

Monosodium Glutamate

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KEY CONCEPTS

- Glutamate is recognized by distinct taste receptors on the tongue as “umami” (savory) along with sweet, sour, salty, and bitter.
- Monosodium glutamate (MSG) is rapidly and efficiently metabolized by the intestinal mucosa and liver in both adults and infants. Despite high maternal intake of MSG, levels remain low in fetal circulation. Therefore, no limitation for MSG ingestion in pregnant women and infants is recommended.
- MSG has been anecdotally associated with a diverse array of conditions including migraine headache, which have not been validated in carefully controlled challenge studies. Low-MSG diets should not be empirically recommended for migraine sufferers, as there is no science to back up such a recommendation.
- MSG symptom complex (formally the Chinese restaurant syndrome) may occur with high-dose MSG (≥ 3 g) in the absence of food in some people and is a self-limited condition.
- MSG is generally recognized as safe by the Food and Drug Administration. Numerous studies have failed to show that MSG causes any serious acute or chronic medical problems in the general population.

A 1968 letter to the editors of the *New England Journal of Medicine* by Dr. Robert Kwok describing what he termed the Chinese restaurant syndrome (CRS) with “numbness at the back of the neck ... radiating to both arms and the back, general weakness and palpitation” which he experienced only when dining in Chinese restaurants, initiated the public controversy surrounding monosodium glutamate (MSG) which continues to this day [1]. Although Dr. Kwok hypothesized that his symptom complex was due to the alcohol in Chinese cooking wine, sodium content, or the flavoring ingredient MSG, attention became focused on MSG. Since the 1960s, the role of MSG has been questioned in not only what has become known as the MSG symptom complex, but also a number of other potential adverse reactions. In addition to the MSG symptom complex, MSG ingestion has been anecdotally associated with asthma, urticaria, and angioedema, headache, shudder attacks in children, psychiatric disorders, and convulsions. In the three decades since the publication of Dr. Kwok’s letter, extensive research has failed to demonstrate a clear and consistent relationship between MSG ingestion and the development

of these or any adverse reactions in humans. Despite this, strong suspicion regarding MSG persists in the public arena.

The fifth taste: L-glutamate

Humans can detect four primary tastes: sweet, salty, bitter, and sour. There is also a fifth taste called umami. Umami describes the palatability or deliciousness of a food, and has been called a “brothy mouth-watering sensation” [2]. Glutamic acid is a non-essential amino acid that constitutes approximately 20% of dietary proteins. When added to foods in the form of a sodium, potassium, or calcium salt, glutamate enhances the palatability of foods. Ikeda first documented the unique taste- and flavor-enhancing qualities of MSG in 1908 after isolating it from the seaweed *Laminaria japonica*, which has been used for centuries in Japanese cooking as a flavor enhancer [3]. Its characteristic taste, umami, is imparted through its stereochemical structure, monosodium L-glutamate; the D-isomer has no characteristic taste. MSG became widely available in the United States during the 1940s.

MSG is commercially synthesized by taking protein, usually derived from wheat or soy, through an acid wash to isolate amino acids. A neutralizing agent, sodium hydroxide, is then added to form the sodium salt of each amino acid.

Table 30.1 Food labeling of MSG

Free glutamate	Bound glutamate
MSG	HVP
Monopotassium glutamate	HPP
Monoammonium glutamate	HSP
Glutamic acid	Natural flavorings
Glutamic acid hydrochloride	Flavor(s) or flavoring
Glutamate	Seasoning
	Kombu extract
	Autolyzed yeast extract

Typically, MSG constitutes 10–30% of the mixture. When other amino acids are present it is referred to as hydrolyzed vegetable protein (HVP). MSG is also produced by fermentation of beetroot pulp or sugarcane. It is then purified to 98% purity. Table 30.1 lists the Food and Drug Administration (FDA) approved names of MSG. Since 1986, the FDA has permitted glutamate to be indirectly identified on food labels as HVP (hydrolyzed vegetable protein), HPP (hydrolyzed plant protein), or HSP (hydrolyzed soy protein) [4]. The glutamate salts are used widely in the food manufacturing and restaurant industries and flavor a wide spectrum of foods including crackers, potato chips, canned and dry soups, canned seafood, meats, frozen dinners, salad dressings, Chinese, and other Asian foods. When MSG is added to food, the FDA requires “MSG” to be listed on the label. Other salts of glutamic acid – such as monopotassium glutamate and monoammonium glutamate – also have to be declared on labels and cannot be lumped together under “spices,” “natural flavoring,” or other general terms. The salts quickly dissociate in aqueous solution releasing free glutamate.

Normal dietary intake of MSG in the United States is approximately 1 g/day in its free form. An additional 0.55 g/day comes from added MSG. Some foods contain naturally occurring high levels of free glutamate such as tomatoes (0.34% MSG), Parmesan cheese (1.5% MSG), and soy sauce (1.3% MSG) [5]. In the body, the turnover rate for MSG is 5–10 g/hour [5]. Glutamate is metabolized in a number of ways, including oxidative deamination, transamination, decarboxylation, and amidation. MSG is readily transaminated to α -ketoglutarate, which is converted to energy by the Krebs cycle [6]. Studies on humans indicate that MSG ingested with meals results only in a very small increase in plasma glutamate concentration when compared with the levels achieved when it is consumed while dissolved in water or consommé [7]. The presence of carbohydrates appears to greatly reduce the levels of free glutamate in plasma after meals, even those containing very high levels of MSG. Even when MSG is administered in large quantities (>30 mg/kg body weight) without food, serum levels are

only slightly elevated due to the very efficient metabolism of glutamate in the intestines and liver [8]. Elevated plasma levels due to doses exceeding 5 g of MSG return to basal levels in less than 2 hours [8].

Fetal and neonatal exposure to glutamate is likely to be small. Though glutamate can cross the placenta, fetal plasma concentrations do not increase significantly even with maternal ingestion of 100 mg/kg of MSG [9]. Studies by Stegink *et al.* in pregnant rhesus monkeys showed that it was not until the maternal plasma level of MSG exceeded 2000 μ mol/l that there was a slight increase in fetal MSG levels [10]. This data suggests that transfer of glutamate from the mother to the fetus is unlikely even with very high maternal oral intake. Infants, including premature babies, can metabolize greater than 100-mg MSG/kg body weight administered in infant formulas [11]. Free glutamate is found in breast milk in conjunction with other free amino acids and is among the most prevalent amino acids along with glutamine and taurine [12]. The free glutamate in breast milk is speculated to have a protective role in assuring intestinal growth and supplying functional substrates to the nervous tissue [13].

Monosodium glutamate and neurotoxicity

By the late 1960s, concerns were raised regarding the possible neurotoxicity of MSG. Olney reported MSG-induced toxicity in the nervous system of rodents when glutamate was given in large amounts by non-dietary routes to neonatal mice [14]. The resulting focal necrosis of the arcuate nucleus of the hypothalamus led to functional alteration of the reproductive capability and body weight regulation in mice. The proposed mechanism for neuronal damage is passage across the blood–brain barrier by glutamate whereby glutamate, as an excitatory transmitter, leads to continuous excitation of the glutaminergic receptors, depleting ATP and leading to cell death. This appears to be a phenomenon to which neonatal mice are particularly susceptible. There have been at least 21 studies looking for effects of MSG-induced neurotoxicity in primates and only two were positive and came from the same laboratory [15,16]. The threshold blood levels associated with neuronal damage in the mouse are 100–130 μ mol/dl in neonates rising to 380 μ mol/dl in weanlings and greater than 630 μ mol/dl in adult mice [17]. In humans, such levels have not been recorded even after very high bolus doses of MSG. It has been noted by the Joint Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO) Expert Committee on Food Additives (JECFA) that the oral ED₅₀ for production of hypothalamic lesions in the neonatal mouse is ~500-mg MSG/kg body weight by gavage. In humans, the largest palatable dose of MSG is ~60 mg/kg body weight with higher doses causing nausea, making voluntary ingestion of higher doses very unlikely [17].

Neuroendocrine effects of high-dose glutamate administration have been demonstrated in rodents including a reduction in hypothalamic growth hormone releasing hormone (GHRH) release and pituitary growth hormone (GH) secretion as well as an increase in serum leutenizing hormone (LH) levels [5,18,19]. Such effects have not been shown in humans and the implications of these findings remain unknown. Acute toxicity of glutamate has been determined with a LD₅₀ value of 16–20 g/kg body weight [20]. There is no evidence to date of MSG-associated carcinogenicity or teratogenicity [21–26].

MSG is classified by the FDA as generally recognized as safe (GRAS). The amount of MSG that can be added to foods is limited only by its palatability. The Joint FAO/WHO JECFA has evaluated MSG and has determined that no numerical limitation is necessary for its use in food [27]. In addition, there was no evidence to support recommendations limiting intake of MSG in pregnant women or infants. However, they did contend that food additives, in general, should not be added to infant foods to be consumed before 12 weeks of age [27]. Around the time of the discovery of MSG-induced neurotoxicity in mice, large amounts of MSG were routinely added to infant formulas in the United States. After these data became available, however, manufacturers of infant formula voluntarily removed MSG from their products.

MSG symptom complex

The controversy surrounding MSG as a food additive first came to light after Dr. Kwok published a letter to the editors in the *New England Journal of Medicine* in 1968 detailing a set of symptoms he experienced when eating at Chinese restaurants [1]. He described the experience of numbness at the back of the neck, general weakness, and palpitations. This set of symptoms became known as the CRS. More recently, it has been renamed as the MSG symptom complex. As defined by Settupane, a restaurant syndrome is an adverse reaction to foods occurring within 20 minutes of ingestion, frequently while patients are still dining in restaurants [28]. After Dr. Kwok's letter in 1968, a series of anecdotes implicated MSG as the agent responsible for the CRS. In 1968, Schaumburg reported on his own experiences which included tightening of facial muscles, lacrimation, periorbital fasciculations, numbness of the neck and hands, palpitations, and syncope occurring within 20 minutes of eating Chinese food on separate occasions, with symptoms resolving in 45 minutes. He reported having as many as eight experiences per day without sequelae [29]. Over the ensuing 30 years, numerous human challenge studies have been conducted in an attempt to determine the association of MSG with the clinical entity of the MSG symptoms complex.

In general, challenge studies with MSG pose great difficulty because of the distinct taste properties of MSG that makes adequate blinding hard to achieve. Interpretation of

some reported challenge studies has been hampered by the lack of a food vehicle. As pointed out earlier, the metabolism of MSG is greatly enhanced by the presence of metabolizable carbohydrates, which characterizes most dietary encounters with MSG. Extrapolation of food-free challenges to "in-use" situations may not be valid [30].

In one of the first challenge studies with MSG, Schaumburg *et al.* found an oral dose–response curve to MSG and concluded that all of the subjects they tested would eventually experience the sensory phenomena if they ingested enough MSG [31]. Double-blind studies by Kenney [32] and Kenney and Tidball [33] identified individuals who experienced symptoms specific to MSG on a relatively regular basis but only when the MSG was given in amounts or concentrations far greater than that normally encountered in a regular diet. Double-blind studies from Italy and the United Kingdom found no difference between the sensation experienced after MSG or placebo [34,35].

Geha *et al.* [36,37] undertook an ambitious multi-center double-blind placebo-controlled (DBPC) challenge study with a crossover design to evaluate reactions allegedly due to MSG in 130 self-identified MSG-sensitive subjects. Their efforts included meeting the criteria set forth by the August 1995 Federation of American Societies for Experimental Biology (FASEB) report on MSG which recommended that in order to confirm the MSG symptom complex, three DBPC challenges administered on separate occasions must reproduce the symptoms with ingestion of MSG and produce no response with placebo [38]. In three of their four protocols (A–D), MSG was administered without food. A positive response was defined as the presence of at least two of ten symptoms reported to occur after ingestion of MSG-containing foods. They had 110 subjects who underwent four consecutive 5-g MSG placebo-controlled challenges. Only 2 of the 110 subjects or 1.8%, who had previously self-identified themselves to be MSG reactors, responded to 5 g of MSG in the four challenges. The data from their study suggests that large doses of MSG given without food may elicit more symptoms than 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 responses was very low [36,37]. The responses were not observed when MSG was given with food. Their data again confirms the rarity of the MSG symptom complex even among individuals who believe themselves to be MSG sensitive.

Determining the prevalence of MSG sensitivity in the general population has been difficult. Estimating adverse reactions to a particular food ingredient through questionnaires is potentially fraught with subjectivity and bias. This has complicated the estimation of incidence of the MSG symptom complex in the general population. Reif-Lehrer reported that 25% of a population surveyed by questionnaire felt they had experienced MSG-related symptoms [39]. This survey

included several leading, close-ended questions, which likely evoked many false-positive responses. In a 1977 questionnaire survey, Kerr *et al.* showed that in the Harvard University Medical School community, no one reported experiencing the triad of symptoms in the CRS and that 3–7% of subjects could be classified as having experienced “possible CRS” [40]. In a 1979 study, Kerr *et al.* used a National Consumer Panel to select a representative group to improve the accuracy of extrapolation to the US population at large, and found the prevalence of the MSG symptom complex to be 2% [41]. As the clinical studies have shown, the incidence of MSG symptom complex appears to be quite low.

The pathophysiology of the MSG symptom complex remains elusive. It is clearly not the result of an IgE-mediated process. Many theories have been put forth to explain the condition. Ghadimi *et al.* proposed that the symptoms of the MSG symptom complex are linked to an increase in acetylcholine; this group was able to show an attenuation of symptoms in subjects pretreated with atropine [42]. Gajalakshmi *et al.* lent further support to this theory when they demonstrated MSG’s ability to produce spasmogenic effects on isolated guinea pig ileum; these effects were also blocked with by atropine [43]. Glutamic acid is a precursor to acetylcholine, which may account for these findings. Folkers *et al.* suggested that vitamin B6 deficiency may play a role in the development of the MSG symptom complex [44,45]. While Kenney has suggested that the clinical symptoms result from esophageal dysfunction or reflux esophagitis [33]. More recently, Scher and Scher have proposed that nitric oxide production may be the mediator in the pathogenesis of the MSG symptom complex [46]. Nguyen-Duong in 2001 demonstrated that glutamate-induced vasorelaxation of porcine coronary arteries was potentiated by glycine and proposed that this vasodilatory action might be responsible for the flushing and palpitations associated with the complex [47]. Despite these assorted hypotheses and 30 years of research, the causative mechanism remains unknown.

Asthma

In the early 1980s, several reports suggested that MSG could provoke bronchospasm in asthmatics. In 1981, Allen and Baker reported their experience with two young women who had developed life-threatening asthma after ingestion of MSG in meals from Chinese restaurants [48]. The asthma developed 12–14 hours after ingestion of the MSG-containing meals. Allen and Baker performed single-blind, oral challenge studies on both patients and found that 2.5-g MSG capsules resulted in asthma 11–12 hours after ingestion. Subsequently in 1987, Allen *et al.* performed in-hospital, single-blind, placebo-controlled MSG challenges in 32 asthmatic subjects; 14 were suspected MSG reactors by history and 18 were unstable asthmatics with bronchospasm due to aspirin, benzoic acid, tartrazine,

or sulfites [49]. As described by Stevenson in 2000, several problems were associated with this study: theophylline was discontinued 1 day prior to placebo challenges, some patients received inhaled bronchodilator therapy within 3 hours prior to their first challenge, bronchospasm was measured by effort-dependent peak expiratory flow rates (PEFR) rather than flow-volume loops, and baseline PEFR exhibited large variations consistent with unstable asthma [50]. Although Allen *et al.* concluded that 14 patients developed asthma exacerbations 1–12 hours after ingesting MSG, these limiting factors rendered the results difficult to interpret [49]. What was interpreted by the study authors, as MSG-provoked asthma may merely have been peak flow variability indicative of underlying active asthma.

Five additional studies attempted to clarify the issue of whether MSG induces bronchospasm in asthmatics using double-blind challenges. Schwartzstein *et al.* found no exacerbation of asthma from MSG in 12 asthmatics challenged with 25-mg MSG/kg body weight [51]. This study involved mild asthmatics with no history of MSG or Chinese restaurant meal-induced symptoms. In addition, the doses of MSG were lower than those used by Allen and Baker’s 1987 study. In a second study, Moneret-Vautrin published a report of delayed bronchospasm occurring in 2 of 30 asthmatics challenged with MSG [52]. Evidence of bronchoconstriction was defined by a 15% decline in peak flow rate determinations. If the same criteria for bronchospasticity found in the Allen and Baker paper (20% decline from baseline or the lowest value recorded during placebo single-blind challenge) were applied to Moneret-Vautrin’s subjects, the two patients would not fit the definition of a positive response, as the decline was less than 20%.

A third study by Germano *et al.* reported that 1 of 30 asthmatics, during single-blind screening oral challenges with MSG (up to 6g), experienced a significant reduction in FEV1 values [53]. However, when the one preliminary reactor was re-challenged with the same dose (6-g MSG), under double-blind, placebo-controlled conditions, the response to MSG challenge was negative. This study was criticized for having only 2 of their 30 asthmatics with a positive history of asthma exacerbations after a Chinese restaurant meal. The report also exists in abstract form. A 1998 double-blind, placebo-controlled study by Woods *et al.* [54] challenged 12 asthmatics who reported that MSG caused them to have asthma attacks. They incorporated elaborate controls in their study, including strict dietary avoidance of MSG, home spirometry (PEFR measurements) before and after the challenges, as well as a double-blind, placebo-controlled protocol. The patients were challenged with 1 and 5g of MSG. The study was completely negative, with none of the subjects reacting at either dose. One minor criticism of this paper is the small number of subjects.

Although it had been previously suggested by Allen *et al.* that those asthmatics with bronchoconstriction due to food

additives or aspirin were more likely to experience MSG-related bronchospasm, a study by Woessner *et al.* [55] in 1999 demonstrated this not to be the case. In this study, two groups were tested: 30 asthmatics who believed MSG ingestion exacerbated their asthma, and 70 subjects with proven aspirin exacerbated respiratory disease (AERD), a population identified by Allen and Baker as being at high risk for MSG-provoked bronchospasm [49]. Asthma maintenance medications including inhaled and systemic corticosteroids and theophylline were continued, though inhaled β -agonists were not. Patients were enrolled in an in-patient DBPC challenge if their FEV1 values were at least 70% predicted off on inhaled bronchodilators. The first day consisted of a single-blind placebo day to assess pulmonary baseline. If FEV1 values varied by 10% or less on placebo day, the patients were challenged with 2.5-g MSG after a low-MSG breakfast. Adverse symptoms and FEV1 values were recorded during the following 24 hours. Patients whose FEV1 values decreased by at least 20% next underwent two additional MSG challenges in a blinded, placebo-controlled manner. On initial MSG challenge, only 1 of the 30 patients experienced a decline in FEV1 of 20% although she remained asymptomatic. She did not have any drop in her FEV1 on the two subsequent DBPC MSG challenges. None of the 70 AERD patients had a positive MSG challenge.

There does not appear to be any strong evidence that MSG can provoke bronchospasm in asthmatics. Because of the limited number of studies performed to date, further research is needed before any firm claims can be made that MSG provokes bronchospasm.

Urticaria and angioedema

Very few case reports of MSG-induced angioedema or urticaria have appeared in the literature. A report by Squire [56] in the *Lancet* described a 50-year-old man with recurrent angioedema of the face and extremities that was temporally related to the ingestion of a soup mix high in MSG. A single-blind, placebo-controlled challenge with the soup base resulted in angioedema 24 hours after the ingestion. In a graded challenge using only MSG, angioedema was provoked 16 hours after challenge. Avoidance of MSG-containing foods reportedly caused remission of the angioedema episodes.

Though not extensively evaluated, there have been several studies evaluating the role of MSG in urticaria. Genton *et al.* [57] in 1985 studied 19 subjects with chronic idiopathic urticaria (CIU) for sensitivity to 28 food additives, including MSG. In a single-blind protocol, 4 of the 19 subjects reacted, defined by an increase in urticaria within 18 hours following challenge. In 1986, Supramaniam and Warner [58] evaluated 36 children with asthma or urticaria. There were three reactors in this placebo-controlled study in which one placebo, eight additives, and aspirin were administered at 4-hour increments. Whether the reactions were pulmonary

or dermatologic was not specified. A 1998 study in Spain by Botey *et al.* [59] detailed the work-up of five children with angioedema or urticaria who presented for evaluation of possible drug allergy. Particular attention was paid to the dietary history regarding additives including MSG. Following a 2-day diet without known additives, these patients were administered 50-mg MSG orally in a single-blinded fashion: if there was no reaction in 1 hour, an additional 100 mg was given. Three of the five children had recurrence of urticaria at 1, 2, and 12 hours following ingestion; one developed pruritic erythema of the skin at 1 hour; and the fifth developed abdominal pain and diarrhea following ingestion of 50-mg MSG.

Reports in the literature of possible MSG-induced urticaria or angioedema do not clarify whether MSG was the inciting agent. Evaluation of MSG-induced urticaria or angioedema must be approached in a double-blind, placebo-controlled protocol to obtain a clearer picture of the role of MSG in urticaria and angioedema. Simon [60] addressed these concerns in a 2000 report of food additive challenges in 65 patients with chronic urticaria. The subjects initially underwent single-blinded 2.5-g MSG challenges. A baseline urticaria skin score (reminiscent of a burn score) was obtained. This scoring system is based on the "rule of nines" in which the body is divided into areas of 9%. Each of these body areas is then scored on a scale from 0 to 4 (0 = no urticaria; 1 = urticaria involving up to 25% of that surface area; 2 = up to 50% of that area; 3 = urticaria involving up to 75%; and 4 = diffuse urticaria in that area). A score of 9 or a 30% increase in the score from baseline urticaria was considered a positive challenge. Two subjects had positive single-blind challenges. Neither had a positive DBPC MSG challenge. Therefore, as is the case for MSG provoking the MSG symptom complex and bronchospasm, the role in development of urticaria and angioedema is likely to be quite rare.

Headache

Though many people believe they have adverse reactions to foods and food additives, few people have confirmed sensitivity on objective examination. It is not surprising, therefore, that MSG has been associated with a myriad of physical and psychiatric complaints. Of all the adverse symptoms thought to be attributable to MSG ingestion, headache was the symptom most often reported to the FDA's Adverse Reaction Monitoring System between 1980 and 1995 [61]. In 1969, Schaumburg *et al.* [31] performed one of the first formal studies of the symptoms potentially associated with MSG ingestion. Their study suggested that the three main symptoms consisted of a burning sensation, facial pressure or tightness, and chest pain. Headache occurred in a minority of the subjects. Ratner *et al.* [62] in 1984 described four patients with MSG-related headaches. They were evaluated with double-blind testing consisting

of sublingually administered soy sauce with and without 1.5–2.0 g added MSG. These patients developed recurrent headaches within 15 minutes to 2 hours of sublingual administration of MSG soy sauce but not to “placebo” soy sauce, and reportedly had relief with of symptoms with MSG avoidance. No attempt was made to disguise the taste of the two soy sauce formulations. Furthermore, it could be argued that they truly did not have a negative control due to the high glutamate content naturally occurring in soy sauce. Scopp in 1991 described two chronic headache patients who decreased the frequency of their headaches through MSG avoidance. No objective testing was performed [63]. Yang *et al.* [64] undertook placebo-controlled 5-g MSG challenge in self-identified MSG-sensitive subjects. A positive response was two or more index symptoms. The rates of reaction to MSG or placebo were not statistically different in this group of 61 self-identified MSG-sensitive subjects. If the subjects had a positive challenge they were brought back for blinded placebo-controlled graded MSG challenges. Again, there was a high rate of response to placebo but they did have some patients who developed statistically significant associations of symptoms with MSG such as headache, flushing, muscle tightness, numbness/tingling, and generalized weakness.

Theories regarding the etiology of MSG-induced headache are scarce. Merritt *et al.* in 1990 found that high concentrations of glutamate caused concentration-dependent contractions of excised rabbit aorta [65]. These authors suggested that a similar vascular response might account for MSG-induced headache. However, there is little data that suggests that MSG can cross the intact blood–brain barrier. Despite a widespread belief that MSG can trigger migraine headaches, there is a striking paucity of literature to support this claim. As a result, low-MSG diets should not be empirically recommended for the chronic headache patients since they are not based on clear scientific fact and are only likely to be an unnecessary burden for these patients.

Monosodium glutamate and the Food and Drug Administration

Because of continuing reports of adverse reactions to MSG, the FDA contracted with FASEB in 1992 to perform a scientific safety review of the effects of glutamates in foods. The FASEB report was submitted in 1995. The MSG symptoms complex was defined as an acute, temporary, and self-limiting complex including the following: (1) a burning sensation at the back of neck, forearms, and chest; (2) facial pressure or tightness; (3) chest pain; (4) headache; (5) nausea; (6) upper body tingling and weakness; (7) palpitation; (8) numbness at the back of the neck, arms, and back; (9) bronchospasm (in asthmatics only); and (10) drowsiness. The report concluded that, although there was no scientifically verifiable evidence of adverse effects in most individuals exposed to high levels

of MSG, there is sufficient documentation to indicate that there is a subgroup of presumably healthy individuals that responds, generally within 1 hour of exposure with manifestations of the MSG symptom complex when exposed to an oral dose of MSG of 3 g in the absence of food [66]. This report pointed out that the key data relate to single-dose challenges in capsules or solutions and are limited in their ability to predict adverse reactions resulting from the use of MSG in food. It is well known that carbohydrates greatly modulate the uptake of MSG making extrapolation to real-world experience very difficult. The Hattan memorandum also indicates that the FDA did not consider the evidence regarding the sensitivity of asthmatics to MSG to be compelling and questioned its inclusion in the MSG symptom complex [66].

The FASEB report concludes that there is no evidence to support a role for dietary MSG or other forms of free glutamate in causing or exacerbating serious, long-term medical problems resulting from degenerative nerve cell damage [67]. It was accepted that neurotoxicologic effects of MSG are limited to animals given very large doses by parenteral, pharmacologic, or other non-dietary conditions.

Conclusion

Overall, the available data on MSG reflect that it is safe for use as a food additive in the population at large. MSG toxicologic data has not demonstrated serious nervous system effects in humans. Furthermore, metabolic studies performed in infants and adults have shown ready and rapid utilization of excess glutamate with failure of serum glutamate levels to rise even when very large amounts of MSG were ingested with carbohydrate. The carefully done DBPC studies indicate that MSG ingestion is likely to be without adverse effect even in people suspecting themselves to be MSG reactors [36,37,55]. MSG has not been clearly documented to cause bronchospasm, urticaria or angioedema, or migraine headache. It is possible that large doses in excess of 3 g of MSG ingested on an empty stomach without concomitant food administration may elicit the MSG symptom complex. This syndrome is likely to be infrequent and transient, resolving without treatment. In conclusion, there is no clear evidence in the current scientific literature documenting MSG as cause of any serious acute or chronic medical problem in the general population.

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