

Multicenter, double-blind, placebo-controlled, multiple-challenge evaluation of reported reactions to monosodium glutamate

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Background: The frequency of reactions reported to occur after the consumption of monosodium glutamate (MSG) is the subject of controversy.

Objective: We conducted a multicenter, multiphase, double-blind, placebo-controlled study with a crossover design to evaluate reactions reportedly caused by MSG.

Methods: In 3 of 4 protocols (A, B, and C), MSG was administered without food. A positive response was scored if the subject reported 2 or more symptoms from a list of 10 symptoms reported to occur after ingestion of MSG-containing foods within 2 hours. In protocol A 130 self-selected reportedly MSG-reactive volunteers were challenged with 5 g of MSG and with placebo on separate days (days 1 and 2). Of the 86 subjects who reacted to MSG, placebo, or both in protocol A, 69 completed protocol B to determine whether the response was consistent and dose dependent. To further examine the consistency and reproducibility of reactions to MSG, 12 of the 19 subjects who responded to 5 g of MSG but not to placebo in both protocols A and B were given, in protocol C, 2 challenges, each consisting of 5 g of MSG versus placebo.

Results: Of 130 subjects in protocol A, 50 (38.5%) responded to MSG only, 17 (13.1%) responded to placebo only ($P < .05$), and 19 (14.6%) responded to both. Challenge with increasing doses of MSG in protocol B was associated with increased response rates. Only half ($n = 19$) of 37 subjects who reacted to 5 g of MSG but not placebo in protocol A reacted similarly in protocol B, suggesting inconsistency in the response. Two of the 19 subjects responded in both challenges to MSG but not placebo in protocol C; however, their symptoms were not reproducible in protocols A through C. These 2 subjects were challenged in protocol D 3 times with placebo and 3 times with

5 g of MSG in the presence of food. Both responded to only one of the MSG challenges in protocol D.

Conclusion: The results suggest that large doses of MSG given without food may elicit more symptoms than a placebo in individuals who believe that they react adversely to MSG. However, neither persistent nor serious effects from MSG ingestion are observed, and the responses were not consistent on retesting. (*J Allergy Clin Immunol* 2000;106:973-80.)

Key words: Monosodium glutamate, monosodium glutamate symptom complex, sensitivity to food additives

Monosodium glutamate (MSG) is used worldwide as a flavor enhancer. The average daily intake of MSG is estimated to be 0.2 to 0.5 g in the United States and 1.6 g in Korea.¹ In the United States the Food and Drug Administration has classified MSG as "generally recognized as safe." MSG has been reported to cause many ills. A complex of symptoms that reportedly follows ingestion of a Chinese meal and consists of numbness at the back of the neck gradually radiating to both the arms and the back, general weakness, and palpitations was first described in 1968.^{2,3} MSG, along with cooking wine and high sodium in food, was proposed to trigger those symptoms that have collectively been referred to as the *Chinese restaurant syndrome*. More recently, in its 1995 report, the Federation of American Societies for Experimental Biology (FASEB) proposed the term *MSG symptom complex* to denote the reactions reported to occur after the consumption of MSG.⁴ The MSG symptom complex was considered to begin within 1 hour of ingestion of a greater than 3-g oral bolus of MSG in the absence of food. Ingestion of MSG has also been reported to cause or exacerbate numerous conditions, such as unstable asthma,⁵ severe atopic dermatitis,⁶ and, in anecdotal case reports, possibly atrial fibrillation and ventricular tachycardia.⁷ Headaches, facial burning, and abdominal pain were reported after double-blind challenges.⁸ However, there is an ongoing debate about the prevalence of reactions to MSG and even about whether MSG indeed causes reactions.

Some of the controversy about reactions to MSG is due to the paucity of vigorously controlled challenge studies. The majority of reports of MSG sensitivity are

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Abbreviations used

FASEB: Federation of American Societies for Experimental Biology

MSG: Monosodium glutamate

RR: Relative risk

anecdotal. The challenges performed to date have primarily involved too few patients, were single blind, or failed to effectively disguise the taste of MSG. Some studies have reported a statistically significant incidence of symptoms in response to MSG,^{3,9} and others have not.^{10,11} A recent study with 61 self-identified MSG-sensitive subjects revealed no significant difference in symptoms reported after challenge of MSG versus placebo.¹² Another recent study found no significant response to MSG in 100 asthmatic patients, which included 30 self-identified MSG-sensitive subjects.¹³

We conducted a multicenter, double-blind, placebo-controlled, multiple-challenge study with a crossover design to evaluate reactions reportedly caused by the consumption of MSG in 130 self-identified subjects who believed they had experienced reactions to MSG.

METHODS**Subject recruitment**

Subjects who reported having experienced a reaction after ingesting an Asian meal that might have contained MSG were recruited from responses to advertisements in local newspapers placed by the 3 study centers in Boston, Chicago, and Los Angeles. Subjects were initially screened by a clinical coordinator through a telephone interview by using a toll-free number. Subjects were then carefully evaluated for enrollment by the investigator at the study site closest to their location. Inclusion criteria were the report of at least 2 of the following complaints within 4 hours of a meal reported to contain added MSG: feeling of general weakness, feeling of muscle tightness, feeling of muscle twitching, feeling of flushing, sweating sensation, burning sensation, headache-migraine, chest pain, palpitations, and feeling of numbness-tingling. Exclusion criteria were as follows: report of life-threatening reactions associated with ingestion of MSG-containing meals (no such subjects presented to the study), age less than 18 or greater than 60 years, pregnancy, history of unexplained loss of consciousness, uncontrolled hypertension, heart disease evidenced by angina, congestive heart failure, history of myocardial infarction, heart surgery, pulmonary disease, oxygen treatment, steroid-dependent asthma, hospitalization for pulmonary disease in the past year, chronic neurologic diseases (ie, seizure, stroke, or multiple sclerosis), AIDS, cancer, other chronic illnesses, employment at companies that manufacture MSG, being a relative of employees of companies that manufacture MSG, members of the International Glutamate Technical Committee, and relatives of members of the International Glutamate Technical Committee. Study subjects received financial compensation.

Study design

The study design was a multicenter, randomized, double-blind, placebo-controlled, multiple-challenge crossover design.¹⁴ The study was performed in the outpatient clinic at each of the 3 study centers and was conducted in 4 consecutive phases, each with its own individual protocol (A, B, C, and D). On the first day of each phase of the study, each subject received a detailed explanation of

the study and reviewed and signed an informed consent form after review. The study was approved by the institutional review board or research ethics committee at each of the 3 study centers.

Criteria for a response

A positive response was defined as the occurrence of any 2 or more symptoms among the 10 symptoms listed in the enrollment inclusion criteria. In protocols C and D the reproducibility of the response to MSG was also assessed according to the recommendations of the 1995 FASEB report on MSG that became available after the completion of protocols A and B. The FASEB report states that, "For confirmation of the symptom complex, double blind placebo controlled challenges on separate occasions must reproduce symptoms with the ingestion of MSG and produce no response with placebo."⁴ A reproducible response for this analysis was defined as the same 2 or more symptoms among those listed in the enrollment inclusion criteria, which were reproducible in separate challenges, with no symptoms produced by placebo.

Challenge procedures

All challenges began in the morning between 8 and 9 AM. No food was ingested starting the preceding midnight and for 2 hours after the challenge, except in protocol D, in which the test article was administered during a standardized breakfast.

All subjects who satisfied the inclusion and exclusion criteria were enrolled in protocol A. If they had symptoms of any kind on the morning of testing, subjects were rescheduled. In the absence of symptoms, subjects were given a limited physical examination, and a medical history was taken. After verifying that the subject had fasted overnight, the testing began. Subjects were randomized to receive placebo on day 1 and MSG on day 2 (arm 1) or MSG on day 1 and placebo on day 2 (arm 2). The test articles consisted of a 200-mL citrus-flavored beverage containing 0 or 5 g of MSG. Results of previous taste panel tests had suggested that the citrus flavor might be capable of masking the presence of MSG.¹⁵ The beverage contained, in addition to the MSG dosage, sodium citrate (2.6 g), citric acid (1.64-1.68 g), saccharin (0.023-0.034 g), citrus flavor (0.2 g), and naringin (0.66 g).

Subjects who had responded with 2 or more symptoms to at least one test article in protocol A were eligible to be enrolled in protocol B, which was initiated after completion of protocol A before the blinding codes in protocol A were broken. Protocol B consisted of 4 challenges for each subject, with each challenge performed on a separate day. Each subject was randomly administered test articles consisting of 0 (placebo), 1.25, 2.5, or 5 g of MSG in 200 mL of citrus-flavored beverage.

Subjects who had responded with 2 or more symptoms to 5 g of MSG but not placebo in both protocols A and B were eligible to be enrolled in protocol C. This phase of the study was undertaken to confirm the reproducibility of the responses reported in protocols A and B in a manner compliant with the recommendation of the FASEB report.⁴ Attempts were also made in protocol C to eliminate some of the possible bias inherent in the challenge procedure and data collection of the earlier trials. In protocol C subjects were randomly assigned to receive MSG or placebo first in each of 2 sets of challenges administered on 4 separate days, designated protocols C1 and C2. The test articles consisted of opaque capsules containing 5 g of MSG or placebo (5 g of sucrose) taken with 200 mL of bottled water.

Subjects who responded to 5 g of MSG but not placebo in both sets of challenges in protocol C were eligible to be enrolled in protocol D. This phase of the study was initiated to assess the clinical features of reactions to MSG versus placebo when ingested with food. The design of this phase of the study is believed to represent the gold standard of such a study.¹⁶ Protocol D consisted of 6 chal-

lenges, each performed on a separate day. Each subject randomly received capsules 3 times containing 5 g of MSG and capsules 3 times containing placebo (5 g of sucrose) along with 200 mL of bottled water during a standardized breakfast consisting of a box of Frosted Flakes (sugared corn flakes) and 2% cow's milk (8 oz).

Sample preparation

For protocols A and B, the study statistician received powdered beverage packets from the sponsor and then randomized the treatments to subjects and shipped to each center one box per subject containing the appropriate test articles with coded labels. Two series of consecutively numbered and sealed envelopes, one for male and one for female subjects, were mailed to each site. Each envelope contained 6 packets containing the assigned test article labeled according to challenge number. The citrus-flavored beverage powder was dissolved in 200 mL of water on the morning of the challenge. For protocols C and D, capsules were prepared by the University of California at Los Angeles pharmacy and shipped to the study statistician for coding and dispensing. Five samples of each packet were retained to allow for future analysis of the contents if needed.

Randomization

A stratified randomization was used, and separate randomization schemes were developed for each site-sex stratum as follows. First, permuted blocks of size 4 were used to randomly assign subjects to arm 1 or arm 2 in protocol A. Subjects assigned to arm 1 were challenged first with placebo and then with 5 g of MSG; those assigned to arm 2 were challenged first with 5 g of MSG and then with placebo. A 4×4 Latin square design was used to assign the order of challenges for the 4 doses (0, 1.25, 2.5, and 5 g) compared in protocol B. Patients were randomized to receive MSG followed by placebo or, vice versa, in protocols C1 and C2. Three of the 6 challenges in protocol D were randomly assigned to MSG, and 3 were randomly assigned to placebo. Stratified randomization was not used in protocols C and D because of the small number of subjects expected.

Data collection

Each subject received a limited physical examination, including measurements of pulse, blood pressure, respiratory rate, and temperature. The skin was inspected. Blood pressure and pulse were recorded every 30 minutes. Respiratory rate was measured if respiratory symptoms were reported. For protocols A and B, after the administration of test articles, the subjects were queried about symptoms by a nurse or a physician using a checklist of 10 specific symptoms, as well as categorization of their symptoms every 15 minutes, and responses were recorded. For protocols C and D, subjects were given blank sheets of paper and asked to record any symptoms every 15 minutes for 2 hours. The frequency of the occurrence of a symptom in each challenge represents the fraction of subjects who reported the presence of that symptom within 2 hours after challenge. A physician was readily available during the entire time of the study. Subjects were allowed to leave 2 hours after administration of the test articles, unless they were complaining of symptoms, in which case they were followed longer until they reported clearing of all symptoms (always <4 hours). All subjects were unaware of the definition of a response.

Statistical analysis

In protocols A and B relative risk (RR) was used to describe the crude effect of MSG versus placebo on individual symptoms and on the overall response (defined as exhibiting at least 2 symptoms among the 10). The McNemar test for correlated proportions was used to perform significance testing. In protocol A stratification by site, sex, age groups, and challenge order (arm 1 or arm 2) was used to describe and test for treatment effects within strata. Homo-

geneity of the effect of MSG among the strata was assessed by using the Breslow-Day test. Results were tested separately for the 2 challenge days. Each challenge day's analyses are based on the entire set of patients, half of whom received MSG, and half of whom received placebo. RRs are presented, and χ^2 tests and Fisher exact tests were used where appropriate for significance testing. Protocol B was conducted to further investigate subjects who responded to at least one of the challenges (either MSG, placebo, or both) in protocol A. All subjects who completed protocol B were analyzed by using conditional logistic regression with dummy variables. Statistical testing was not performed on data collected in protocols C and D because of the small sample size. However, the objectives of these latter protocols justified their being undertaken, even with the limited sample sizes.

RESULTS

Protocol A

A total of 178 subjects called to enroll in the study. One hundred thirty-two subjects satisfied the inclusion criteria and were enrolled. One of these subjects withdrew before completing the protocol, and one subject was excluded because he presented himself twice. Thus 130 subjects (46 male and 84 female subjects) completed protocol A (Fig 1). In protocol A subjects were challenged with 5 g of MSG versus placebo in beverage form and were asked about their symptoms. Table I summarizes the results obtained. Fifty (38.5%) of 130 subjects reported 2 or more symptoms (positive response) during the MSG challenge and had 0 or 1 symptoms after placebo. Nineteen (14.6%) subjects reported 2 or more symptoms to both MSG and placebo, whereas 17 (13.1%) subjects reported 2 or more symptoms to placebo and 0 or 1 symptoms after MSG. Forty-four (33.8%) subjects reported 0 or 1 symptoms to both MSG and placebo (Table I). Administration of 5 g of MSG was associated with a significantly higher ($P < .05$) frequency of response (ie, occurrence of 2 or more symptoms) and with a significantly higher frequency of occurrence of 4 of the 10 symptoms (Table II). Furthermore, when the occurrence of symptoms other than the 10 symptoms that were listed in the inclusion criteria was examined, the frequency was significantly higher after MSG challenge than after placebo challenge (0.57 vs 0.31, $P < .001$). None of these other symptoms were associated with any objective signs or findings.

Table III presents the frequency of occurrence of 2 or more symptoms by site, sex, age group, and challenge order. Although the RRs of response to MSG versus placebo were not significantly different among any of the strata evaluated, the RRs for subjects studied in Chicago were lower than that for subjects studied at the other 2 sites and did not achieve statistical significance. The proportion of subjects who responded to placebo with 2 or more symptoms was much higher in subjects challenged with placebo first (arm 1) than in subjects challenged with 5 g of MSG first (arm 2), whereas the proportion of subjects who responded with 2 or more symptoms to 5 g of MSG was similar in the two arms. This resulted in a higher RR in arm 2 than in arm 1. However, this difference was not statistically significant.

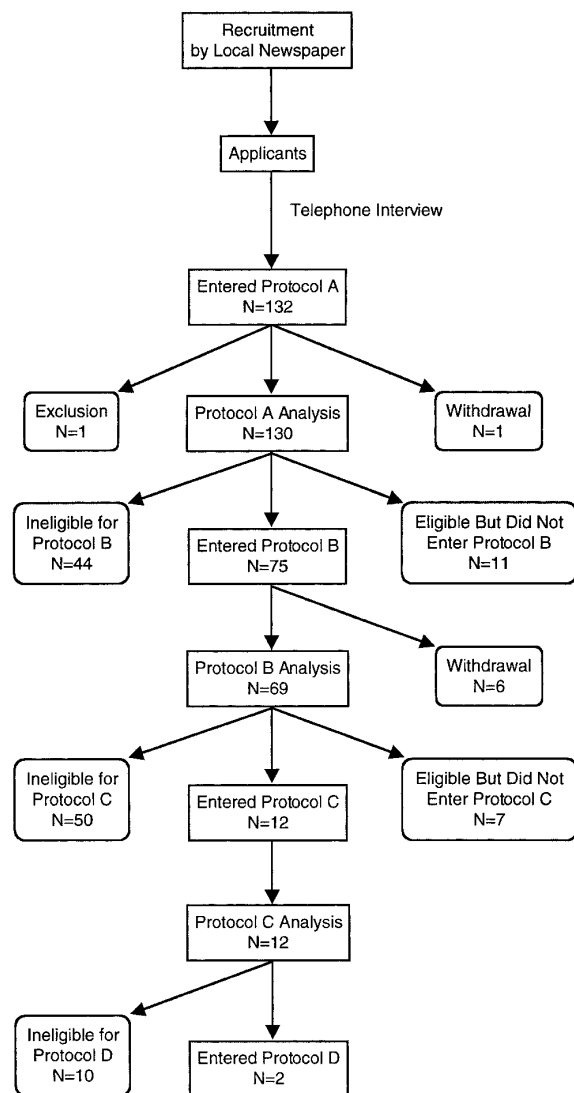


FIG 1. Schema of multicenter, double-blind, placebo-controlled, multiple-challenge evaluation of reported reactions to MSG.

There was no significant increase in heart rate or blood pressure over baseline after challenge with either MSG or placebo challenge, and there was no significant difference between MSG versus placebo. There was also no significant increase in heart rate over baseline when subjects who reported palpitations were analyzed separately. Furthermore, no subject reported wheezing, and there were no changes in the physical examination.

Protocol B

Eighty-six subjects who responded with 2 or more symptoms to at least one of the 2 challenges in protocol A were eligible for protocol B. Of these 86 subjects, 17 either chose not to participate ($n = 11$) or did not complete protocol B ($n = 6$, Fig 1). In protocol B each of the

subjects was challenged with placebo and 1.25, 2.5, and 5 g of MSG in beverage form and was asked about the symptoms. Table IV summarizes the results obtained from the 69 subjects who completed protocol B. Administration of 1.25, 2.5, and 5 g of MSG was associated with significantly increased frequency of response. There was no significant increase in frequency of response for any of the 10 symptoms with 1.25 g of MSG. An increased frequency of response was observed for only numbness-tingling with 2.5 g of MSG and for 6 of 10 symptoms (general weakness, muscle tightness, flushing, sweating, headache-migraine, and numbness-tingling) with 5 g of MSG. Furthermore, when the occurrence of symptoms other than the 10 symptoms that were listed in the inclusion criteria was examined, it was significantly higher after MSG challenge with 5 g than after placebo challenge (RR, 6.25; $P < .001$) but not after challenge with 1.25 g or 2.5 g of MSG.

Of the 69 subjects who completed protocol B, 19 reported 2 or more symptoms to 5 g of MSG but not to placebo in both protocols A and B. Thus only half ($n = 19$) of 37 subjects who reacted to 5 g of MSG but not placebo in protocol A reacted similarly in protocol B (Table V). Of these 19 subjects, 2 reacted to 1.25 and 5 g of MSG but not to 2.5 g of MSG. In 14 of the 19 subjects, the response was reproducible (ie, the same 2 or more symptoms occurred with MSG in both protocols A and B).

Protocol C

As this study was in progress, the August 1995 FASEB report on MSG was published.⁴ The report recommends that to confirm the MSG symptom complex, 3 double-blind placebo-controlled challenges administered on separate occasions must reproduce symptoms with the ingestion of MSG and produce no response with placebo. The FASEB report also notes that given the subjective nature of the symptoms, 5 double-blind placebo-controlled challenges would be needed for highly suggestible individuals. The report also recommends use of capsules as test articles to ensure the greatest control over dose and blinding and to obviate the potential role of the oral cavity in the precipitation of adverse effects.

Of the 19 subjects who reported at least 2 symptoms after 5 g of MSG but not placebo in protocols A and B, 12 subjects were available for protocol C (Fig 1). In protocol C subjects were challenged twice, each time with capsules containing 5 g of MSG and with capsules containing sucrose placebo (challenges C1 and C2) and were asked to report their symptoms. Capsules were used to circumvent the possibility that some of the subjects were able to detect a difference in the texture or taste of MSG and placebo when they were given in beverage form. Table VI summarizes the results obtained in protocol C. Only 2 of the 12 subjects (subjects 1114 and 2138) reported 2 or more symptoms after 5 g of MSG challenges but not after placebo in both challenges. However, neither of these 2 subjects reported the same 2 or more symptoms during the MSG challenges in protocols A through C.

TABLE I. Summary of results from protocol A (placebo vs 5 g of MSG, n = 130)

Center	No. of subjects			
	Responded* to placebo but not to MSG	Responded* to MSG but not to placebo	Responded* to both placebo and MSG	Responded* to neither placebo nor MSG
Boston	6	17	2	19
Chicago	6	10	6	17
Los Angeles	5	23	11	8
Total	17 (13.1%)	50 (38.5%)	19 (14.6%)	44 (33.8%)

*A positive response is defined as having 2 or more symptoms from a list of 10 symptoms that are alleged to occur after ingestion of MSG.

Protocol D

The above 2 subjects were enrolled in protocol D, which consisted of 6 challenges, 3 with 5 g of MSG and 3 with placebo. The test articles were administered with capsules in the middle of a standard breakfast (cereal and milk), and the subjects were asked to report their symptoms. Table VII shows that each of the 2 subjects reported 2 or more symptoms in only one of the 3 MSG challenges. In both subjects the symptoms reported differed from those reported in the previous 3 protocols.

DISCUSSION

This study was designed to test whether a large dose of 5 g of MSG reproducibly induces symptoms in subjects who believe themselves to be reactive to MSG in food. The results obtained indicate that a higher rate of response to MSG than to placebo was observed in reported MSG-reactive subjects. However, the response was not reproducible on repeated challenges.

Included in the present study were 130 subjects who identified themselves as having reacted to a meal containing MSG. Subjects who reported responses to 5 g of MSG were challenged repetitively to determine the consistency and reproducibility of the responses. A 5-g MSG challenge dose was chosen because it has been reported in previous studies to have elicited symptoms.^{9,15} In the present study a positive response was defined as the occurrence of 2 or more symptoms among the 10 symptoms commonly reported by individuals reportedly sensitive to MSG. When any additional reported symptom or symptoms are included in the analysis under "other" for a total of 11 categories of symptoms and response is defined as the occurrence of 2 or more symptoms among a total of 11 possible symptoms, analysis of the data gave similar results for protocols A and B (data not shown). Our study excluded patients with steroid-dependent asthma. However, a recent study by Woessner et al¹³ found no evidence of asthma exacerbation after MSG challenge.

Results from the first phase of the study (protocol A), which involved a single MSG challenge and a single placebo challenge with 130 subjects, suggested that administration of 5 g of MSG was associated with a statistically significant higher response rate than placebo. In protocol A 28% (36/130) of the subjects reported 2 or

TABLE II. Protocol A (n = 130): Frequency of symptoms reported to challenge with 5 g of MSG versus placebo

Symptom	Frequency		RR
	Placebo	5 g of MSG	
General weakness	0.14	0.30	2.17*
Muscle tightness	0.18	0.34	1.83*
Muscle twitching	0.06	0.13	2.13
Flushing	0.08	0.25	3.30*
Sweating	0.04	0.07	1.80
Burning sensation	0.05	0.14	3.00*
Headache-migraine	0.28	0.54	1.89*
Chest pain	0.02	0.06	2.67
Palpitations	0.04	0.10	2.60
Numbness-tingling	0.20	0.28	1.38
At least 2 symptoms	0.27	0.53	1.97*

* $P < .005$.

more symptoms after placebo, and 50% (65/130) of the subjects reported at least one symptom to placebo. This is consistent with the previously observed 20% to 25% rate of reactions to placebo in healthy volunteers.¹⁷ However, the proportion of subjects with 2 or more symptoms to placebo was much higher in subjects challenged with placebo first than in subjects challenged with 5 g of MSG first. Consequently, the rate of reaction to first challenge with MSG and placebo was not significantly different ($P > .1$). In contrast, the proportion of subjects with 2 or more symptoms to 5 g of MSG was similar in the 2 arms. These results indicate that there was indeed demand bias. In addition, the possibility of taste recognition by a subgroup of the subjects cannot be ignored. The beverage used in protocols A and B had been reported to be effective in masking the taste of MSG.¹⁵ However, it had not been tested rigorously on a group of individuals believing themselves to react adversely to MSG. Therefore the possibility that there is a subgroup better at detecting the taste of MSG than the general population cannot be ruled out.

The results of our protocol A differ from those of Yang et al.¹² The Yang study, which ran concurrently with the initial phase of our study, adopted protocols A and B exactly as designed by our multicenter study group. That study found no statistical difference in the reaction rate to MSG versus placebo in 61 self-identified MSG-sensitive

TABLE III. Protocol A (n = 130): Frequency of occurrence of 2 or more symptoms to challenge with 5 g of MSG versus placebo by site, sex, age, and challenge arm

Strata	n	Frequency		RR
		Placebo	5 g of MSG	
Site				
Boston	44	0.18	0.43	2.38*
Chicago	39	0.28	0.41	1.33
Los Angeles	47	0.34	0.72	2.13*
Sex				
Female	83	0.29	0.52	1.79*
Male	47	0.26	0.55	2.17*
Age (y)				
≤30	54	0.24	0.44	1.85*
31-45	50	0.32	0.52	1.63
≥46	26	0.27	0.73	2.71*
Challenge arm				
1. Placebo-MSG (5 g)	64	0.38	0.50	1.33
2. MSG (5 g)-placebo	66	0.18	0.56	3.08*

No comparisons of RR among strata are statistically significant.

* $P < .05$.

TABLE IV. Summary of results from protocol B (n = 69)

Center	No. of subjects	No. of subjects who responded* to			
		Placebo	1.25 g of MSG	2.5 g of MSG	5 g of MSG
Boston	23	3	7	8	9
Chicago	18	5	7	5	12
Los Angeles	28	8	14	19	18
Total	69	16	28	32	39
RR			1.75*	2.00*	2.44*

A positive response is defined as having 2 or more symptoms from a list of 10 symptoms that are alleged to occur after ingestion of MSG.

* $P < .05$.

TABLE V. Reproducibility of symptoms in protocols A and B

Center	No. of subjects		
	Responded* to MSG but not placebo in protocol A and completed protocol B	Responded* to MSG but not placebo in both protocols A and B	Reproducible reactions† across protocols A and B
Boston	15	7	2
Chicago	8	5	5
Los Angeles	14	7	7
Total	37	19	14

*A positive response is defined as having 2 or more symptoms from a list of 10 symptoms that are alleged to occur after ingestion of MSG.

†A reproducible reaction is defined as the repeated occurrence of the same 2 or more symptoms after 5 g of MSG with absence of placebo-induced symptoms.

TABLE VI. Summary of results from protocol C (n = 12)

Center	No. of subjects			
	Responded* to MSG but not placebo in protocol C1	Responded* to MSG but not placebo in protocol C2	Responded* to MSG but not placebo in both protocols C1 and C2	Reproducible responses† in protocols A through C
Boston (n = 4)	1 (1114)‡	2 (1018, 1114)	1 (1114)	0
Chicago (n = 4)	2 (2138, 2143)	1 (2138)	1 (2138)	0
Los Angeles (n = 4)	1 (3123)	0	0	0
Total	4	3	2	0

*A positive response is defined as having 2 or more symptoms from a list of 10 symptoms that are alleged to occur after ingestion of MSG.

†A reproducible reaction is defined as the repeated occurrence of the same 2 or more symptoms after 5 g of MSG with absence of placebo-induced symptoms.

‡Numbers in parentheses refer to subject number.

TABLE VII. Summary of results from protocol D (n = 2)

Center	Placebo challenges: No. of symptoms reported with each challenge			MSG challenges: No. of symptoms reported with each challenge			No. of reproducible responses
	1	2	3	1	2	3	
Boston (n = 1)	0	0	0	0	0	3	0
Chicago (n = 1)	0	0	1	2	0	1	0

subjects. The difference between the 2 studies may simply be due to the difference in the number of subjects studied. However, given the inconsistency of the reactions on subsequent challenges that we have observed in our study and the possible demand bias in our study, the clinical significance of the higher response rate to MSG that we observed remains to be established.

In the second phase of the study, we examined the dose dependency and consistency of the response to MSG. Because protocol B was carried out before obtaining the results of protocol A, all subjects who had a response to one or both challenges in protocol A were invited to participate in protocol B, which consisted of 4 random challenges with placebo and 1.25, 2.5, and 5 g of MSG. Administration of 1.25, 2.5, and 5 g of MSG was associated with significantly increased frequency of response. This is in agreement with the findings of Yang et al,¹² who observed that the frequency of reported symptoms was significantly higher with 2.5 and 5 g, but not 1.25 g, in MSG challenges compared with placebo.

Among the 130 subjects who completed protocol A, 13 subjects who had responded to 5 g of MSG but not to placebo in protocol A did not complete protocol B. We therefore could only assess the consistency of the response in the remaining 117 subjects. Of these subjects, 19 reacted to 5 g of MSG but not to placebo in both protocols A and B, a frequency of 16.2% in a population of subjects who believed they were reactive to MSG. More importantly, only half (n = 19) of 37 subjects who reacted to 5 g of MSG but not placebo in protocol A reacted similarly in protocol B. These observations suggest that the response to MSG of self-proclaimed MSG reactors may not be consistent.

To comply with the FASEB recommendations⁴ and to further evaluate the consistency and reproducibility of reactions to MSG, 2 additional challenges, each with 5 g of MSG versus placebo in capsules (protocol C), were administered to 12 of the 19 subjects who responded to 5 g of MSG but not placebo in both protocols A and B. Of these 12 subjects, only 2 responded to MSG and not to placebo in both protocol C challenges. Given the fact that 7 of the 19 eligible subjects did not enter protocol C, the number of subjects that could be evaluated for response to 5 g of MSG in 4 consecutive challenges was 110. Thus on 4 consecutive challenges, a response (≥ 2 symptoms) could be elicited in only 1.8% (2/110) of subjects who had self-reported reactions to MSG. In neither of these 2 subjects were the symptoms reported in protocols A and B reproducible in either of the 2 challenges of protocol C.

Reported reactions to MSG are reported after consumption of MSG in foods, and hence the FASEB report also recommends that the effects of food ingestion should be evaluated.⁴ We therefore asked whether the 2 subjects who responded to 5 g of MSG but not placebo in 4 consecutive challenges would respond when the same dose of MSG was administered in the course of a light meal. Each of these subjects responded to only one of 3 such MSG challenges. In neither case were the symptoms the same as those reported in the previous protocols. Thus subjects who appear to consistently respond to MSG in the absence of food may not do so when MSG is administered in the food. Although too few patients were studied in protocols C and D to allow statistical analysis, the results of these protocols support the notion of the lack of consistency of the response to MSG observed in protocols A and B.

This study is the largest to date to analyze the response in multiple challenges of subjects who report symptoms from ingesting MSG. The results suggest that large doses of MSG given without food may elicit symptoms more than placebo in individuals who report they react adversely to MSG. However, neither persistent nor serious effects from MSG ingestion are observed, and the responses were not consistent on retesting. Given these results, double-blind, placebo-controlled, challenge testing according to the FASEB guidelines can be recommended for individuals who suspect that they have reactions to MSG.

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