

Respiratory pathophysiologic responses

The effects of monosodium glutamate in adults with asthma who perceive themselves to be monosodium glutamate-intolerant

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Background: Many previous clinical studies of food-induced asthma suffer from inadequate baseline or control data. A statistically valid, randomized, double-blind, placebo-controlled, monosodium glutamate (MSG)-challenge protocol was developed for identifying early and late asthmatic reactions in an individual.

Objective: We sought to determine whether MSG would induce bronchoconstriction in a group of adults with asthma who perceived that they were MSG sensitive.

Methods: Twelve subjects (seven women, mean age 35.3 years) with clinically documented asthma and a perception of MSG-induced asthma were recruited. FEV₁ and peak expiratory flow data were obtained for 3 whole control days, as well as time-matched data for 3 separate challenge days (1 gm MSG, 5 gm MSG, and 5 gm lactose [placebo]). Opaque capsule challenges were given as a single dose in the morning after an overnight fast. Subjects complied with an elimination diet throughout the study. Nonspecific bronchial hyperresponsiveness was measured at baseline, after the control days, and at the conclusion of the challenges. Venous blood samples were taken at baseline and on each challenge day to determine soluble inflammatory marker (eosinophil cationic protein and tryptase) activity. **Results:** No immediate or definite late asthmatic reactions occurred. One subject's FEV₁ declined more than 15% on MSG challenge, but 95% confidence limits for the control-day spirometry showed that this decline was within her daily variation, hence the challenge was deemed to be negative. No significant changes in bronchial hyperresponsiveness or soluble inflammatory markers were found.

Conclusions: MSG-induced asthma was not demonstrated in this study. This study highlighted the importance of adequate baseline and control data and indicated that such a rigorous protocol for individual assessment is feasible. (*J Allergy Clin Immunol* 1998;101:762-71.)

Key words: Monosodium glutamate, asthma, randomized double-blind, placebo-controlled trial

Abbreviations used

BHR:	Bronchial hyperresponsiveness
ECP:	Eosinophil cationic protein
MSG:	Monosodium glutamate
PEF:	Peak expiratory flow

Monosodium glutamate (MSG) is the sodium salt of the nonessential amino acid glutamic acid. It exists in both free form and bound in proteins. The free form (L-glutamic acid) is used as a flavor enhancer in many packaged foods and is also found naturally in a wide range of foods, such as tomatoes and cheese.^{1,2}

Although 23% to 67% of persons with asthma perceive that food additives exacerbate their asthma,³⁻⁵ various double-blind, placebo-controlled trials report a prevalence rate of less than 5%.^{6,7} However, public concern about the role of food additives remains high. We have previously found that MSG is perceived as the food chemical most likely to cause bronchoconstriction and that MSG is the fourth most frequently avoided foodstuff.⁸

A small number of studies have been conducted to investigate MSG as a trigger factor for asthma. The results to date have been conflicting. Four studies have not shown any association between MSG and asthma,⁹⁻¹² whereas another two concluded that some people with asthma were MSG sensitive.^{13,14} These latter studies have been criticized for their lack of blinding of observers, inadequate baseline and control data, and cessation of antiinflammatory and bronchodilator medications before the challenge sequence, which in themselves may have worsened the airways' obstruction. None of these studies have incorporated measurement of immunologic inflammatory markers or changes in airway responsiveness. Despite this conflicting data, a recent report from the United States Life Sciences Research Institute concluded that there was limited evidence that some people with asthma are more likely to have adverse effects from MSG than members of the general population.¹⁵

Many previous clinical studies of food-induced asthma can be criticized for inadequate baseline or control data. Significant asthmatic responses, particularly late asthmatic reactions, can be difficult to document because of

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TABLE I. MSG study: Summary protocol

	Visit no.								
	1	2	3	4	5	6	7	8	9
Average days after visit 1	0	5	7	10	12	15	18	20	21
Introduction/explain protocol	X								
Commence additive-free diet	X								
Provide spirometer/check use	X	X	X	X		X	X	X	
Provide and explain diary cards	X								
Check daily diary cards		X	X	X	X	X	X	X	X
Baseline lung function tests	X				X				X
Lung function tests (3 hrs in lab and up to 12 hrs at home)		X	X	X					
Soluble inflammatory marker activity (ECP and tryptase)		X				X	X	X	
Nonspecific BHR to methacholine	X				X				X
Challenge 1 (8 hrs in lab and 4 hrs at home)						X			
Challenge 2 (8 hrs in lab and 4 hrs at home)							X		
Challenge 3 (8 hrs in lab and 4 hrs at home)								X	

Visit 9 was conducted the day after visit 8 except in subject 2, for whom it was conducted 2 days later.

the prolonged time course and may be confounded by the effect of random and diurnal variation in ventilatory function. Most double-blind, placebo-controlled food challenge responses are deemed positive when a fall in FEV₁ or peak expiratory flow (PEF) exceeds an arbitrarily predetermined value, often 15%. We report a new application of a statistical method developed by Stenton et al.¹⁶ for identifying early and especially late asthmatic reactions in occupational asthma. This is the first time that this well-validated statistical method has been used in a research trial of food-induced asthma. The aim of this study was to determine whether MSG would induce bronchoconstriction in a group of adults with asthma who perceived that they were MSG sensitive.

METHODS

Subjects

Sixteen subjects were recruited between March 1995 and September 1996, and 12 subjects successfully completed the study. The four subjects who did not complete the study withdrew because of time constraints. All subjects had previously completed a food and asthma questionnaire, which investigated perceptions and practice in regard to potential contributions of dietary factors to each patient's asthma. The details have been published elsewhere.⁸ All questionnaire respondents were ranked according to their responses to thirteen MSG-related questions (see Appendix), with the maximum achievable score being 19 points. No one achieved the maximum score. The higher the MSG score, the more plausible the perception that MSG might be responsible for a worsening of asthma symptoms. All subjects perceived that MSG made their asthma worse.

All subjects had a documented history of reversible airways obstruction but had been clinically stable, with no changes in their regular asthma medications in the 4 weeks before the commencement of the study. For safety and ethical reasons, the exclusions from the study were a previous life-threatening attack of asthma (as defined by respiratory arrest, endotracheal

intubation, admission to an intensive care unit, or pCO₂ >50 mmHg), life-threatening anaphylaxis, females who were pregnant or lactating, and those whose baseline FEV₁ measurement was less than 60% predicted or less than 1.5 L. All subjects gave informed consent before the commencement of the study, and the study was approved by the Alfred Healthcare Group Ethics Review Committee.

Protocol

This study was conducted as a randomized, cross-over, double-blind, placebo-controlled trial. At the baseline visit (visit 1) spirometry and nonspecific bronchial hyperresponsiveness (BHR) to methacholine were performed. Each subject was asked to describe what happened to their asthma when they ingested MSG to confirm their responses from the previously administered questionnaire. Table I outlines the protocol sequence.

Baseline (visit 1) spirometry. Baseline spirometry was conducted by using a dry wedge-bellows spirometer (Vitalograph, Buckingham, U.K.), according to American Thoracic Society criteria for spirometry equipment and methodology¹⁷ and by using the European Community for Coal and Steel predicted values for lung function.¹⁸

Dietary control. To exclude the possibility of a positive reaction occurring because of the ingestion of a food chemical other than MSG, food chemicals that have been reported to potentially exacerbate asthma symptoms were also minimized throughout the study. Therefore an elimination diet, which excluded added MSG, colorings, and preservatives (including sulphites) and minimized naturally occurring MSG, amines, and salicylates, was commenced after the baseline visit.^{19,20} Subjects were required to comply with the diet for a minimum of 5 days before their next visit and for the remainder of the study. A food and beverage diary was kept for the duration of the study to assess dietary compliance.

Medication control. Subjects continued on their usual inhaled bronchodilators and antiinflammatory asthma medications throughout the study period. On each of the control days, subjects were requested to withhold their short-acting β_2 -agonist bronchodilator medication for at least 4 hours before attending the laboratory. If relief medication was required

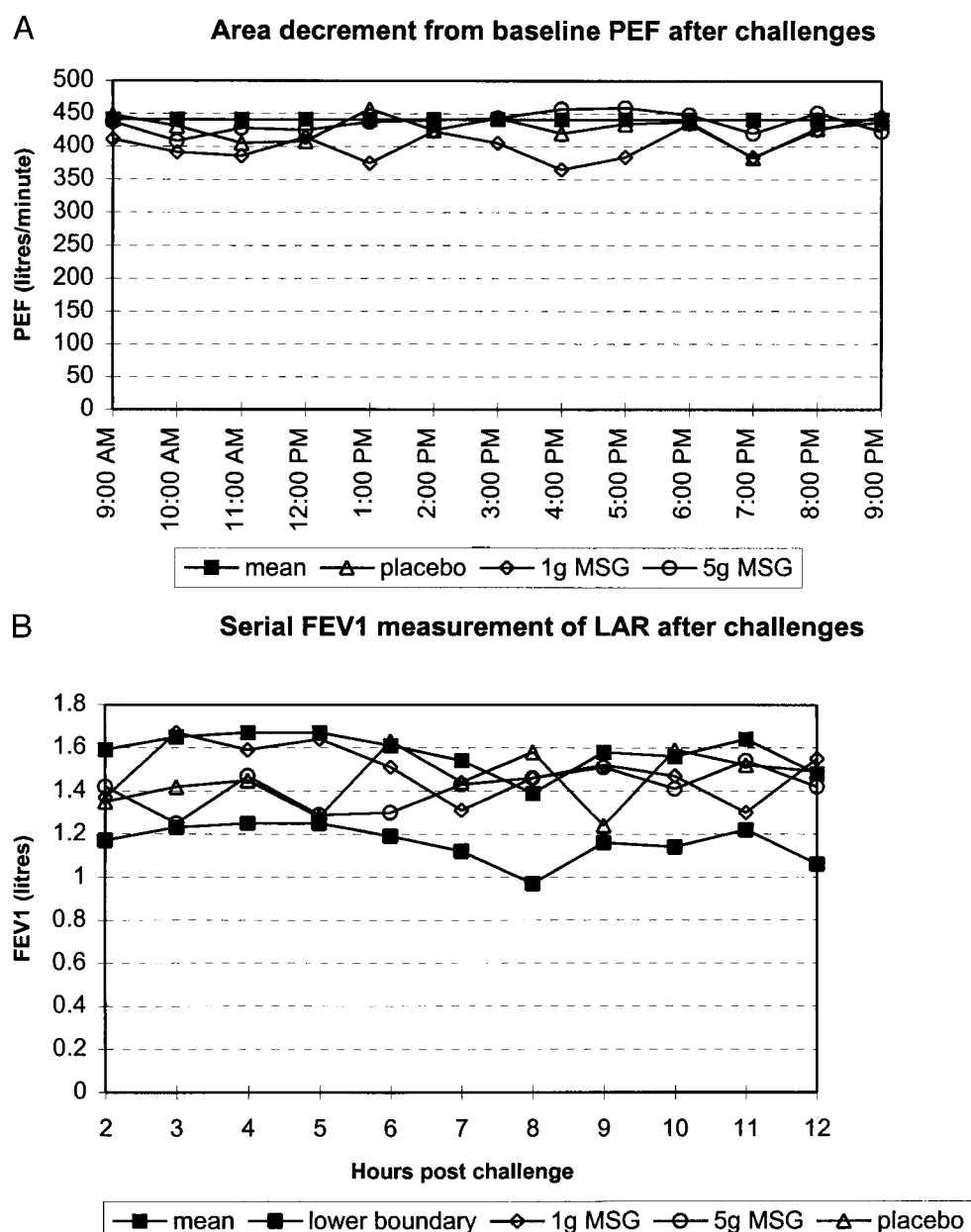


FIG. 1. **A**, Area decrement from baseline. Area decrement is calculated as area ($1 \times \text{hour}$) between line extrapolated from mean baseline and actual PEF/FEV₁ measurements 2 to 12 hours after challenge. This subject (number 1) showed significant change in PEF after 1 gm MSG challenge only. As her other LAR analyses were not significant, challenge response was deemed to be negative. **B**, Significant change ($p < 0.05$) on MSG challenge days has occurred if postchallenge FEV₁ or PEF values cross lower 95% boundary for 2 consecutive hours. This subject (number 12) showed decline in FEV₁ by greater than 15% on both 1 gm MSG and 5 gm MSG challenges. However, as graph shows, challenge data did not cross lower 95% confidence limit boundary, and hence challenge was deemed to be negative.

throughout the control day, the amount used and the time it was taken were recorded, and this use was duplicated on the subsequent control and challenge days.

Nonspecific BHR. The purpose of BHR testing in this study was to ascertain whether any underlying change had occurred even in the absence of an overt episode of asthma. Nonspecific BHR to methacholine was conducted by using the Newcastle dosimeter technique.²¹ Measurements were conducted at the

baseline visit, after the control days (visit 5) to determine whether the elimination diet had altered nonspecific BHR, and after the challenge visits (visit 9) to determine whether the MSG was associated with a change in nonspecific BHR. Visit 9 was conducted the day after the final challenge in 11 subjects and 48 hours after the last challenge for one subject.

Skin prick testing. Skin prick testing was conducted on the volar surface of the arm with standardized allergen extracts

TABLE II. Subject characteristics

Subject no.	Age (yrs)	Gender	BMI (kg/m ²)	Bronchodilator use	Antiinflammatory drug use	Visit 1 FEV ₁ (% predicted)	MSG score (maximum = 19)
1	19	F	27.7	Salbutamol	Budesonide 800 µg/day	93.7	6.0
2	30	M	26.0	Salbutamol	—	88.5	4.0
3	29	F	24.2	Salbutamol, salmeterol 150 µg/day	Budesonide 3200 µg/day, sodium cromoglycate 20 mg/day	71.0	13.5
4	57	M	27.1	Salbutamol, salmeterol 100 µg/day	Fluticasone 1000 µg/day	82.6	3.0
5	34	F	25.2	Salbutamol	—	83.0	11.0
6	31	M	25.1	Salbutamol	Budesonide 800 µg/day	90.5	8.0
7	31	M	30.8	Salbutamol	—	82.1	7.5
8	49	F	30.0	Salbutamol	Budesonide 3200 µg/day	60.8	11.0
9	33	M	28.7	Salbutamol	—	75.2	4.0
10	20	F	21.2	Terbutaline	Budesonide 1600 µg/day, sodium cromoglycate 20 mg/day	61.1	11.0
11	46	F	34.1	Terbutaline	Budesonide 800 µg/day	104.0	11.0
12	47	F	30.7	Salbutamol	—	74.5	6.0

BMI, Body mass index.

(*Dermatophagoides pteronyssinus*, cat hair, *Aspergillus* mix, *Cladosporium herbarium*, *Lolium perenne*, Southern grass mix, and feather mix), histamine (positive control) and a negative control (Bayer Corporation, Sydney, Australia). A positive skin test response was defined as a wheal equal to or greater than 3 mm in diameter to at least one of the allergens.

Inflammatory marker assays. A venous peripheral blood sample (10 ml) was taken for baseline measurement (visit 2) of the soluble markers eosinophilic cationic protein (ECP) and tryptase in serum by using Becton-Dickinson SST tubes. Both of these markers reflect inflammatory cell activity.^{22, 23} ECP is a measure of eosinophil activation. In asthma it reflects the severity of disease and efficacy of treatment and is associated with the occurrence of a late asthmatic reaction. Tryptase is a measure of mast cell degranulation. Venous blood samples were also taken at 1 hour for tryptase activity and 8 hours for ECP after each challenge.

Blood was allowed to clot at room temperature (20° to 24° C) for 60 minutes (± 10 minutes) and then centrifuged at 1300 g for 10 minutes. Serum was decanted in duplicate and stored at -20° C until assayed. Analysis of ECP and tryptase were performed by using the Pharmacia (Uppsala, Sweden) ECP-RIA and Tryptase-RIACT radioimmunoassay kits, respectively, according to the manufacturer's instructions. All samples were run in duplicate. Normal ranges of serum ECP were less than 20 µg/L, and for tryptase, they were less than 5 U/L with these procedures.

Control-day visits (visits 2, 3, and 4). Subjects attended the laboratory in the morning for monitoring of spirometry over 3 hours using a hand-held electric spirometer, which has previously been evaluated and shown to produce similar results to a rolling seal spirometer.²⁴ The spirometer did not have memory to store data electronically. The best of three expiratory maneuvers for both FEV₁ and PEF was recorded every 15 minutes for the first hour and every 30 minutes for the next 2 hours. Subjects were then allowed to leave the laboratory to resume their normal daily routine, but they continued recording their FEV₁ and PEF every hour in exactly the same manner and using the same hand-held spirometer as in the laboratory until

retiring to bed that night. These results were recorded in a diary.

Challenge vehicle. Challenge doses consisted of 1 gm MSG, 5 gm MSG, and 5 gm lactose (placebo). These doses of MSG were chosen because the amount of MSG suggested to elicit possible MSG-induced asthma in previous studies was 2.5 gm.^{13, 14} Each challenge dose comprised 10 size 00 opaque capsules, which were manufactured with a capsule machine filler (Sandell, Switzerland) by a pharmacist not otherwise involved in the study. All capsules were wiped clean after filling and rolled in lactose powder to prevent any MSG being detected on the outside of the capsules.

Challenge visits (visits 6, 7, and 8). Subjects arrived in the laboratory in the morning after an overnight fast. Short-acting β₂-agonist bronchodilator medication was withheld for at least 4 hours before attending the laboratory when possible. On average, the subjects had complied with the diet for 15 days before receiving their first challenge. Spirometry with the hand-held electric spirometer was conducted every 15 minutes for 45 minutes before the challenge. Subjects received 1 gm MSG, 5 gm MSG, and placebo (lactose) challenge doses as single doses, which were administered under double-blind conditions. Subjects always received the lowest dose (1 gm) of MSG before the highest dose (5 gm), with the placebo randomly interspersed. The capsules were randomly allocated and administered by a respiratory scientist who was not otherwise involved in the study.

Subjects continued to monitor their FEV₁ and PEF at the following times after each challenge: 15, 30, and 45 minutes and 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours. Breakfast (consisting of some or all of the following: pears, cereal, toast, eggs, and decaffeinated coffee) was consumed 30 minutes after each challenge.

Subjects were allowed to leave the laboratory 8 hours after the challenge but continued to monitor their FEV₁ and PEF each hour for a further 4 hours using the same hand-held spirometer, and recorded these results and their symptom scores in the diary provided. The diary cards were checked at each visit for completeness, accuracy, and dietary compliance.

TABLE III. Positive late asthmatic reactions (area decrement and serial methods) after challenges

Subject no.	Challenge sequence	FEV ₁ AD	PEF AD	PEF serial
1	P, 1, 5	—	1	—
2	P, 1, 5	1	—	—
3	1, 5, P	—	—	—
4	1, P, 5	—	P, 1, 5	P, 1, 5
5	1, 5, P	—	—	—
6	1, P, 5	P, 1, 5	1	—
7	1, P, 5	—	—	—
8	P, 1, 5	—	—	—
9	1, 5, P	—	—	—
10	P, 1, 5	—	—	—
11	1, P, 5	P, 1, 5	P, 1, 5	—
12	1, 5, P	—	—	—

None of the subjects had a late asthmatic reaction using the serial FEV₁ method.

P, Placebo; 1, 1 gm MSG; 5, 5 gm MSG; AD, area decrement.

Definition of a positive reaction and statistical analyses. An immediate reaction after a challenge was defined as a fall in FEV₁ and PEF of greater than 15% from both that morning's prechallenge spirometry and from the time-matched control-day data.

The three control days of spirometry allowed a mean FEV₁ and PEF time-curve (plus 95% confidence limits) to be defined for each participant for all waking hours. From the challenge data obtained, it was then possible to apply two different statistical methods to determine whether a late asthmatic reaction had really occurred, according to the analysis developed by Stenton et al.¹⁶ for occupational challenges.

The first statistical method was based on a summary measure. Late asthmatic changes for FEV₁ and PEF were quantified using the 2- to 12-hour area decrement. This was calculated as the area between a line extrapolated from the daily mean prechallenge measurement and the actual measurements from 2 to 12 hours after the time of the challenges (Fig. 1, A). An unpaired Student's *t* test was used to compare area decrement measurements on the 3 control days with the measurements after the active challenges. A *t* value of greater than 2.92 was regarded as significant at the 5% level.

The second method of statistical analysis was based on serial hourly measurements of FEV₁ and PEF. The pooled standard deviation of the 11 hourly measurements (i.e., 2 to 12 hours after challenge) was obtained from a one-way analysis of variance by time. By using this figure, each hourly measurement (for FEV₁ and PEF) on a challenge day could be tested against the mean hourly measurement for that time point on the control days. This method is best represented graphically in the form of a lower boundary (i.e., a time-response curve with a lower 95% confidence limit) (Fig. 1, B). A positive reaction was deemed to have occurred if the time-response curve for any of the active challenges crossed the lower boundary for 2 consecutive hours in the absence of such a change after placebo challenge. This method has a false-positive rate of 1%,¹⁶ although the sensitivity of this method has not been determined.

When both of these methods provided statistically significant results by both measured indices (FEV₁ and PEF) and without

change on placebo challenge, the challenge test response was considered to be unequivocally positive. When only one method or one index was positive, the result was deemed equivocal. The 3 days of control data were also used to assess spirometric variability.

Descriptive statistics were generated by using the SPSS computer package (SPSS, Inc., Chicago, Ill.).²⁵ Chi square tests were used to assess associations between categorical data, and Student's *t* test was used to assess differences between the means of continuous data. To assess marginal heterogeneity, McNemar's test was performed on the symptom-score data. A *p* value of less than 0.05 was regarded as significant for all tests. To assess the agreement between paired PD₂₀ measurements, the method of Bland and Altman was used.²⁶

RESULTS

Description of subjects

Twelve subjects (seven women and five men), with a mean age of 35.3 years (SD = 11.7 years) completed the study. All subjects were atopic to at least one of seven common aeroallergens. All subjects were using short-acting β_2 -agonist bronchodilators as required at the commencement of the study, and seven subjects were also using regular inhaled corticosteroids (mean dose = 1771 μ g beclomethasone dipropionate or equivalent per day). None were currently using oral steroids. Three subjects (numbers 7, 8, and 10) required short-acting β_2 -agonist bronchodilators on each of the control and challenge days, with the timing of these being uniformly maintained throughout each control and challenge day. Two subjects continued with their usual daily long-acting bronchodilators (numbers 3 and 4), and two subjects continued with sodium cromoglycate (numbers 3 and 10) throughout the study.

At the baseline visit, the mean baseline spirometry (percent predicted FEV₁) was 80.6% (SD = 12.9%), and the mean body mass index of subjects was 27.5 kg/m² (SD = 3.5 kg/m²). The mean MSG score of the group was 8.0 (range, 3 to 13.5 points). Seven subjects were employed outside of the home, two were fully occupied with home duties, one was a pensioner, and the other two were students. The demographic and medication details for each subject are outlined in Table II.

Challenge days

Spirometry. No immediate bronchoconstrictor reactions were observed for early asthmatic reactions. None of the subjects had either a definite or equivocal late asthmatic reaction (Table III). Fig. 1 shows two examples of the graphic representations of the statistical analysis for determining whether a late asthmatic reaction has occurred.

Eight subjects did have a fall in FEV₁, PEF, or both of greater than 15% of their prechallenge spirometry for that day. Two participants had this change (numbers 5 and 10) after placebo only, three after both active and placebo treatment (numbers 4, 8, and 11), and two to the 1 gm MSG challenge only (numbers 3 and 7) but not the 5 gm MSG challenge. One subject (number 12) had a greater than 15% fall in spirometry to both 1 gm MSG

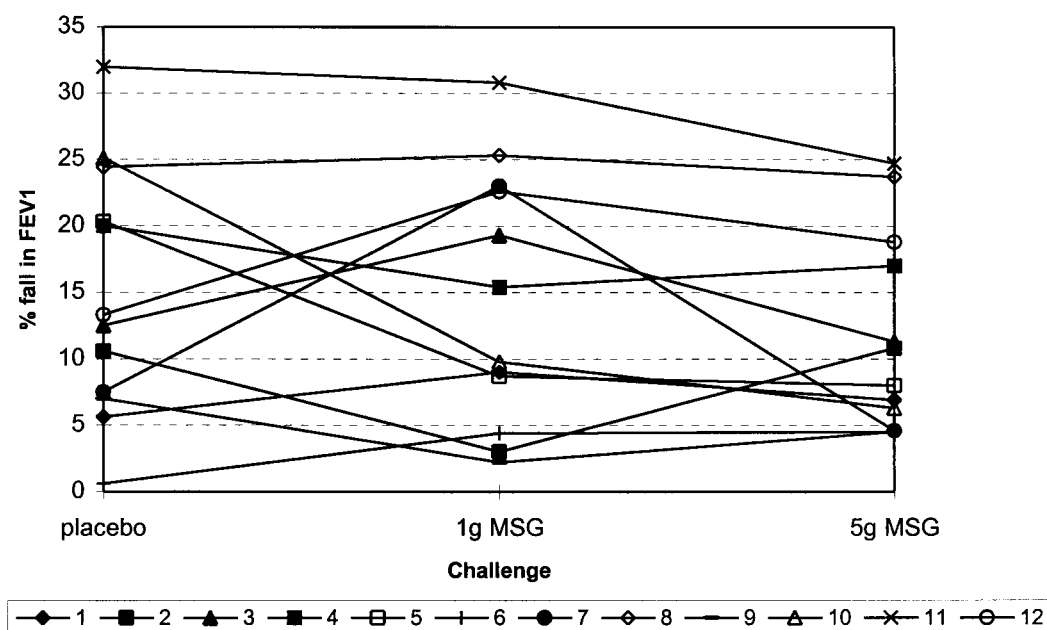


FIG. 2. Maximum fall in FEV₁ after challenges.

and 5 gm MSG (Fig. 2), but the maximum change did not cross the lower 95% confidence limit boundary and the response was therefore deemed to be negative (Fig. 1, B). Indeed, with the exception of subject number 3, all of these subjects had falls in FEV₁, PEF, or both of greater than 20% of their prechallenge spirometry. We therefore did not find any conclusive evidence of true MSG-induced asthma by using this rigorous method of analysis (Table III).

Symptoms reported during challenges. Eleven subjects reported symptoms after at least one of the challenge visits. However, there were no statistically significant differences in reported symptoms after placebo versus 1 gm MSG challenges (chi square = 0.19, $p = 1.0$), placebo versus 5 gm MSG challenges (chi square = 0.69, $p = 0.58$), or 1 gm MSG versus 5 gm MSG challenges (chi square = 2.74, $p = 0.22$). In all subjects, reported symptoms were self-limiting and did not require relief medication. No one described the classic MSG symptom complex (burning cutaneous sensation, facial pressure, chest pain, headache, nausea, palpitations, numbness in back of neck, tingling, bronchospasm, drowsiness, and weakness) with either MSG challenge.

Symptom scores. There were no statistically significant differences in daytime or nighttime symptom scores after placebo and 1 gm MSG challenges ($p = 0.5$ and $p = 1.0$, respectively), placebo and 5 gm MSG challenges ($p = 1.0$ and $p = 1.0$, respectively), or 1 gm and 5 gm MSG challenges ($p = 0.25$ and $p = 1.0$, respectively). All four subjects who reported asthma symptoms after 5 gm MSG challenge also reported asthma symptoms on both the placebo and 1 gm MSG challenge days. Therefore no

evidence of a dose-response relationship was found with asthma symptom scores.

Nonspecific BHR

For the group as a whole, there were no statistically significant differences between the mean baseline PD₂₀ methacholine value after the diet control (95% CI: -0.27, 0.45) or the challenge sequence (95% CI: -0.65, 0.70) or between the mean diet control PD₂₀ value and the challenge sequence (95% CI: -0.35, 0.48) (Fig. 3). That is, there was no evidence of MSG having affected underlying nonspecific BHR overall.

However, one subject (number 11) did show an individual statistically significant worsening in nonspecific BHR after the MSG challenge sequence (PD₂₀ after challenge = 41 μ g) beyond the 95% confidence limits (103.2, 10775.8 μ g) calculated by the method of Bland and Altman from the two preliminary PD₂₀ values (PD₂₀ baseline = 9318 μ g and PD₂₀ diet = 860 μ g).

Two subjects (numbers 6 and 9) did not achieve a 20% fall in FEV₁ after administration of 6.4 mg methacholine (19% and 18% falls, respectively). The dose-response slope to methacholine was calculated for both of these subjects by using the method outlined by O'Connor et al.²⁷ and did not show any significant difference in nonspecific BHR after the MSG challenge sequence ($p = 0.61$).

Soluble inflammatory marker activity

Five subjects were found to have elevated ECP levels (Fig. 4). However, in four of these subjects, baseline ECP levels were also elevated, probably indicating underlying active asthmatic inflammation rather than a

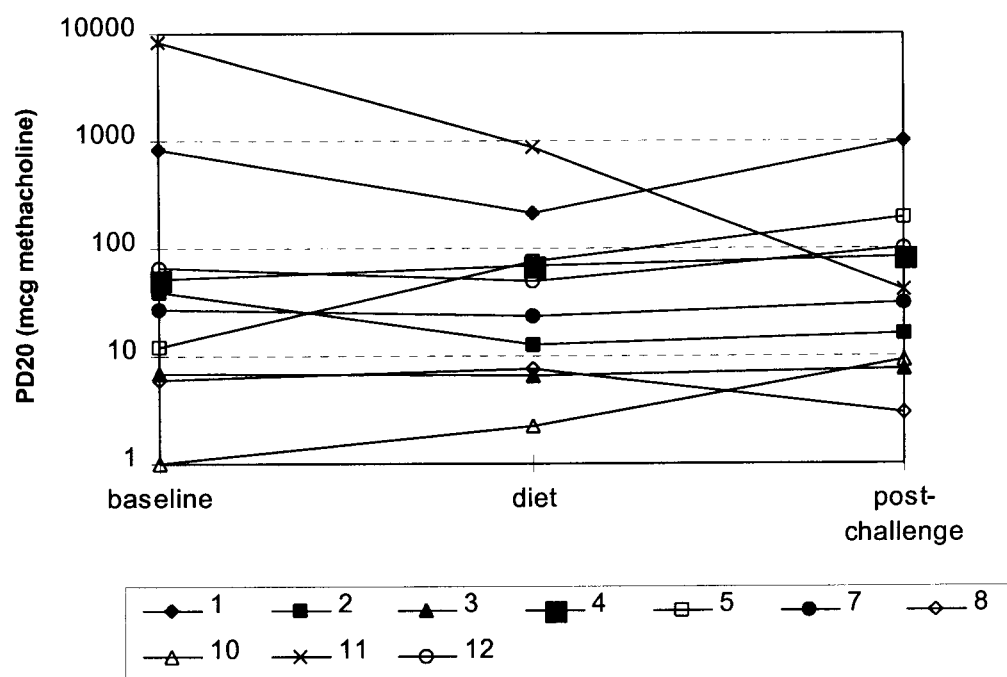


FIG. 3. Nonspecific BHR responses at baseline, after run-in elimination diet period, and at end of MSG challenge sequence.

positive response to MSG ingestion. In the fifth subject (number 12), the ECP level was raised after both the 1 gm and 5 gm MSG challenges, although the level was higher after the 1 gm (24.9 $\mu\text{g/L}$) than the 5 gm (22.2 $\mu\text{g/L}$) MSG challenge, and the ECP after the placebo challenge was close to being considered elevated (19.4 $\mu\text{g/L}$).

The only elevated tryptase level occurred on a baseline sample (5.5 U/L, subject number 9) before any MSG ingestion.

DISCUSSION

We have been unable to demonstrate any definite or even equivocal asthma reactions (by the definitions used) after oral ingestion of up to 5 gm MSG by using conventional spirometric measurements. These findings are consistent with those of Schwartzstein et al.⁹ and Germano et al.,¹⁰ who also failed to detect MSG-induced asthma in adults. Furthermore, there was little suggestion of relevant changes in nonspecific BHR to methacholine after MSG challenges and no changes in soluble inflammatory marker activity.

This study had a stronger design than that of Allen et al.¹³, which did document MSG-induced asthma. First, this study collected 3 days of control-day data, which allowed a statistical definition of what fall in spirometry was significant for each individual. Previous studies, including that of Allen et al.,¹³ have relied on an arbitrarily defined fall in spirometry for the definition of a positive reaction. Our study also measured nonspecific

BHR and soluble inflammatory marker activity, which have the ability to provide additional information on whether the challenge was eliciting a cellular reaction that may not have been evident on spirometry alone. Importantly, this study did not cease antiinflammatory medications and strictly controlled the use of bronchodilator medications to avoid positive reactions occurring because of inappropriate withdrawal of medications. It is possible that some positive reactions reported by Allen et al.¹³ were due to the withdrawal of asthma medications.

Seven of the subjects were taking antiinflammatory medication, and two were taking long-acting β_2 -agonists, which could potentially have confounded these results. However, the aim of the study was to determine whether people who perceive that they are MSG sensitive while taking their usual medication objectively bronchoconstrict after MSG challenge. Furthermore, the regular use of long-acting β_2 -agonists does not offer good protection against challenge-induced bronchoconstriction.²⁸

Three subjects did require short-acting β_2 -agonist bronchodilator use on the control and challenge days. In all subjects, this use was accurately duplicated on all of the control and challenge days. The spirometry results in these subjects did not suggest that bronchodilator use masked an asthmatic reaction. Furthermore, in all of these subjects, significant spirometry variability (>15%) was seen on both the control and challenge days, suggesting that the airway continued to be labile and capable of induced bronchoconstriction. Indeed, this

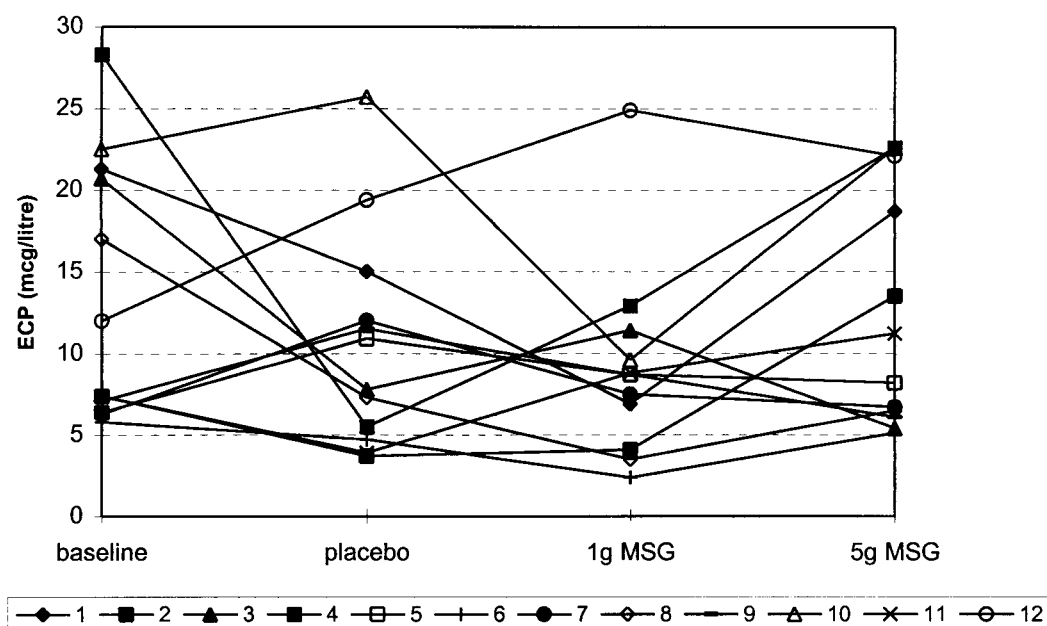


FIG. 4. ECP values at baseline and 8 hours after placebo, 1 gm MSG, and 5 gm MSG challenges.

lability emphasizes how difficult, and potentially unethical, it would be in such a study to stop prophylactic medication.

Another possible confounder in this study was that spirometry monitoring for the control days was undertaken under supervision in the laboratory for only 3 hours, whereas the subjects did not leave the laboratory until 8 hours after each challenge. This may have led to more variability in spirometry measurements on the control days than on the challenge days and therefore an underestimation of potential late asthmatic reactions. The general lack of change in nonspecific BHR, soluble inflammatory marker activity, and symptoms after each challenge do not support this hypothesis. To overcome this possibility, however, future studies should use spirometers that can electronically store FEV₁ and PEF data.

In the two subjects (numbers 11 and 12) who showed the greatest changes in FEV₁ and PEF measurements, there was no convincing evidence of a dose-response relationship to MSG ingestion. Furthermore, in one subject (number 11) the maximum fall in FEV₁ after placebo was 32% compared with a maximum fall in FEV₁ of 25% after the 5 gm MSG challenge. In both subjects there was no clinically relevant change in soluble inflammatory marker activity or asthma symptoms after the MSG challenges. Subject 11 also had a worsening of nonspecific BHR after the challenge sequence. The actual PD₂₀ level was high at baseline and showed an almost linear decline during the subsequent measurements. In the context of her spirometry, soluble inflammatory marker activity, asthma symptom scores, and reported symptoms, the change in PD₂₀ after challenge

is unlikely to be an indication of MSG sensitivity but rather a reflection of the variability of the PD₂₀ measurement in that individual. It has previously been shown that a worsening in BHR alone is not a sensitive measure of detecting food-chemical intolerance in asthmatic subjects.^{29, 30}

Even in the subject who showed a greater than 15% fall in FEV₁ only after MSG challenges (number 12), a dose-response relationship was not observed, and the change did not fall outside of the 95% confidence limits. In addition, there was no significant change in nonspecific BHR to methacholine, no clinically relevant increase in soluble inflammatory marker activity, or any change in asthma symptom scores and reported symptoms. This suggests that no reaction had occurred. These individual data emphasize the need for a multifactorial approach to analysis, with the ability to overview the global response after MSG to decide whether it is likely that a true reaction has occurred.

Given that the purpose of BHR testing in this study was to ascertain whether any underlying change had occurred even in the absence of an overt episode of asthma, we are unable to answer the question of whether MSG affects underlying nonspecific BHR, particularly in view of the negative results obtained.

It is unlikely that giving a higher MSG dose would be more discriminating because although there is no data on average MSG consumption for Australians, English data suggest an average MSG intake of 0.59 gm/day, with extreme users having an intake of 2.33 gm/day.³¹ Data from France shows a similar profile.³²

Although this study did not detect MSG-induced asthma in a group of individuals who regarded them-

selves as being MSG sensitive, it cannot necessarily exclude MSG-induced asthma completely. However, after the negative results it should allow the ethical design of studies that use the same protocol to investigate even patients previously labeled as having experienced an MSG reaction.

Although the method described is time consuming and requires a high degree of commitment from both investigator and subject, it has proved to be feasible and is highly rigorous in terms of interpreting inherently variable physiologic changes. Without such rigor, false-positive responses caused by spontaneous variability are quite possible.¹⁶ Our data confirms, however, that it is extremely important to obtain adequate control data to accurately determine whether a positive reaction has truly occurred after double-blind, placebo-controlled food challenges and to put a 15% change in spirometry into perspective. In some subjects a substantially greater than 15% response can be shown to be no more than random fluctuation in airway caliber, whereas it is quite possible to pick up a late asthmatic response of much less than 15% change in spirometry if baseline values are relatively stable throughout the control days. Furthermore, the inclusion of 3 whole days of time-matched, control spirometry data enhances the ability of such studies to make a definitive diagnosis for each individual.

It is important that the correct diagnosis of any food-induced asthma, including MSG-induced asthma, is made. The current treatment for food-induced asthma is avoidance or elimination of the food or foods and beverage or beverages concerned.³³ In the case of MSG, patients are often advised to avoid both added MSG and those foods, such as tomatoes and cheese, which contain relatively high amounts of naturally occurring MSG. If false-positive diagnoses are made, then patients will be unnecessarily restricting their dietary intakes. Data from a recent questionnaire survey in Melbourne⁸ suggests that perception of food-induced asthma symptoms is very high. Furthermore, many subjects with asthma are modifying their diets on the basis of these perceptions or, indeed, on the basis of medical advice, without any objective evidence that foods are really implicated. Such dietary restrictions may have significant nutritional, social, and financial consequences.

In conclusion, we were unable to demonstrate MSG-induced asthma in a group of adults who perceived that MSG did affect their asthma control in a rigorously designed study, which highlighted the importance of adequate control data. This method of investigation is expensive in terms of time, resources, and commitment and therefore is not suitable for large screening studies. However, the protocol is feasible for small numbers with a positive screening challenge and in which a definite diagnosis is required.

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APPENDIX

Appendix. MSG-related questions on food and asthma questionnaire

Question	Points awarded
MSG restriction advised	1
Currently avoiding MSG	1
Asthma symptoms after Asian meals	2 if definite, 1 if possible
Asthma symptoms after Italian meals	2 if definite, 1 if possible
MSG listed as food additive, code number avoided	1
MSG provokes asthma symptoms	2 if definite, 1 if possible
Parmesan cheese provokes asthma symptoms	2 if definite, 1 if possible
Sauces provoke asthma symptoms	1 if definite, 0.5 if possible
Soups provoke asthma symptoms	1 if definite, 0.5 if possible
Tomato provokes asthma symptoms	1 if definite, 0.5 if possible
Tomato juice provokes asthma symptoms	1 if definite, 0.5 if possible
Tomato paste provokes asthma symptoms	2 if definite, 1 if possible
Extruded cheese snacks provoke asthma symptoms	2 if definite, 1 if possible