The monosodium glutamate symptom complex: Assessment in a double-blind, placebo-controlled, randomized study

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Background: Considerable debate swirls about the validity of symptoms described by many people after ingestion of monosodium glutamate (MSG), and the question has remained unresolved largely because of a paucity of well-designed challenge studies.

Methods: We conducted oral challenge studies in self-identified MSG-sensitive subjects to determine whether they had a statistically significant difference in the incidence of their specific symptoms after ingestion of MSG compared with placebo. First, 5 gm MSG or placebo was administered in random sequence in a double-blind fashion. Subjects who reacted only to a single test agent then underwent rechallenge in random sequence in a double-blind fashion with placebo and 1.25, 2.5, and 5 gm MSG. A positive response to challenge was defined as the reproduction of ≥2 of the specific symptoms in a subject ascertained on prechallenge interview.

Results: Sixty-one subjects entered the study. On initial challenge, 18 (29.5%) responded to neither MSG nor placebo, 6 (9.8%) to both, 15 (24.6%) to placebo, and 22 (36.1%) to MSG ($p = 0.324$). Total and average severity of symptoms after ingestion of MSG (374 and 80) were greater than respective values after placebo ingestion (232 and 56; $p = 0.026$ and 0.018, respectively). Rechallenge revealed an apparent threshold dose for reactivity of 2.5 gm MSG. Headache ($p < 0.023$), muscle tightness ($p < 0.004$), numbness/tingling ($p < 0.007$), general weakness ($p < 0.040$), and flushing ($p < 0.016$) occurred more frequently after MSG than placebo ingestion.

Conclusions: Oral challenge with MSG reproduced symptoms in alleged sensitive persons. The mechanism of the reaction remains unknown, but symptom characteristics do not support an IgE-mediated mechanism. According to Food and Drug Administration recommendations, the symptoms, originally called the Chinese restaurant syndrome, are better referred to as the MSG symptom complex. (J Allergy Clin Immunol 1997;99:757-62.)

Key words: Monosodium glutamate, monosodium glutamate symptom complex, randomized double-blind challenge

Abbreviations used

CI:	Confidence interval
FASEB:	Federation of American Societies for Experimental Biology
MSG:	Monosodium glutamate
RR:	Relative risk

In 1968, Kwok[1] described postprandial symptoms of numbness at the back of the neck and arms, weakness, and palpitations after the ingestion of a Chinese meal and suggested monosodium glutamate (MSG) as one of the possible etiologic agents. Since then, MSG has been blamed in causing numerous adverse reactions including asthma,[2-5] headache,[6, 7] urticaria,[6] abdominal pain,[7] atopic dermatitis,[8] neuropathy,[9] orofacial granulomatosis,[10, 11] neuropsychiatric disorders,[12] and ventricular tachycardia.[13, 14] Conversely, many dispute the existence of MSG-induced symptoms.

Much of the ongoing debate about sensitivity to MSG can be attributed to the lack of controlled challenge studies. The majority of reports have been anecdotes, and the few studies done to date have assessed too few subjects, have been open or single-blind, and if double-blind have failed to disguise the taste of MSG.[1-29] Some studies have reported significant increases in symptoms after ingestion of MSG,[22, 24, 30] but others have not.[31-33] To address the issue of the validity of the symptoms described by many people, we conducted a double-blind, placebo-controlled challenge study in self-identified MSG-sensitive subjects in which the taste of MSG was disguised.

METHODS

The objective of the study was to address the validity of the symptom complex referred to as the Chinese restaurant syndrome and not to assess alleged reactions such as anaphylaxis or asthma. The study was approved by the research ethics committee of the Ottawa Civic Hospital. Newspaper advertisements between March 14 and November 2, 1993, requested replies from persons who believed they had had reactions to MSG. Respondents were screened by telephone to ascertain inclusion and exclusion criteria and eligible subjects were invited to participate in the challenge study. No psychologic assessments of respondents were done to differentiate those more or less

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likely to respond to placebo. Subjects received financial compensation.

Subjects had to be between 18 and 60 years old. They had to have had, within 3 hours of a meal alleged to have contained MSG, two or more of the following symptoms: feeling of general weakness, feeling of muscle tightness, feeling of muscle twitching, feeling of flushing, sweating sensation, burning sensation, headache/migraine, chest pain, palpitation/heart pounding, and feeling of numbness/tingling or one of these symptoms and at least one additional symptom the subject attributed to MSG. Symptoms identified by each subject before challenge were designated as index symptoms. All nonindex symptoms noted after challenge were designated as other symptoms. The designation of some symptoms as inclusion criteria suggested prejudgment of their value in relationship to MSG. However, beyond that all index and other symptoms were assigned equal value. A sample size was calculated before subject enrollment. Because review of previous studies did not provide reliable estimates of the likelihood of responses to MSG, we estimated rates of reactions to placebo of 5% and 10% and of reactions to 5 gm of MSG of 30% and 40%. To demonstrate a difference between placebo and MSG at a significance level of 0.05 and power of 80%, sample sizes between 27 and 71 subjects were required (27 for 5% placebo, 40% MSG; 43 for 5% placebo, 30% MSG; 38 for 10% placebo, 40% MSG; and 71 for 10% placebo, 30% MSG). A sample size of 60 subjects was selected.

Subjects were excluded if they were pregnant or nursing, had had an unconscious episode after ingestion of MSG or any unexplained loss of consciousness, described symptoms that suggested exquisite sensitivity as judged by an investigator, were receiving beta-blocker therapy, had uncontrolled hypertension, or had significant medical disease (disease of heart, lung, or central nervous system, acquired immunodeficiency syndrome, cancer, and so on). Subjects who were unable to comply with study procedures or provide informed consent and employees and their relatives of companies that manufacture MSG or of the International Glutamate Technical Committee were also excluded.

Study design

The two-phase study was designed to identify subjects who responded to MSG, if indeed they existed. All subjects underwent an initial challenge in which they ingested on an empty stomach 5 gm of MSG or placebo in random order on different days. The intent of this phase was to screen out negative and ambivalent responders. The remaining subjects who responded to one but not both challenge doses underwent a rechallenge in a second phase in which a greater number of challenges could assess a dose-response curve and decrease sequence effects and the likelihood of placebo responses.

The MSG (supplied by the International Glutamate Technical Committee) was dissolved in 200 ml of a strongly citrus-tasting beverage, which disguised its taste and contained sucrose as a sweetening agent. The beverage without MSG was the placebo. An unblinded study member prepared the beverage but had no direct contact with the test subject or observer. Patients who described any unusual symptoms on arriving at the clinic did not receive a test dose and the challenge was rescheduled for a different day.

A positive reaction to a test dose was defined as the occurrence of ≥ 2 index symptoms; subjects were unaware of the definition of response. Occurrence of fewer than the required number of index symptoms was considered a negative response, even if other symptoms were present. Subjects were questioned about symptoms every 15 minutes and vital signs were recorded every 30 minutes. Subjects who did not have any symptoms were released from the clinic after 2 hours of observation. Subjects with symptoms were followed up longer. Subjects were challenged on a subsequent day with the alternate agent and observed as on the first day. The interval between tests was never less than 1 day and depended on the availability of the subject.

Subjects who responded to neither test agent or to both were concluded to be nonresponders or inconsistent responders and did not undergo further study. Subjects who had responded only to one test agent underwent rechallenge in double-blind fashion in random sequence with placebo and MSG at doses of 1.25, 2.5, and 5 gm.

Symptoms and vital signs were followed up as in the initial challenge. Subjects who had not had a reaction within 1 hour but had reacted within that time on initial challenge received a second test agent. Similarly, subjects free of symptoms after 2 hours but who had symptoms within 2 hours on initial challenge received a further dose. If a subject had any single symptom on exposure to a test dose, no further tests were administered that day. Subjects returned to the clinic for further challenges until all test procedures were completed.

Reports of symptoms were elicited by asking subjects whether they were experiencing anything unusual. The severity of a symptom was rated as 1 (mild, noticeable but causing only slight discomfort), 2 (moderate, definitely troublesome but not incapacitating), or 3 (severe, having significant impact on the subject). Total severity was calculated by adding the rating for all symptoms that occurred, and average severity was calculated by dividing total severity by the number of positive symptoms. Subjects described similar symptoms in a variety of terms and for purposes of analysis groups of similar descriptions were coded under a single symptom type; for example, lightheadedness and dizziness were grouped as one symptom.

Statistical analysis

Statistical analyses were done with nonparametric tests suitable for the testing of proportions or ordered variables with "nonnormal" distributions and included the McNemar change test, Cochran Q test, Friedman two-way analysis of variance by ranks, and Wilcoxon paired and unpaired tests. A Bonferroni adjustment was made for multiple comparisons. A conditional logistic model was used to evaluate the relative risk (RR) of responding to placebo versus MSG. All statistical analyses were done with the SAS (SAS Institute) and Systat (Systat Inc.) computer programs.

RESULTS

Of 634 respondents, 122 could not be contacted for an interview, 397 were not eligible, and 5 were excluded because their described symptoms were not considered to be part of the Chinese restaurant syndrome. Of 110 eligible subjects, the first 61 who agreed to participate were entered into the study.

Fifteen subjects (25%) were male and 59 were white (1 black, 1 oriental). The mean age was 38 ± 9 (standard deviation) years, weight 75 ± 17 kg, and height 170 ± 9 cm. Thirty-four subjects (58%) had a history of atopy.

Prechallenge vital signs (pulse, blood pressure, temperature) were within normal limits and remained unchanged during and after MSG and placebo challenges. No subjects had adverse reactions including hives,

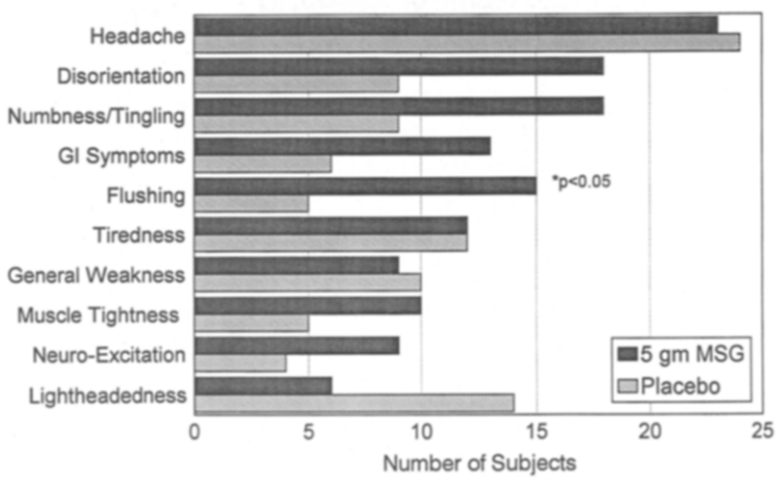

FIG. 1. Initial challenge: adverse reactions in 61 subjects. *GI,* Gastrointestinal tract.

TABLE I. *Rechallenge in 36 subjects*

	Placebo	MSG (gm)			p Value
		1.25	2.5	5	
Number (%) responding*	8 (22)	12 (33)	21 (58)	25 (70)	0.000†
Median no. of symptoms (sum)					
Index	0 (23)	1 (41)	2 (64)	2 (76)	0.000‡
Other	0 (22)	0 (26)	1 (57)	1 (49)	0.008‡
Total	0 (45)	1 (67)	3 (121)	4 (125)	0.000‡
Median severity of symptoms (sum)					
Sum of severity of index symptoms	0 (35)	1 (55)	2 (99)	4 (143)	0.000‡
Average severity of index symptoms	0 (22.5)	1 (28.2)	1 (41.5)	1.5 (55.2)	0.000‡
Sum of severity of other symptoms	0 (36)	0 (41)	1.5 (84)	1.5 (95)	0.016‡
Sum of severity of total symptoms	0 (71)	1.5 (96)	4.5 (183)	6 (238)	0.000‡
Average severity of total symptoms	0 (22.3)	1 (29.1)	1.3 (44.7)	1.6 (56.7)	0.000‡

*Response defined by ≥2 index symptoms after ingestion of test agent.
†Statistically significant, Cochran test.
‡Statistically significant, Friedman test.

wheezing, vomiting, or diarrhea on challenge. Laboratory testing (white blood cell count, differential, mast cell products) was not part of the challenge protocol.

Initial challenge

Of 61 self-identified MSG-sensitive subjects, 18 (29.5%) responded to neither 5 gm MSG nor placebo, 6 (9.8%) responded to both, 15 (24.6%) responded to placebo only, and 22 (36.1%) responded to MSG only. The rates of reaction were not statistically different (p = 0.324, McNemar's test) with a greater than expected rate of reactivity to placebo.

The 10 most frequently reported symptoms in the total group of 61 patients after challenge are shown in Fig. 1. More symptoms were reported after ingestion of MSG (104 index and 105 other symptoms) than placebo (79 index and 76 other symptoms); however, the differences were not statistically significant. Nevertheless, flushing occurred at a statistically increased frequency after MSG ingestion compared with after placebo. In addition, there were statistical differences in favor of MSG when the severity of symptoms was considered. Total severity and average severity values for all MSG responders (374 and 80, respectively) were greater than respective values for all placebo responders (232 and 56; p = 0.026 and 0.018, respectively, Wilcoxon rank sum test).

The concern that a simple challenge study could be biased by the sequence of administration was confirmed when the data were analyzed for sequence effects. An unbalanced response to placebo was demonstrated. Fourteen of the 31 subjects who received placebo first responded positively compared with only 7 of 30 when placebo was administered second (p = 0.073, chi square

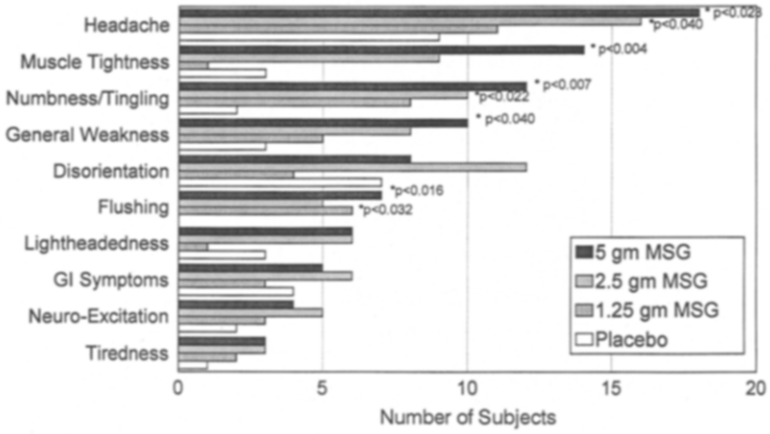

FIG. 2. Rechallenge: adverse reactions in 36 subjects. *GI,* Gastrointestinal tract.

TABLE II. Trend or threshold effect with increasing dose of MSG (n = 36)

	Placebo vs 1.25 gm MSG	Placebo vs 2.5 gm MSG	Placebo vs 5.0 gm MSG
No. of index symptoms	0.129	0.000*	0.000*
No. of other symptoms	0.503	0.001*	0.021
No. of total symptoms	0.191	0.0000*	0.000*
Sum of severity of index symptoms	0.310	0.003*	0.000*
Average severity of index symptoms	0.515	0.022	0.001*
Sum of severity of other symptoms	0.598	0.002*	0.003*
Sum of severity of total symptoms	0.334	0.000*	0.000*
Average severity of total symptoms	0.340	0.001*	0.000*

Comparisons use Wilcoxon tests to explore paired relationships after significant results to Friedman tests for all dose levels; $p < 0.017$ considered statistically significant after Bonferroni adjustment.
*Statistically significant.

test). Subjects who received placebo first had more index and other symptoms and symptoms of greater severity than those who received placebo second ($p < 0.05$ for all tests). In contrast, identical numbers responded to MSG administered either first or second (14/30 first and 14/31 second) and without differences in the magnitude of the response. Response dependent on order of administration was also demonstrated by a conditional logistic model performing self-match crossover analysis to evaluate the RR of a response to placebo versus MSG. The overall RR of a positive response to MSG versus placebo was not statistically significant (RR = 1.5, 95% confidence interval [CI] = 0.81 to 3.06). When placebo was administered first the RR was neutral (31 subjects receiving placebo first, RR = 1, 95% CI = 0.04 to 2.51). The subgroup given MSG first demonstrated an RR value of 2.6 in favor of reactivity to MSG (95% CI = 0.94 to 4.55).

Rechallenge

The rechallenge phase maintained the double-blind state and was started after each subject had completed the initial challenge. Of the original 37 uniresponders, only 1 declined rechallenge, which was done in random sequence with placebo and MSG at doses of 1.25, 2.5, and 5 gm. The analysis of the rechallenge data revealed no effect of sequence of administration on the responses.

The results of the rechallenge of the 36 uniresponders showed that response to placebo was still a confounding part of the data. However, analysis of the response of the entire population by a Friedman test found that the frequency and severity of responses increased clearly with increasing doses of MSG (Table I).

There appeared to be a threshold dose for response to MSG. By paired Wilcoxon tests with Bonferroni adjustment for the number of paired assessments there was no difference between responses to placebo and 1.25 gm of MSG. However, responses at 2.5 and 5 gm MSG differed from those of placebo (Table II). Statistically significant differences were not detected between 2.5 and 5 gm doses of MSG; however, a trend toward more reactivity at 5 gm was apparent.

The analysis of the adverse reactions of the 36 sub-

jects on rechallenge revealed several statistically significant associations of symptoms with MSG, which are often cited as characteristic of the Chinese restaurant syndrome, such as headache, flushing, muscle tightness, numbness/tingling, and generalized weakness (Fig. 2).

DISCUSSION

MSG is used worldwide as a flavor enhancer. In the United States, MSG has been classified as "Generally Recognized as Safe." As part of its general review of pre-1958 Generally Recognized as Safe food ingredients, the Food and Drug Administration of the United States recently sponsored extensive reviews on the safety of MSG by the Federation of American Societies for Experimental Biology (FASEB).[34] In its final report presented in August 1995, the FASEB proposed the term *MSG symptom complex* instead of Chinese restaurant syndrome to denote the reaction after the ingestion of MSG.[34]

It is estimated that the average daily intake of MSG in industrialized countries is 0.3 to 1 gm, but in a highly seasoned restaurant meal as much as 5 gm may be ingested. Published reports have not been able to provide a reliable estimate of the prevalence of MSG sensitivity, but indications are that this is <1% of the general population.[35, 36] Nevertheless, MSG has been blamed for many ills. The debate continues in large measure because of a paucity of scientifically sound challenge studies. The present study was done in a double-blind fashion and used strong citrus flavoring and sucrose sweetening to disguise the sensory characteristics of MSG. This type of beverage has been used previously with indications that the beverage containing MSG could not be discriminated from the placebo beverage.[37, 38] The results of this study indicate that among persons who have identified themselves as reacting to MSG, many have the specific symptoms under experimental conditions that they had identified as representing their sensitivity to MSG.

The difficulty of studying adverse reactions attributed to MSG is that symptoms are subjective and a placebo response is expected to play a significant role. Indeed, we observed adverse effects after administration of placebo. In addition to underestimating the magnitude of the placebo response, we noted an unbalanced placebo response on initial challenge. This placebo effect is documented in controlled experimental studies,[39] is often strongest at the beginning of a blinded study,[40] and is exhibited strongly by normal volunteers and by patients with an established illness.[41] On rechallenge, a placebo response rate was still apparent; however, the trend to increasing symptoms with increasing MSG dose was clear with a discernable threshold dose of 2.5 gm for the induction of symptoms. We are encouraged about the validity of our positive results because of our conduct of a similar negative challenge study of aspartame in self-identified sensitive subjects.[42]

How MSG induces symptoms is unknown, but it is assumed that systemic absorption of ingested MSG is required. Therefore dose and mode of administration of MSG would have substantial effects on plasma glutamate levels, which in turn would influence the results of challenge studies. Ingestion of MSG dissolved in water by fasting subjects leads to dose-dependent plasma concentrations that peak by 1 hour after ingestion and revert to baseline by 2 hours.[43] Levels are greatly decreased when MSG is ingested in a capsule or with protein or carbohydrates as in meals, to the extent that measurable plasma concentrations are not achieved.[43] In fact, the FASEB concluded that an effect of MSG will be seen only when MSG is ingested on an empty stomach and when large doses, 3 gm or more of MSG or other free glutamate, are consumed without food.[34] Our results support this conclusion. The results of challenges when MSG is administered with food may differ from ours as a consequence of the failure to attain serum concentrations of glutamate.

Nevertheless, we chose to administer MSG in liquid on an empty stomach for several reasons. First, we wanted to enhance the likelihood of a positive response and to evaluate our challenge protocol to design subsequent challenge studies of MSG with food. We believe that the requirement for recapitulation of a specified number of index symptoms (≥2) as a predefined definition of a positive response was a strength of the study design. It imposed a conservative estimate of reactivity and allowed for the identification of consistent MSG responders. Of the 61 subjects who entered the study, 18 did not respond to two placebo challenges but responded to MSG.

Second, subjects report symptoms with meals. The assumption that induction of symptoms by MSG requires absorption of MSG, which is decreased by meals, has called into question the integrity of the claims of subjects. However, meals do not administer MSG in a stereotypical manner. In some cases, large doses of MSG may be ingested at the beginning of a meal, akin somewhat to receiving MSG on an empty stomach and quite different from receiving MSG equally throughout the meal or most of the MSG toward the end of the meal. Thus reproduction of symptoms is a first step to validate the symptoms reported by subjects who receive MSG in uncontrolled circumstances in restaurants.

The results of our study suggest that sensitivity to MSG exists, at least in the clinical setting described herein, and is characterized by unpleasant reactions such as numbness, tingling, headache, muscle tightness, general weakness, and flushing. During and immediately after MSG oral challenge, no patient had the development of rhinoconjunctivitis, asthma, urticaria, angioedema, or anaphylactoid reaction, which suggests that conventional allergic mechanisms involving IgE and mast cells probably do not play a role in the MSG symptom complex. Future challenges of MSG with food will provide further insights into the mechanism of MSG-associated symptoms and the entity known as the MSG symptom complex.

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