, TAG, AST and ALT did not differ between groups (Table 2).

Retroperitoneal fat depots and liver relative weights were significantly higher in the MSG group (Table 1 and Table 3).

**Table 1:** Final body weight, weight increase, feed intake, efficiency, retroperitoneal (RP) and epididimal (EP) fat pads relative weight.

| | Control | | MSG | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | P |
| Final Body weight (g) | 354.6 | 61.36 | 377.42 | 45.1 | 0.495 |
| Weight increase (g) | 108.6 | 33.9 | 129.75 | 25.44 | 0.267 |
| Total feed intake (g) | 1046.51 | 88.79 | 1104.51 | 52.4 | 0.209 |
| Food conversion efficiency | 10.2 | 2.56 | 11.7 | 2.05 | 0.319 |
| RP pads relative weight | 2.85 | 0.61 | 3.71 | 0.51 | 0.033 |
| EP pads relative weight | 1.75 | 0.34 | 2.02 | 0.49 | 0.338 |

Control: n = 6; MSG: n = 6; P < 0.05 significantly different. Student´s T test.

**Table 2:** Final blood parameters: Glycemia, T. cholesterol, HDL Chol, LDL Chol, TAG, AST, ALT.

| | Control | | MSG | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | P |
| Glycemia (mg/dl) | 161.6 | 23.9 | 176 | 25.67 | 0.365 |
| Total cholesterol (mg/dl) | 133.2 | 5.17 | 125.83 | 6.46 | 0.07 |
| HDL Chol (mg/dl) | 39 | 3.39 | 39.16 | 3.25 | 0.936 |
| LDL Chol (mg/dl) | 31 | 20.54 | 21 | 11.73 | 0.301 |
| TAG (mg/dl) | 318.2 | 108.2 | 329 | 67.99 | 0.844 |
| AST (IU/dl) | 133.8 | 34.12 | 110.33 | 40.09 | 0.329 |
| ALT (IU/dl) | 43.6 | 2.97 | 44.83 | 3.65 | 0.56 |

Control: n = 6; MSG: n = 6; P < 0.05: significantly different. Student´s T test.

Liver total lipid content was significantly higher in the MSG group; liver triacylglycerols and total cholesterol did not show differences between groups.

## Discussion

Numerous studies have evaluated the eventual various physiologic/metabolic effects of MSG on laboratory animals administered orally, by intubation or by injection. The age at which the effects of the additive were studied varies from fetal development to adult age. The doses used in the experiments cover a wide range going from the usual concentration employed by food industry, as a food enhancer, to very high ones [18]. MSG has been frequently employed to induce obesity in new born laboratory rodents, administered subcutaneously in a concentration of 2-4 mg/g body weight during 5-8 days. MSG destroys neurons of the hypothalamic arcuate nucleus, one of the principal sites that regulate energy homeostasis, producing hyperinsulinemic obesity [19]. Reported effects of the administration of MSG on new born rodents include hepatic manifestations of metabolic syndrome, such as steatohepatitis [20].

The aim of this preliminary research was to evaluate the eventual effects of the oral intake of MSG as a food additive on adult IIMb/Beta obese and diabetic rats by adding it to the commercial feed. The IIMb/Beta line of rats develops spontaneous non-hyperphagic peri-pubertal hypertriacylglycerolemic obesity with progressive glucose intolerance that evolves towards type 2 diabetes at adult age [21]. It also shows diet dependent hepatic steatosis. The obesity -of moderate degree- affects both sexes, although it is more noticeable in males, and is determined by both the overweight and the volume of the adipose panicles. These characteristics support the use of this animal model for evaluating the effects of different diets, nutrients and food additives on the metabolic syndrome risk factors it presents.

The amount of MSG added was 1 g/kg feed, a concentration usually employed [3]. Rat´s daily MSG intake (30 ± 2 mg) would represent nearly 2.6-fold the ADI established for humans by EFSA on July 2017. However, epidemiological data show an average daily intake of MSG of 4.0 ± 2.2 g/day (range 0.4-14.0 g/day) in rural Thailand adult population. This represents an average of nearly 60 mg/kg body weight per day, and a range of 31 to 86 mg MSG/kg body weight per day [22]. In other

**Table 3:** Liver parameters: liver relative weight, total liver lipids, total cholesterol and TAG.

| | Control | | MSG | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | P |
| Liver relative weight | 3.19 | 0.56 | 4.14 | 0.23 | 0.004 |
| Total liver lipids (g/100 g) | 3.15 | 0.69 | 3.98 | 0.44 | 0.039 |
| Total cholesterol (mg/100 g) | 196.58 | 16.83 | 221.8 | 38.08 | 0.206 |
| TAG (mg/100 g) | 771.6 | 175.5 | 792.2 | 248.9 | 0.892 |

Control: n = 6; MSG: n = 6; P < 0.05: significantly different. Student´s T test.

countries daily intake of MSG goes from 0.58 g per day in USA and UK to 1.2-1.7 g in Japan and Korea [13].

There were no effects in the total feed intake, which showed no significant differences between groups (Table 1), thus we can presume that there were no changes in palatability derived from the flavour enhancer. A similar behavior was observed by Tordoff, Aleman and Murphy when MSG in a concentration of 1% and 3% was added to AIN 76 diet or a high energy diet and offered to male Sprague Dawley rats during 8 weeks [23]. In our experiment, no significant differences were detected on final weight or in body weight increase.

Plasma glucose and lipid profile did not show differences between groups; both expressed the usual high glycemia and TAG levels, typical of the metabolic syndrome features on this line of rats. No differences were detected on liver aminotransferases, which were in normal levels (Table 2). In a study, on adult Wistar rats (100-150 g body weight), fed the commercial rat chow and receiving intraperitoneally a daily 4 g/kg bw and 8 g/kg bw dose of MSG during 28 days, Inyang, Ojewunmi and Ebuchi detected significant increase in the levels of AST and ALT as well as in total cholesterol and TAG concentrations in the high dose group [24].

Controversial results have been published about the effects of MSG on weight gain and fat deposition. Collison and colleagues found that C57BL/6J mice fed a high trans-fatty acid diet and given a 0.064% MSG solution to drink had a larger increase in abdominal girth than the controls [25]. Kondoh and Tori investigated the effects of spontaneous ingestion of a 1% MSG water solution on food intake and body weight in male Sprague Dawley rats fed diets with different caloric density and fat and carbohydrate content. The group that drank the MSG solution showed a significantly lower weight gain, reduced abdominal fat pads compared to the group that drank only water [26]. The effect of MSG to reduce body weight is congruent with evidence that MSG stimulates thermogenesis, which in the absence of a compensatory increase in feed intake, would lead to weight loss [27].

In our experiment, an important finding was the significantly higher retroperitoneal fat pads relative weight registered in the MSG group. This abdominal fat depot is usually considered as one of the risky parameters defining the metabolic syndrome and can be considered as a negative effect of the addition of MSG.

Another relevant issue detected was the higher liver relative weight and the significantly higher total liver lipid content in the MSG group. In an experiment on adult rats treated with 0.6-1.6 mg/g body weight of MSG for 2 weeks Thawfik and Al-Badr showed increased ALT and Y-Glutamyltransferase (GGT) levels as well a significant increase in liver and kidney relative weights [28].

According to Onyema, et al. rats treated with MSG 0.6 mg/g body weight for 10 days expressed symptoms of liver damage; increases in lipid peroxidation, and elevated activities of ALT, AST and GGT in serum were observed [29]. In coincidence with our results in Beta rats, Nakanishi and coworkers detected the development of steatohepatitis in 12-months-old mice treated with MSG [30].

The important and original contribution of our research lies on the fact that we worked with MSG levels frequently reached in the human diet when it is used as food additive, in contrast with the reports of other researchers, in which the doses of MSG administered exceeded the sensorial and technological limits [28].

## Conclusion

In conclusion, in this study, the group of rats that received the chow with MSG did not show the deleterious effects that have been reported about increased food intake, and body weight as well as effects on lipidic profile or liver aminotransferases. Nevertheless, the negative effects of MSG were expressed as larger abdominal fat depots and liver relative weight as well as in their liver steatosis; two risk factors of the metabolic syndrome. Further investigations, both in animal models and humans, and for longer experimental periods, employing MSG doses similar to the daily intake in different populations are required to check and verify the diverse health effects reported in this preliminary study.

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## Disclosure Statement

All authors read and approved the final version of the manuscript.

The authors have no financial or personal conflicts to declare. On behalf of all authors, the corresponding author states that there is no conflict of interest.

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