

Glutamate Safety in the Food Supply

Review of Alleged Reaction to Monosodium Glutamate and Outcome of a Multicenter Double-Blind Placebo-Controlled Study^{1,2}

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ABSTRACT Monosodium glutamate (MSG) has a long history of use in foods as a flavor enhancer. In the United States, the Food and Drug Administration has classified MSG as generally recognized as safe (GRAS). Nevertheless, there is an ongoing debate concerning whether MSG causes any of the alleged reactions. A complex of symptoms after ingestion of a Chinese meal was first described in 1968. MSG was suggested to trigger these symptoms, which were referred to collectively as Chinese Restaurant Syndrome. Numerous reports, most of them anecdotal, were published after the original observation. Since then, clinical studies have been performed by many groups, with varying degrees of rigor in experimental design ranging from uncontrolled open challenges to double-blind, placebo controlled (DBPC) studies. Challenges in subjects who reported adverse reactions to MSG have included relatively few subjects and have failed to show significant reactions to MSG. Results of surveys and of clinical challenges with MSG in the general population reveal no evidence of untoward effects. We recently conducted a multicenter DBPC challenge study in 130 subjects (the largest to date) to analyze the response of subjects who report symptoms from ingesting MSG. 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, the frequency of the responses was low and the responses reported were inconsistent and were not reproducible. The responses were not observed when MSG was given with food. *J. Nutr.* 130: 1058S–1062S, 2000.

KEY WORDS: • *monosodium glutamate* • *Chinese Restaurant Syndrome*
• *double-blind, placebo-controlled*

Postprandial discomfort is experienced by many people after eating certain types of foods. There are many reports of adverse reactions to particular food ingredients; the quality of these reports range from anecdotes ascribing symptoms of postprandial discomfort to the ingestion of a particular food ingredient, to clinical studies using double-blind, placebo-controlled (DBPC)⁴ challenges with the food ingredient in question.

Monosodium glutamate (MSG) is used worldwide as a flavor enhancer. L-Glutamic acid is the amino acid component of MSG, and has a long history of use in foods as a flavor enhancer. It is added either as the purified monosodium salt or as a component of a mix of amino acids and small peptides resulting from the acid or enzymatic hydrolysis of proteins. This amino acid is a major constituent of food proteins (in some foods comprising 20% of the total amino acid content), a pivotal metabolic intermediate in amino acid metabolism and a major energy source for cardiac myocytes. Regardless of dietary source (protein, protein hydrolysates or salts of free glutamic acid, including the monosodium salt MSG), all glutamate molecules entering the circulation from the gastrointestinal tract are structurally identical.

The average daily intake of MSG is estimated to be 0.3–1.0 g in industrialized countries, but can be higher occasionally, depending on the MSG content of individual food items and an individual's taste preferences. In the United States, the

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⁴ Abbreviations used: CRS, Chinese Restaurant syndrome; DBPC, double-blind, placebo-controlled; FASEB, Federation of American Societies for Experi-

mental Biology; FDA, Food and Drug Administration; GRAS, generally recognized as safe; MSG, monosodium glutamate; TCA, tricarboxylic acid.

Food and Drug Administration (FDA) has classified MSG as generally recognized as safe (GRAS). Nevertheless, MSG has been alleged to cause many ills. The complex of symptoms that follow ingestion of a Chinese meal and consist of numbness at the back of the neck and arms, weakness and palpitations was first described in 1968. MSG was suggested to trigger these symptoms, which were referred to collectively as Chinese Restaurant Syndrome (CRS). 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 alleged to occur after the consumption of MSG. In addition to the MSG symptom complex, ingestion of MSG has been alleged to cause or exacerbate numerous conditions, including asthma, urticaria, atopic dermatitis, ventricular arrhythmia, neuropathy and abdominal discomfort. An ongoing debate exists concerning whether MSG indeed causes any of the alleged reactions and, if so, the prevalence of reactions to MSG. For example, in the case of asthma, MSG was reported in a single-blind challenge to exacerbate symptoms (Allen 1987). This study suffered from severe methodologic flaws in patient selection, use of bronchodilator during the control period but not during the challenge, drug withdrawal from the patients during the challenge period and, in fact, lack of true single blinding. Using the same protocol, Manning and Stevenson (1991) were not able to confirm asthmatic reactions due to MSG in patients who experienced asthma within 12 h after ingesting MSG in restaurants. Schwartzstein et al. (1987) used a double-blind crossover protocol and did not see any decrease in pulmonary function after MSG challenge in 12 patients. Simon (1986) also reported not finding asthmatic reactors to MSG in double-blind challenges; however, one reactor was found in a single-blind challenge.

Epidemiologic surveys of reactions to MSG. An epidemiologic survey of ~5000 MSG users and nonusers in Hawaii found no increased recall of neurologic symptoms among MSG users. The use of MSG was found to have no relationship to blood glucose or cholesterol, and MSG consumption did not contribute to excessive weight gain (Go et al. 1973). A questionnaire study in a medically oriented population indicated that the prevalence of CRS-sensitive people was as high as 25% (Reif-Lehrer 1977). This study was criticized for many methodological problems such as demand bias in questionnaire design and population bias in survey technique. In a 1977 questionnaire survey, Kerr et al. (1977) showed that, in a medical school community, no one reported experiencing the triad of symptoms for CRS and that 3–7% of subjects could be classified as having experienced “possible CRS.” This figure was increased to 31% when demand-biased questions were introduced. To determine the incidence of CRS symptoms in the general population, Kerr conducted a survey utilizing the National Consumer Panel of the Market Research Corporation of America. Of 3222 respondents, 43% recalled experiencing one or more unpleasant symptoms associated with the consumption of food sometime in their past. The symptoms were relatively nonspecific in nature, and there were no responses that could be categorized as “definite CRS” or “probable CRS.” Only 1.8% of responses could be considered to represent “possible CRS,” and these symptoms associated with Chinese food were linked to only 0.19% of the respondents according to the authors (Kerr et al. 1979). A questionnaire survey in Thailand also showed “no correlation between susceptibility to CRS and MSG intake” (Pothisiri 1983).

Clinical studies with MSG ingested with food. Studies in which MSG was administered with food have shown an absence of CRS symptoms. Oral administration of up to 147 g/d

of MSG to adult humans as the sole source of nonessential nitrogen for 2–6 wk appeared to cause no clinical pathologic changes, and no CRS symptoms were manifest (Bazzano et al. 1970). The only biochemically demonstrable effect was a reduction in serum cholesterol and β -lipoprotein levels. Supplements of glutamate as high as 100 g/d showed no toxic manifestations (Bazzano et al. 1970). When 3 g MSG was administered in 150 mL of beef bouillon at lunch time to 73 healthy subjects either in an open label or double-blind design with each subject acting as his or her own control, no differences in symptomatology were found between the control and MSG-treated groups (Morselli and Garattini 1970, Zanda et al. 1973). In a study to examine the absorption of glutamic acid from solutions of MSG or a casein hydrolysate, 60 mg MSG/kg casein hydrolysate or a mixture of the two were administered to 12 healthy adults; no general ill effects were observed (Marrs et al. 1978). In other studies, 60–150 mg MSG/kg body weight was given to 14 adults and 13 infants with a typical Chinese rice porridge meal. No adverse reactions were observed (Tung and Tung 1980).

Clinical studies with MSG ingested without food. The first clinical study on CRS was performed by Schaumburg et al. (1969). In that study, it was found that intravenous or oral administration of MSG could cause dose-dependent symptoms in nearly all six individuals tested. The symptoms of burning facial pressure and chest pain were reported, and headache was reported to occur in a small number of the individuals. The challenges were open, or when blinded, did not take into consideration the taste of MSG.

In single- and double-blind studies, a total of 169 doses of up to 12 g were given in 99 subjects. Only subjective symptoms of lightheadedness and tightness in the face appeared significantly more often in the MSG group than in control. No subjects reported the triad of symptoms of CRS, and objective measurements of blood pressure, pulse and serum chemistries were not significantly different between the two groups. The samples were osmotically matched, but the tastes were not disguised (Rosenblum et al. 1971).

In a placebo-controlled study in 77 subjects, it was found that symptoms were felt after MSG ingestion but that the classic CRS combination was rare. There was no correlation between the appearance of symptoms and blood glutamate concentrations (Kenney and Tidball 1972). In a nonblind study, 15 subjects were given 100 mg MSG/kg and six subjects reported subjective symptoms. The occurrence of the symptoms was not related to plasma glutamate levels (Hsu and Huang 1985).

In a study to test the effect of aspartame on CRS sufferers, six individuals were found who reported one or more CRS symptoms after drinking tomato juice containing 150 mg MSG/kg but not after drinking tomato juice with 10 mg NaCl/kg. The solutions were administered in a double-blind manner, but the tastes of the substances were not disguised (Stegink et al. 1981).

In a double-blind study with 55 subjects, a significant number reacted more frequently to MSG than placebo, but none complained of any of the classic CRS symptoms. It was noted that there were significant differences in taste and aftertaste of the MSG samples compared with placebo (Gore and Salmon 1980). To test whether CRS symptoms were caused specifically by MSG, symptoms experienced after the ingestion of various common food items were examined. Of 60 subjects tested, it was found that all materials provoked symptoms and that symptoms of burning, tightness or pain in the chest, neck, face or arms, or numbness were reported in response to coffee in six subjects and spiced tomato juice in six subjects, and in

two subjects after the ingestion of a 2% MSG solution. MSG was found not to be unique in producing discomfort after eating (Kenney 1980).

The Chinese Restaurant Syndrome (CRS) or MSG symptom complex

In 1968, a letter appeared in the *New England Journal of Medicine* describing a syndrome which began 15 to 30 min after eating in certain Chinese restaurants, and lasted about 2 h with no residual effects. The symptoms described were the triad of "numbness at the back of the neck, gradually radiating to both arms and the back, general weakness and palpitations." The author noted that these symptoms were similar to those of hypersensitivity to acetylsalicylic acid from which the author also suffered. Numerous possible causes were suggested, among which were alcohol, salt and MSG used in cooking (Kwok 1968).

The syndrome was called "Chinese Restaurant Syndrome (CRS)" and numerous reports, most of them anecdotal, were published after the original observation. Some reported symptoms similar to the original report, whereas others reported symptoms differing from those originally reported. The range of symptoms described in these reports included numbness, headache, migraine, palpitations, tightness, weakness, aching, flushing, sweating, fasciculation, lacrimation, syncope, dizziness, shudder attacks, paresthesias, arrhythmias and tachycardia. Further uncontrolled study indicated that a triad of symptoms, differing from those originally described, of "burning, facial pressure and chest pain" could be induced in individuals given high doses of MSG and that there was a dose response (Schaumburg et al. 1969).

Since then, clinical studies on these acute, temporary and "self-limited" adverse reactions have been performed by numerous groups, with varying degrees of rigor in experimental design ranging from uncontrolled open challenges to DBPC studies. DBPC challenge of individuals believing to be MSG sensitive did not confirm their sensitivity, and studies indicate that the symptoms observed in some experiments are not specific to MSG ingestion and can also be elicited by other foods. Studies in which MSG was administered in food rather than in pure form have generally shown a lack of symptoms altogether. Thus, a causal relationship between MSG and acute, temporary and "self-limiting" adverse reactions is far from established.

Proposed mechanisms to explain MSG symptom complex. Numerous mechanisms have been proposed for CRS but none has been proven. Restriction of circulation by the application of an axillary cuff confined burning sensation to the arm after MSG injection; thus the stimulation of peripheral receptors was proposed as the mechanism for CRS (Schaumburg et al. 1969).

The symptoms of CRS were noted to be similar to those observed after acetylcholine administration. Glutamate can be converted to acetylcholine via the tricarboxylic acid (TCA) cycle, and experiments indicated that drugs affecting the cholinergic mechanisms could modulate CRS symptoms; thus it was proposed that CRS was a form of acetylcholinosis (Ghadimi et al. 1971). However, it should be noted that this should be true for any TCA cycle intermediate.

The symptoms and regions of the body affected by CRS were noted to be similar to those of pain referred from the upper esophagus. Studies indicate that individuals purportedly reacting to MSG may react to concentration rather than dose; furthermore, the same dose of MSG taken in capsules is associated with fewer reactions. Because MSG was found not

to be unique in producing CRS symptoms, it was proposed that CRS may be a manifestation of esophageal irritation (Kenney 1986).

Plasma sodium levels were found to be increased after a Chinese meal, and the high sodium content of Chinese restaurant meals was suggested to be the cause of CRS (Smith et al. 1982).

Folkers and colleagues suggested that subjects experiencing CRS symptoms did not do so after vitamin B-6 supplementation and proposed that CRS was a manifestation of vitamin B-6 deficiency (Folkers et al. 1984).

The symptoms of CRS were suggested to be similar to those of histamine intoxication. When the histamine content of ingredients used in Chinese cooking was measured, it was found that some Chinese meals could contain levels of histamine close to the toxic threshold established by the FDA for histamine in foods, leading the authors to propose that CRS may be caused by histamine (Chin et al. 1989).

MSG challenge studies in subjects claiming to be MSG sensitive. A drink vehicle with a novel taste that could effectively mask the taste of MSG was used to challenge individuals who believed themselves to be MSG sensitive. Of >30 such individuals with whom contacts were made, only six agreed to be tested. When these individuals were challenged with 6 g of MSG in a double-blind, placebo-controlled manner, it was found that four of the six did not react to either substance, whereas two reacted to both MSG and placebo. Of the subjects who reacted, one reported tingling of hands and warmth behind the ears after both MSG and placebo; the other subject experienced tightness of the face after ingesting either substance. The remaining four individuals who had ascribed their previous symptoms such as headache, nausea, tongue swelling and uncontrollable coughing to MSG ingestion, did not react to either substance (Kenney 1986).

In a study designed to monitor flushing, which study participants felt was caused by MSG ingestion, 24 subjects, including 18 who had a history of subjective flushing symptoms after eating Chinese food were challenged with 3–18.5 g MSG. No one reported flushing sensations. Six subjects, three with a history of flushing, were challenged with 35.7–285.7 mg MSG/kg body weight or 7.1–71.4 mg pyroglutamate/kg body weight. None reported flushing sensations and no significant changes in cutaneous blood flow occurred (Wilkin 1986).

Yang et al. (1997) recently conducted a DBPC study of 61 self-identified MSG-sensitive subjects. The subjects were challenged with 5 g MSG or placebo, and a positive reaction was defined as the occurrence of two or more symptoms among 10 symptoms described to occur after MSG ingestion. The rates of reaction to placebo and MSG were not significantly different. Upon rechallenge with placebo and increasing doses of MSG (1.25, 2.5 or 5 g), the frequency and severity of the responses increased with increasing doses, reaching significance for headache, muscle tightness, flushing, general weakness and numbness/tingling.

We recently conducted a multicenter DBPC multiple challenge study with a crossover design to evaluate reactions allegedly due to the consumption of MSG in 130 self-identified subjects who believed they had had reactions to MSG (Geha et al. 1998). In three of four protocols (A-D), MSG was administered without food. A "positive response" was defined as the presence of at least two of 10 symptoms reported to occur after ingestion of MSG-containing foods. In Protocols C and D, a "reproducible response" was defined as the same two or more symptoms among those listed in the enrollment inclusion criteria that were reproducible in separate challenges, with no symptoms produced by placebo.

All subjects who satisfied the inclusion/exclusion criteria were enrolled in Protocol A. Subjects were randomized to receive placebo on d 1 and 5 g MSG (in a citrus-flavored beverage) on d 2 (Arm 1) or 5 g MSG on d 1 and placebo on d 2 (Arm 2). Prior testing on normal volunteers established that the citrus flavor effectively masked the taste of MSG. Subjects who responded with two or more symptoms to at least one test article in Protocol A were eligible to be enrolled in Protocol B. Protocol B was initiated immediately after completion of Protocol A and consisted of four challenges, each on a separate day. Each subject was administered randomly four test articles consisting of placebo, 1.25 g, 2.5 g or 5 g of MSG in 200 mL citrus-flavored beverage. Subjects who responded with two or more symptoms to 5 g MSG but not to placebo in both Protocols A and B were eligible to be enrolled in Protocol C. Subjects were randomly assigned to receive 5 g MSG or placebo first in each of two sets of challenges administered on two separate days. Subjects who responded to 5 g MSG but not to placebo in both sets of challenges in Protocol C were eligible to be enrolled in Protocol D. Protocol D consisted of six challenges each performed on a separate day. Each subject randomly received three times capsules containing 5 g MSG and three times capsules containing placebo (5 g sucrose) during a cereal breakfast consisting of Frosted Flakes.

In Protocol A, 50 (38.5%) of 130 subjects reported two or more symptoms ("positive response") during the MSG challenge and had no symptoms or one symptom after placebo. Nineteen subjects (14.6%) reported two or more symptoms to both MSG and placebo, whereas 17 subjects (13.1%) reported two or more symptoms to placebo and no symptoms or one symptom after MSG. Forty-four subjects (33.8%) reported no symptoms or one symptom to both MSG and placebo. Administration of 5 g MSG was associated with a significantly higher frequency of response, i.e., of occurrence of two or more symptoms and with significantly higher frequency of occurrence of four of the 10 symptoms.

Eighty-six subjects who responded to at least one of the two challenges in Protocol A were eligible for Protocol B. Of these 86 subjects, 17 either chose not to participate or did not complete Protocol B; 69 subjects 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 MSG. An increased frequency of response was observed only for numbness/tingling with 2.5 g MSG and for six of 10 symptoms (general weakness, muscle tightness, flushing, sweating, headache/migraine, numbness/tingling) with 5 g MSG. Nineteen subjects responded to 5 g MSG but not to placebo in both protocols A and B.

Twelve of the 19 eligible subjects participated in Protocol C and underwent two challenges (C1 and C2), each with 5 g MSG vs. placebo. Only two of the 12 subjects responded to MSG and not to placebo in both challenges. However, in none of these subjects did the symptoms in Protocols C1 and C2 reproduce those observed in Protocols A and B.

Subjects who report reactions allegedly caused by MSG ingest MSG in food. It was therefore important to ask whether the two subjects who had responded to 5 g MSG but not to placebo in protocols A through C would react to the same dose of MSG administered with food. Both subjects who responded to MSG in protocol C enrolled in protocol D, which consisted of six challenges, three with 5 g MSG and three with placebo, in which the test articles were administered in the middle of a standard breakfast and the subjects were asked to report their symptoms. Each subject responded to only one of the three MSG challenges with two or more symptoms. In both subjects,

the symptoms reported differed from those reported in the previous three protocols.

The data from the study 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 were observed and the frequency of the responses was low. More importantly, the responses reported were inconsistent and were not reproducible. The responses were not observed when MSG was given with food (Geha et al. 1998).

FDA position on MSG

In 1958 the Food Additive Amendments to the Federal Food, Drug and Cosmetic Act designated L-glutamic acid and hydrolyzed protein products containing L-glutamic acid (including monosodium glutamate and hydrolyzed vegetable proteins) as GRAS. This status was reaffirmed when the FDA's Hypersensitivity Committee in 1986 and the FDA Health Hazards Evaluation Board in 1990 concluded that dietary intake of glutamates does not present a hazard to human health and requires no additional regulatory action. In addition, a report of the FDA Clinical Nutrition Assessment Section prepared in 1989 "... could find no evidence that MSG is a health hazard to large segments of the general population. Although there is some evidence that dose-dependent, mild reactions occur in a small portion of the population, continued label declaration of MSG and surveillance of adverse reactions should be sufficient to protect public health." On June 21, 1991, the FDA published a proposal to not require listing monosodium glutamate on a product label when protein hydrolysates are added to a food product. In presenting this proposal, the FDA again affirmed the lack "of any scientific evidence that establishes that monosodium glutamate causes particularly severe adverse reactions, or that reactions to low doses of monosodium glutamate occur and are life-threatening." The August 1995 FASEB report on MSG reaffirms again the GRAS status of MSG and recommends that in order to confirm the MSG symptom complex, three DBPC challenges on separate occasions must reproduce symptoms with the ingestion of MSG and produce no response with placebo. In addition, the FASEB report recommends the 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.

SUMMARY

The weight of the evidence supports the designation of MSG as a generally safe food flavoring agent. Neither epidemiologic surveys nor challenge studies provide evidence that ingestion of MSG is associated with adverse reactions in the population at large. In subjects who report adverse reactions to MSG, rigorous DBPC challenge studies indicate 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 were observed, and the frequency of the responses was low. More importantly, the responses reported were inconsistent and were not reproducible. The responses were not observed when MSG was given with food.

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