Monosodium L-glutamate–induced asthma

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Ingested chemicals, including aspirin and sulfites, are becoming increasingly recognized as provokers of acute severe asthma. In order to investigate the asthma-provoking potential of the widely used flavor enhancer, monosodium L-glutamate (MSG), we challenged 32 subjects with asthma, a number of whom gave histories of severe asthma after Chinese restaurant meals or similarly spiced meals. The subjects received an additive-free diet for 5 days before challenge and were challenged in hospital, after an overnight fast, with 500 mg capsules of MSG. They were challenged in a single-blind, placebo-controlled fashion with increasing doses of MSG from 0.5 gm to 5.0 gm. Thirteen subjects reacted. Seven subjects (group 1) developed asthma and symptoms of the Chinese restaurant syndrome 1 to 2 hours after ingestion of MSG. Six subjects (group 2) did not develop symptoms of Chinese restaurant syndrome, and their asthma developed 6 to 12 hours after ingestion of MSG. These challenge studies confirm that MSG can provoke asthma. The reaction to MSG is dose dependent and may be delayed up to 12 hours, making recognition difficult for both patient and physician. (J ALLERGY CLIN IMMUNOL 1987;80:530-7.)

MSG is the sodium salt of glutamic acid, a nonessential amino acid that forms 20% of dietary protein. MSG is also present in our diet, most of which is artificially added to enhance the flavor of foods. The flavor-enhancing property of MSG was first noted in 1908 by Ikeda, a Japanese chemist,[1] and it became commercially available in the United States in the early 1950s. Since that time it has been used increasingly by both the manufacturing and restaurant industries. The average daily intake in Western countries is estimated to be 0.3 to 1 gm, but as much as 4 to 6 gm may be ingested in a highly seasoned restaurant meal.

Although it may appear difficult to fault a substance that is one of the building blocks of proteins, considerable evidence exists that MSG, as an additive in food, can indeed cause symptoms.[2-4] MSG is both neuroexcitatory and neurotoxic in animals[5] and in man, and added MSG is reported to cause epileptic-like shudder attacks in children[6] and the CRS.[7] This syndrome, occurring within hours of a CRM, is characterized by headache, a burning sensation along the back of the neck, chest tightness, nausea, and sweating.

Abbreviations used

MSG:	Monosodium L-glutamate
CRS:	Chinese restaurant syndrome
CRM:	Chinese restaurant meal
PEFR:	Peak expiratory flow rate

Provocation of asthma by MSG in two patients was reported by two of the authors of this article in 1981 in a letter to the editor of the *New England Journal of Medicine*.[8] This article describes MSG challenges in 32 patients with asthma during the subsequent 3 years.

METHODS

Patient details

Details of the 32 patients studied are summarized in Table I. Criteria for selection for MSG challenge studies were as follows: either a history of asthma occurring within 24 hours of a CRM or unstable asthma, usually with sudden, severe, unexplained attacks or patients with a history suggestive of another ingested chemical sensitivity. Clinical records of 13 of the 16 patients, whose histories suggested MSG-induced reactions, are presented in more detail.

Patient 1, a 23-year-old registered nurse, with previously documented sensitivities to ingested metabisulfite, tartrazine, benzoic acid, and aspirin, presented to the emergency department at 8 A.M. 11 to 12 hours after ingestion of a 15-course Chinese meal with won ton soup as the first course. On waking the following morning, she rapidly developed severe asthma, unresponsive to her usual inhaled broncho-

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TABLE I. Patient details

Patient No.	Age (yr)	Sex	Indication for challenge			Other allergic diathesis
			Asthma after CRM	Unstable severe attack	Other probable sensitivity	
1	23	F	+		+	Atopic
2	42	F	+			
3	39	F	+			
4	28	M	—	+		
5	24	F	—	+		
6	36	F	—	+		
7	44	F	—		+	
8	29	F	—		+	
9	43	F	—			
10	54	M	—		+	
11	37	F	+		+	
12	38	M	—	+	+	
13	14	M	—	—	+	
14	22	F	—	+		
15	31	F	+	—		
16	25	M	—	+		
17	49	F	+	—	+	Hives/angioedema
18	54	M	—	+		
19	29	F	+	+	+ +	Atopic
20	38	F	+			Atopic
21	18	F	+			Atopic
22	24	F	+		+	
23	30	F	—	+		
24	33	F	—	+		
25	67	F	—	+		Angioedema
26	45	F	+	+	+	
27	22	F	—	+		
28	17	F	+	+	+	Atopic
29	26	F	+	+	+	
30	16	F	—	+		Angioedema
31	21	M	+	+	+	
32	75	M	—	+	+	Atopic

dilators. On arrival at hospital, aggressive treatment was begun with nebulized salbutamol, intravenous aminophylline, and corticosteroids. During the next 3 hours, her asthma increased in severity, and a persistent bradycardia was noted. At 11 A.M., 3 hours after presentation to the emergency department, she was intubated, and mechanical ventilation was instituted. Her bradycardia persisted, and blood pressure began to fall despite the addition of intravenous isoprenaline and epinephrine. At 12.15 P.M., partial cardiopulmonary bypass was instituted for 5 hours until her blood pressure recovered and asthma was improving. She was extubated 24 hours later. Six weeks later she had another small CRM and experienced asthma the following morning.

Patient 2 was a 42-year-old subject who had unstable asthma but had not observed provocation of her asthma by ingested foods or beverages. Her asthma was difficult to control with corticosteroids and bronchodilators with PEFRs varying between 150 and 300 L/min. In order to exclude provocation of her asthma by ingested chemicals or foods, she was placed on a general exclusion diet. Improvement in her PEFRs occurred during a period of 3 to 4 days on the diet. She found the diet very restrictive and broke it one evening to have a CRM. The following morning she had an asthma attack with PEFRs falling to levels similar to those recorded before the diet.

Patient 3, a 39-year-old woman, developed symptoms of CRS shortly after a multicourse Chinese meal, which also included soup. In particular, she recalled a sensation of warmth over her head, together with chest tightness, nausea, and later, headache. Shortly after the onset of these symptoms, she developed severe asthma that rapidly progressed

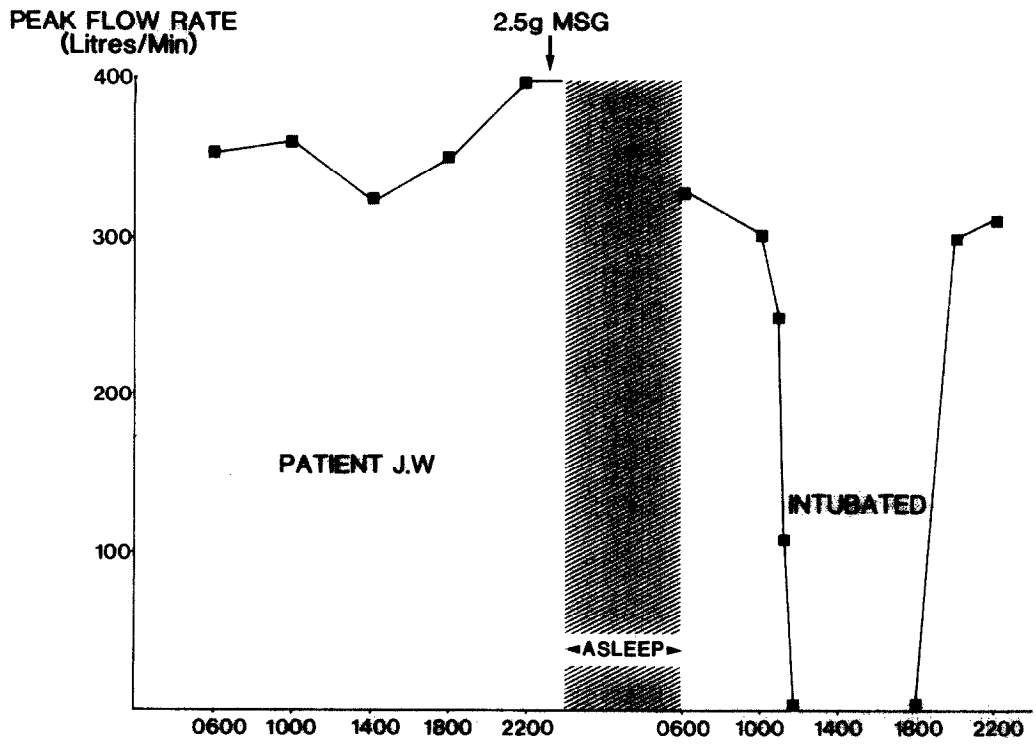

FIG. 1. MSG challenge study for patient 1.

TABLE II. Monosodium glutamate challenge schedule for asthma

	Clinical asthma severity			
	Mild	**Moderate**	**Severe**	**Very severe**
Dose (gm)				
1	2.5	2.5	0.5	0.5
2	5.0	5.0	1.5	1.5
3	—	—	2.5	2.5
4	—	—	5.0	5.0

Note: Only one MSG challenge to be performed per day.

to a respiratory arrest requiring rescusitation by paramedics. She was subsequently challenged at her local hospital with each course of the provoking meal on a separate day. When no adverse reaction was observed, she was referred for ingested chemical provocation studies.

Patient 11, a 37-year-old woman with chronic, steroid-dependent asthma gave a history suggestive of multiple ingested chemical sensitivities and had developed acute asthma requiring hospital admission within hours of a CRM. In addition, her asthma was provoked within minutes of drinking a glass of wine or orange juice preserved with sulfites.

Patient 15, a 31-year-old nonatopic woman with a 6-year history of asthma was referred for investigation of asthma and probable CRS, occurring within 10 hours after a CRM.

Patient 17, a 49-year-old atopic woman with a 30-year history of asthma, gave a history of strawberries provoking urticaria and crustaceans causing angioedema. She had experienced an attack of asthma lasting several hours shortly after a CRM. She was a known aspirin-sensitive individual.

Patient 19 was a 29-year-old atopic woman with a 6-year history of asthma. Sulfite-containing foods and beverages, including sausages, cordials, and dried fruit, rapidly provoked wheezing. CRMs were followed by cough and mucus at about 6 hours but no wheeze.

Patient 20, a 38-year-old atopic woman with a 9-month history of asthma, gave a history of recurrent attacks of asthma occurring within a few hours of a CRM. These attacks were frequently accompanied by an itchy nose but no typical symptoms of CRS.

Patient 21 was an 18-year-old atopic woman with a history of asthma since the age of 3 years. Her asthma was provoked by sulfite-containing foods and beverages such as French fries and white wine. CRMs provoked flushing of

TABLE III. Challenge results

Pat. No.	Food-induced reaction				Chronic asthma			MSG challenge reaction					
	CRA	Sy	Delay hours	Other ingest react	Sev	Mod	Mild	0.5	1.5	2.5	5.0	Delay hours	Sy
1	+	Abdom pain	12	+	+					+		12	Abdom pain
2	+	—	12	—		+				+		12	—
3	+	CRS	1-2	—		+		+	+	+		1-2	CRS
4	—	—	—			+				—	—		
5	—	—	—	—		+				+		6	
6	—	—	—	—		+				—	—		
7	—	—	—	+		+				—	—		
8	—	—	—	+		+				—	—		
9	—	—	—	—		+				+		6	
10	—	—	—	+		+				+			
11	+	—	3-4	+		+			+			4-5	CRS
12	—	—	—	+	+			—	—	—	—		
13	—	—	—	+			+			—	—		
14	—	—	—	—		+				—	—		
15	+	Nausea	10	—		+				+		7	Nausea
16	—	—	—	—			+			—	—		
17	+	—	2	+						+		1-2	CRS
18	—	—	—	—			+			—	—		—
19	+	—	—	+			+			—	—		
20	+	CRS	2-3	—		+				+		3-4	CRS
21	+	CRS	2	+		+				+		1	
22	+	—	3	+		+				+		3	CRS
23	—	—	—	+		+				+		6	CRS
24	—	—	—	+		+				—	—		
25	—	—	—	—		+				—	—		
26	+	—	1	+		+				+		1-2	
27	—	—	—	+		+				—	—		
28	+	—	6	+			+			—	—	—	
29	+	—	—	+		+				—	—		
30	—	—	—	—	+					—	—		
31	+	CRS	2	+		+				—	—		
32	—	—	—	+		+				—	—		

Pat. = patient; Sy = symptoms; delay hours = delay in hours of onset of asthma after MSG challenge or CRM; other ingest react = probable other asthmatic reaction to ingested food or chemical; sev = severe; mod = moderate; abdom = abdominal.

the head and upper body, together with itching under the chin and wheeze at 1 to 3 hours.

Patient 26 was a 45-year-old woman whose asthma was provoked by sulfite-containing foods and beverages, including wine, pickled onions, and sausages. She had also experienced asthma approximately 1 hour after some CRMs.

Patient 28, a 17-year-old atopic schoolgirl, experienced attacks of asthma approximately 6 hours after a CRM and other MSG-containing foods such as tacos, spicy dips, and tomato juice.

Patient 29 was a 26-year-old atopic woman whose asthma was provoked by sulfite-containing foods. She reported vomiting and wheeze 3 hours after a CRM.

Patient 31 was a 21-year-old nonatopic man with a 5-year history of asthma. His asthma was provoked by orange juice, wine, and other sulfite-containing foods. One half to 1 hour after a CRM, he had experienced warmth, localized itch under the chin, and asthma.

Challenge details

Procedures that were followed were in accordance with the ethical standards and requirements of our institution. Patients started a general exclusion diet at least 5 days before challenge. This diet excludes chemicals known to provoke asthma. Corticosteroid medications were continued during the challenge period, but morning theophylline doses were stopped. Inhaled β-agonist bronchodilator was administered once, at 6 A.M., 3 hours before first challenge. The MSG-challenge dose schedule used is presented in Table II. Patients were challenged in a single-blind, placebo-controlled,

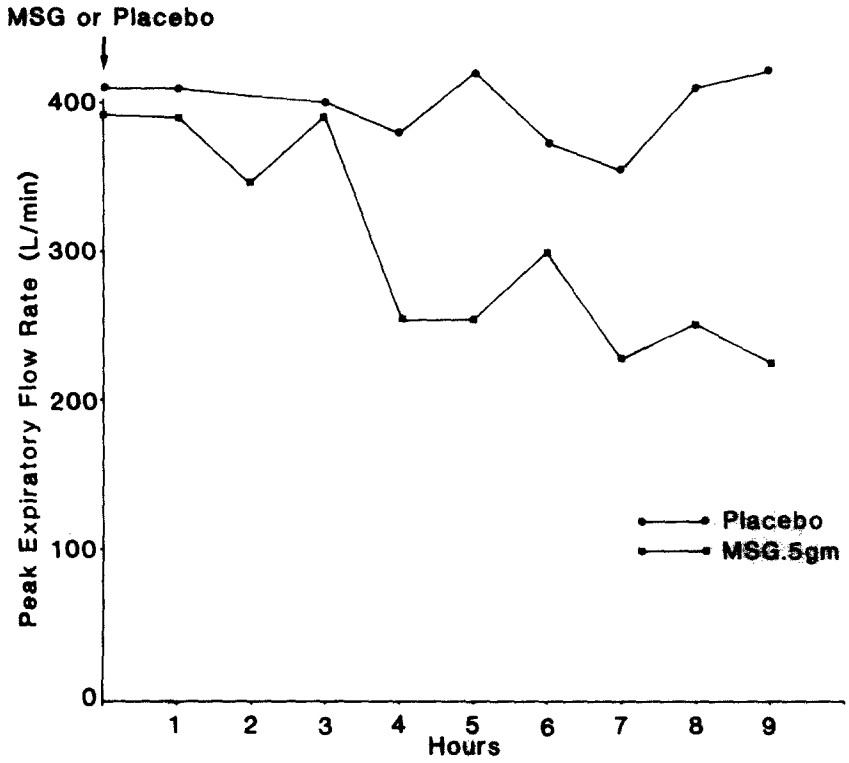

FIG. 2. Placebo and 0.5 gm MSG challenge for patient 3.

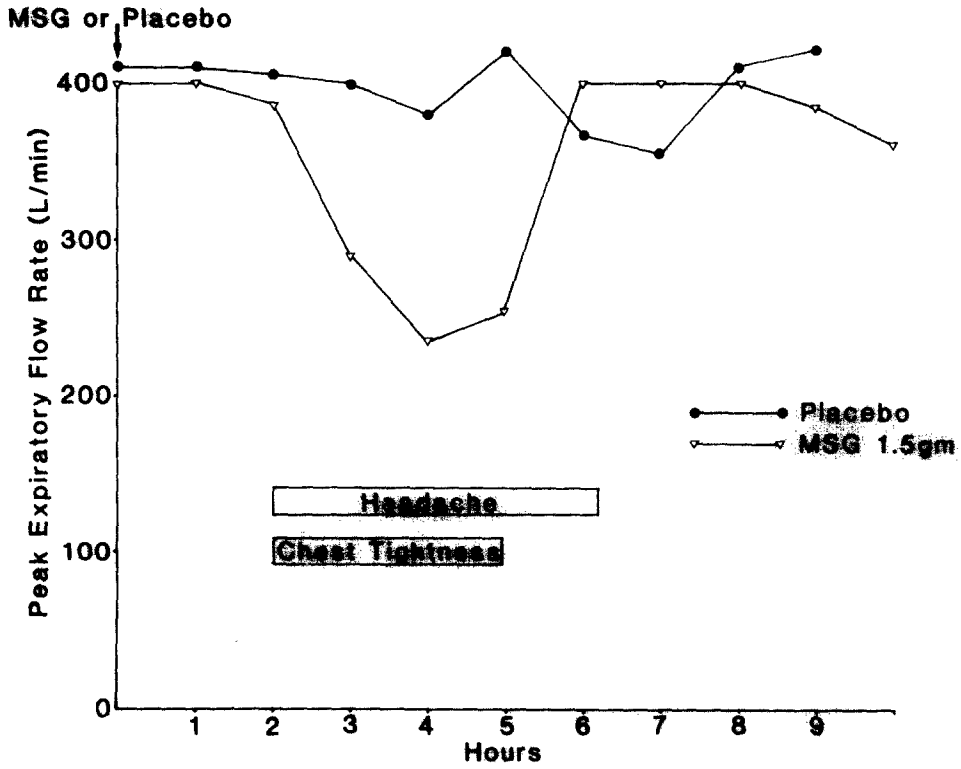

FIG. 3. Placebo and 1.5 gm MSG challenge for patient 3.

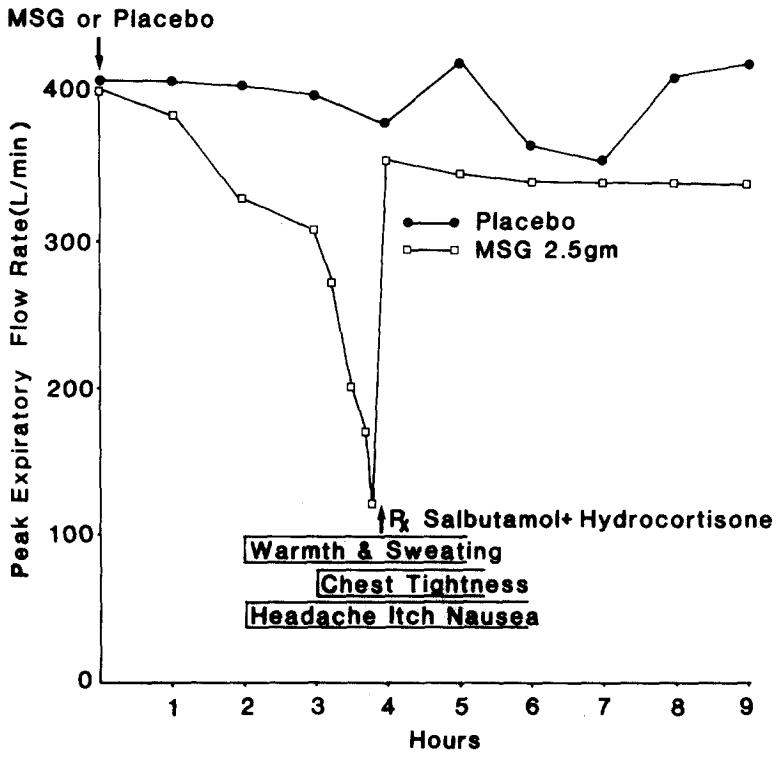

FIG. 4. Placebo and 2.5 gm MSG challenge for patient 3.

dose-response fashion with 500 mg capsules of MSG. Capsule doses of 1.5 to 2.5 gm of MSG were demonstrated in a preliminary study to produce similar blood glutamate levels to a CRM containing 5 to 10 gm of added MSG. The MSG challenges were randomized with other ingested chemical challenges. Patients 1 and 2 had previously been demonstrated to be nonplacebo reactors and were challenged in an open fashion. Patient 1 was challenged on only one occasion because of her extremely severe reaction to the first challenge. Patient 2 was challenged on a second occasion in order to confirm her initial reaction.

Before challenge, each subject was allocated to one of four groups: mild, moderate, severe, and very severe. Allocation was determined by two factors. First, the severity of the asthma and second, the severity of previous CRM- or MSG-induced reactions. Patients were allocated in this way in order to determine challenge doses, as presented in Table II, for each individual and to ensure that patients with potentially severe reactions were challenged cautiously. Challenges with 500 mg capsules of MSG were performed after an overnight fast. Each patient was observed closely, and PEFRs were recorded hourly for 14 hours after each challenge. A challenge was regarded as positive if there was both a >20% fall in PEFR from baseline of the challenge day and if the lowest recorded PEFR was <20% of the lowest flow rate recorded on the control day. In view of the possibility of delayed reactions, only one dose was administered on each day. Doubtful reactions were confirmed by rechallenge.

RESULTS

Results of the challenge studies of all 32 patients are summarized in Table III. Thirteen of the 32 patients challenged with MSG had a positive challenge. Eight of these 13 patients gave a history of asthma after CRMs or other similarly spiced meals. Asthma developed in seven subjects within 1 to 2 hours of ingesting MSG and was accompanied by symptoms of the CRS. Asthma was delayed in the remaining six patients many hours, up to as long as 12 hours after ingestion of MSG. Associated symptoms in this group were variable and included nausea and abdominal pain. Two patients (29 and 31), with histories of asthma after CRMs, did not react to MSG.

The challenge study for patient 1 is illustrated in Fig. 1. After her second attack of CRM-provoked asthma, she agreed to undergo challenge with MSG but insisted that only one dose be administered. A dose of 2.5 gm of MSG was administered. The patient was challenged in the evening around the time she had had her CRM. She was essentially free of asthma during the whole night of her challenge. The following morning she was well until around 10 A.M. when severe acute asthma suddenly developed, and within one half hour she required intubation and ventilatory support for a period of 5 hours. With strict dietary management, this patient's asthma is now well con-

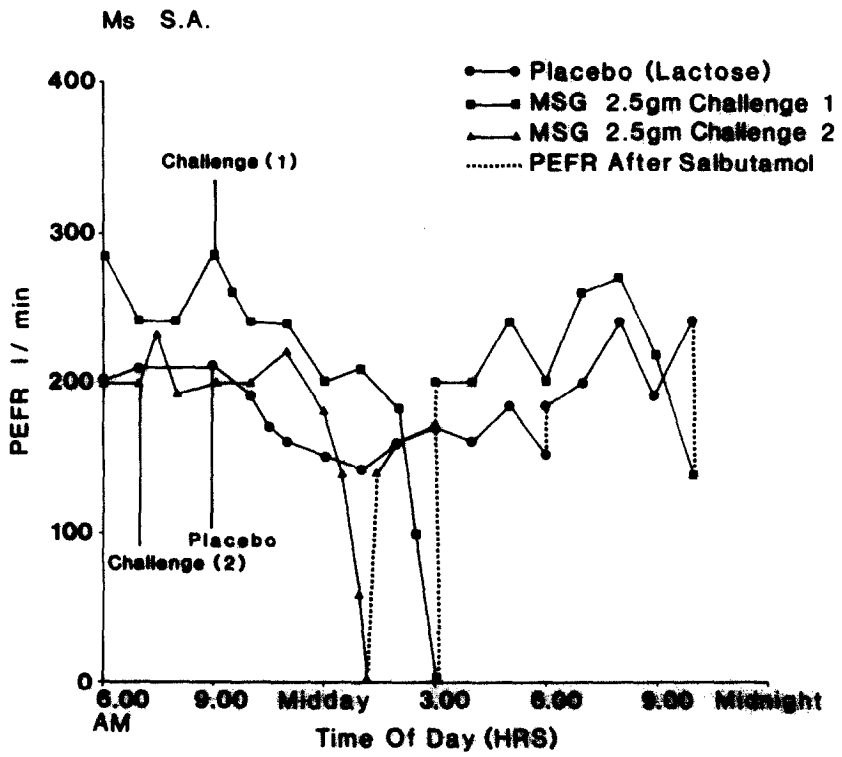

FIG. 5. Illustrated challenges of patient 23 with the same dose of MSG on 2 separate days compared to placebo. Note reproducibility of delay in onset of asthma despite administration of MSG dose at different times in day. "Zero" peak flow indicates flow rate of <60 L/min.

trolled. She has stopped oral corticosteroids, rarely requires admission to hospital, and has not been ventilated in the past 2 years. In the 2 years before the identification of her five ingested chemical sensitivities, she was intubated and ventilated on many occasions.

Figs. 2, 3, and 4 are challenges of patient 3 with 0.5, 1.5, and 2.5 gm of MSG, respectively. A clear dose-response effect can be observed.

Fig. 5 illustrates the reproducibility of the delay after challenge with MSG that we have observed in all our patients. This patient was challenged 1 day with 2.5 gm of MSG. Asthma developed approximately 6 hours after the challenge. On a separate day she was challenged 2 hours earlier with the same dose of MSG. Again, a similar asthmatic reaction developed 6 hours later.

DISCUSSION

The challenge studies reported in this article established that MSG can provoke asthma, which may be severe and life threatening. The reaction is dose dependent and can be delayed up to 12 hours, making recognition difficult for both patient and physician. In addition, our results suggest that MSG is an important cause of asthma after CRMs because nine of 14 patients who reported asthma after such a meal reacted to challenge with MSG. Although 13 of our 32 patients reacted to challenge with MSG, this should not be regarded as the prevalence of MSG-induced asthma in the community at large because our patients were highly selected, many with histories suggestive of MSG-induced asthma. The true prevalence will need to be determined by challenge studies performed in unselected groups of subjects with asthma.

A number of factors were considered when the protocol was designed for MSG challenges, including the form in which MSG was to be administered and the dose and the timing of each dose. MSG was administered in capsule form in order to blind patients to its very characteristic salty, savory taste. Previous challenge studies performed for suspected CRS have demonstrated a 1.5 to 3 gm threshold dose.[4] A similar threshold for MSG-induced asthma was demonstrated in the present study. Thus, a dosage schedule commencing well below the threshold of 0.5 gm, with subsequent doses of 1.5 gm and 2.5 gm to a maximum of 5 gm was used. Six of the 13 MSG-sensitive patients experienced reactions delayed 6 to 14 hours after ingestion of MSG. Thus, a single daily-dose challenge of MSG is recommended.

MSG differs from other ingested chemical provok-

ers of asthma, such as aspirin and metabisulfite, in a number of important ways. It is a naturally occurring substance, ingested by all of us in free and bound form every day. In addition, there is a circulating blood glutamate level that has important physiologic functions in the body. In addition to being one of the building blocks of protein and involved in general metabolic functions, it is a neurotransmitter in the central nervous system. It has recently been demonstrated to be a central nervous system transmitter of baroreceptor afferents[9] and is neuroexcitory in the peripheral nervous system.[10] It is the latter quality that probably accounts for its flavor-enhancing properties.[10] The development of asthma in close association with the onset of symptoms of the CRS suggests a peripheral neuroexcitatory effect, such as the stimulation of irritant receptors in the lung, leading to reflex bronchoconstriction. The delayed asthmatic reaction observed in several patients was not associated with other neuroexcitory symptoms. In view of the central effects of MSG, a possible explanation for delayed asthmatic reactions would be a central augmentation of reflex activity to the lung. Further studies will be required to elucidate the mechanism of MSG-induced asthma.

It is quite possible in a typical meal to consume a total of 10 gm of glutamate, including approximately 1 gm of free glutamate. If MSG is used in such a meal as a flavor enhancer, the intake of free glutamate is increased by 4 to 6 gm. Patients sensitive to MSG need to know the amount of free glutamate present in meals, particularly highly seasoned restaurant meals. This is the sum of naturally occurring free glutamate and added MSG. Foods high in free glutamate are savory foods such as cheeses, tomatoes, and mushrooms. It is meals containing 5 to 10 gm of free glutamate that are likely to provoke severe asthma. It therefore follows that if MSG is not artificially added to a particular meal, the small amount of naturally occurring glutamate will be unlikely to provoke asthma. It is difficult, if it is not impossible, for patients at the present time to obtain information on the amount of glutamate contained in a particular food because of its unrestricted addition in large amounts to both manufactured and restaurant foods. If our findings are confirmed by other groups, then there will be an urgent need for the Food and Drug administration to review listings of MSG as "generally regarded as safe." This study suggests that MSG is not safe for some individuals with asthma.

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