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REVIEW

Monosodium glutamate 'allergy': menace or myth?

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Summary
Monosodium glutamate (MSG) is a salt form of a non-essential amino acid commonly used as a food additive for its unique flavour enhancing qualities. Since the first description of the 'Monosodium glutamate symptom complex', originally described in 1968 as the 'Chinese restaurant syndrome', a number of anecdotal reports and small clinical studies of variable quality have attributed a variety of symptoms to the dietary ingestion of MSG. Descriptions of MSG-induced asthma, urticaria, angio-oedema, and rhinitis have prompted some to suggest that MSG should be an aetiologic consideration in patients presenting with these conditions. This review prevents a critical review of the available literature related to the possible role of MSG in the so-called 'Chinese restaurant syndrome' and in eliciting asthmatic bronchospasm, urticaria, angio-oedema, and rhinitis. Despite concerns raised by early reports, decades of research have failed to demonstrate a clear and consistent relationship between MSG ingestion and the development of these conditions.

Introduction

Monosodium glutamate (MSG) is one of a number of salt forms of glutamic acid, a non-essential amino acid, with unique flavour-enhancing qualities, that is widely used as a food additive. Since 1959, the United States Food and Drug Administration has classified MSG as 'generally recognized as safe' [1]. Over the past 40 years, anecdotal reports and small uncontrolled studies alleging a variety of MSG-induced reactions have been published. These reports have raised concerns regarding the safety of dietary consumption of MSG. While numerous studies have failed to demonstrate that dietary consumption of MSG causes any significant allergic or non-allergic medical problems in the general population, allergists continue to be called upon to evaluate patients suspecting 'allergic' reactions to MSG. The focus of this narrative review is to summarize the available literature regarding the possible role of MSG in the most commonly alleged reactions for which patients seek evaluation for suspected 'allergy' to MSG, namely components of the 'Monosodium glutamate symptom complex', asthma, urticaria, and rhinitis.

Monosodium glutamate, glutamic acid, and taste

Glutamate salt food additives are commercially synthesized through acid or enzymatic hydrolysis of protein or purified from fermentation products of beetroot or sugarcane. While MSG is the most widely recognized food additive source of glutamate, other sources of glutamate commonly used as flavour-enhancing food additives include hydrolysed vegetable protein, hydrolysed plant protein, hydrolysed soy protein, and autolysed yeast extract [2]. Glutamate is also produced as a result of metabolism of dietary or endogenous peptides. Glutamic acid constitutes approximately 20% of dietary proteins. Some foods with high levels of naturally occurring glutamic acid include tomatoes, meat, Parmesan cheese, mushrooms, and soy sauce. Dietary intake of naturally occurring free glutamate has been estimated to average approximately 1 g/day in Europe and the United States, with an additional 0.3–1 g/day from food-additive sources of glutamate [3].

In an aqueous solution, MSG and other glutamate salts dissociate, releasing free glutamate. Glutamate is recognized by distinct G-protein-coupled taste receptors on the

tongue and is perceived as 'unami' or savoury [4]. Glutamate is more than merely a flavour enhancer. The majority (up to 95%) of dietary glutamate is used as an energy source for intestinal enterocytes. Glutamate is also a precursor for the synthesis of the amino acids arginine and proline and for the tripeptide glutathione. Glutamate is also known to be an excitatory neurotransmitter [3]. Experiments in rats have shown that oral, gastric, and intestinal infusions of MSG result in afferent and efferent activity of the vagus nerve, suggesting the presence of MSG receptors in the gastrointestinal tract [5].

Glutamate is rapidly metabolized by enterocytes and hepatocytes, and studies have shown that even when MSG is administered in quantities much larger than a typical dietary intake (> 30 mg/kg/day), serum levels are only slightly and transiently elevated [6].

Monosodium glutamate symptom complex

The first report implicating MSG in any type of food additive-induced reaction was published as a letter to the editor of the *New England Journal of Medicine* in 1968 by Kwok [7]. In his letter, Kwok described a recurring symptom complex consisting of numbness in the back of the neck that radiated to the arms and down the back, accompanied by generalized weakness and palpitations. Hypothesizing that his symptoms were due to alcohol from Chinese cooking wine, sodium, or MSG, he proposed the term 'Chinese restaurant syndrome'. The correspondence that followed included six letters, each describing similar and/or additional symptoms including facial numbness, lacrimation, periorbital fasciculations, syncope, and headache [8–13]. In 1995, the *Federation of American Societies for Experimental Biology* (FASEB) published a report of a comprehensive analysis of the safety of MSG and established a list of symptoms that constitutes the syndrome (Table 1). The less pejorative and more inclusive term 'Monosodium glutamate symptom complex' was also proposed [14].

Table 1. Symptoms of the MSG Symptom Complex*

Burning sensation in back of neck, forearms, and chest
Facial pressure/tightness
Chest pain
Headache
Nausea
Palpitation
Numbness in back of neck, radiating to arms, and back
Tingling, warmth, weakness in face, temples, upper back, neck, and arms
Bronchospasm (observed in asthmatics only)
Drowsiness
Weakness

*Adapted from [14].
MSG, monosodium glutamate.

The first reported challenge study of MSG involved oral and intravenous administration of MSG in six subjects. The authors concluded that they had identified dose-dependent responses to MSG whereby all subjects would eventually experience sensory phenomena if they ingested enough MSG [15]. The significance of these findings has been questioned on the basis that subjects were unblinded, statistical significance was not demonstrated, and due to the limited clinical relevance of responses to intravenous administration of MSG [16].

Subsequent more scientifically rigorous studies designed to address the question of a possible association between MSG and the symptoms of the 'Monosodium glutamate symptom complex' have shown mixed results. Three double-blind, placebo-controlled (DBPC) studies published in the early 1970s involving healthy volunteers found no difference between symptoms experienced after MSG or placebo [16–18]. A study of DBPC challenges by Kenney and Tidball identified a number of individuals who experienced symptoms of the 'Monosodium glutamate symptom complex' only after ingesting 3–5 g of MSG, an amount much higher than that normally found in the typical western diet [19]. Furthermore, subjects were asked to avoid eating for at least 2 h before testing and the MSG was not accompanied by other food. This design contrasts to another double-blind study by Tarasoff and Kelly in which subjects were given 1.5–3.15 g of MSG or placebo immediately before a standardized breakfast [20]. There was no difference in the incidence of MSG symptom complex-associated symptoms between MSG and placebo groups. The authors observed that food appeared to negate the effects of large MSG doses and cautioned against extrapolating results from food-free experiments to 'in-use' situations. Yang et al. conducted a DBPC study in 61 self-identified MSG-sensitive subjects. Subjects were given placebo or 5 g MSG on an empty stomach, and a significant increase in the frequency of MSG-attributed symptoms in the MSG group was observed [21].

In 2000, Geha et al. [22] published the results of their multi-centre DBPC challenge study designed to evaluate alleged MSG-induced reactions in 130 self-identified MSG-sensitive subjects. In an attempt to conform to the strict criteria set forth by the 1995 report of the FASEB recommending that confirmation of the 'Monosodium glutamate symptom complex' requires three DBPC challenges administered on separate occasions and reproducing the symptoms with MSG but not with placebo, the investigators utilized a study design consisting of four consecutive 5 g placebo-controlled MSG challenges (fasting and without accompanying food in three of the four challenges). Only those subjects with at least two of 10 possible MSG-attributed symptoms after the first challenge were eligible to proceed with subsequent testing. For the first challenge, there was a significantly higher frequency of positive challenges with administration of 5 g

of MSG than with placebo. However, only two of the 130 self-identified MSG-sensitive subjects (1.8%) responded to 5 g of MSG in all four challenges. Thus, the authors concluded that while there was a higher rate of response to high-dose MSG in self-identified MSG-sensitive individuals than to placebo, the response was not reproducible.

MSG consumption has been linked to headaches both as a component of the 'Monosodium glutamate symptom complex' and as a potential trigger for migraines [14]. In the 1969 study by Schaumberg et al. [15] of the 'Monosodium glutamate symptom complex', MSG challenges were associated with headaches in a small minority of subjects. Case reports of patients reporting MSG-induced headaches with and without double-blind objective challenge testing but with an apparent improvement in symptom frequency with MSG avoidance have been published [23, 24]. The DBPC study of the validity of the 'Monosodium glutamate symptom complex' in self-identified MSG-sensitive subjects by Yang et al. [21] identified a higher rate of headache following ingestion of high-dose MSG than placebo.

MSG has been listed as one of many dietary triggers of acute migraine [25], but strong evidence for the connection between MSG and migraine headaches is lacking. The contention that MSG can trigger migraine may arise from three possible sources. First, the inclusion of headache as a component of the 'Monosodium glutamate symptom complex' may lead some to inappropriately extrapolate data linking MSG to this entity as being relevant to migraines. Second, patients suffering from migraines may report an association between MSG and migraine onset. Third, a possible vasoactive effect of MSG was suggested by a 1990 study demonstrating that high concentrations of glutamate caused arteriospasm in an *ex vivo* rabbit model. The authors concluded that a similar vascular response might account for MSG-induced headache [26]. In short, whereas the non-specific term 'headache' has generally been considered a feature of the 'Monosodium glutamate symptom complex', there is a paucity of data to support MSG as a cause of migraine.

Taken together, these studies suggest that there may be a small number of people at risk for developing symptoms consistent with the 'Monosodium glutamate symptom complex' when consuming large amounts of MSG on an empty stomach without accompanying food. Importantly, the overall incidence of 'Monosodium glutamate symptom complex' appears to be low, even in self-identified MSG-sensitive patients. Furthermore, current evidence does not suggest that this entity is associated with persistent or serious effects.

Monosodium glutamate and asthma

In the 1995 analysis of adverse effects of MSG by the FASEB, an expert panel reviewed 11 available reports (involving 321 asthmatic patients) of the possible role of MSG-provoked asthma attacks. While the panel identified design flaws in all the studies reviewed, they were able to conclude, largely on the basis of one 'reasonably well-designed' study, that there was sufficient evidence 'to support the existence of a subgroup of asthmatic responders to MSG' [14, 27]. The study cited by the panel has been criticized by others as having a number of limiting factors that render the results difficult to interpret [2, 28, 29]. Thus, while the report by the FASEB considers oral ingestion of MSG to be a possible asthma trigger in a subset of patients, this view remains controversial and has not been supported by other studies.

The controversy surrounding the possible role of MSG in inducing asthmatic bronchospasm was initiated by a report by Allen and Baker [30] of two women who had developed life-threatening asthma 11 and 14 h after ingestion of MSG in meals from Chinese restaurants. Single-blind oral challenges with 2.5 g capsules containing MSG were associated with the development of 'severe asthma' 12 h after ingestion in both patients. Subsequently in 1987, Allen et al. [27] performed graded single-blind, placebo-controlled MSG challenges with escalating doses of MSG (0.5–2.5 g) in 32 asthmatic subjects: 14 self-identified MSG-reactors and 18 unstable asthmatics with a history of bronchospasm due to aspirin, benzoic acid, tartrazine, or sulphites. The authors identified 13 subjects who had a $>20\%$ decrease in peak expiratory flow rate (PEFR) within 1–12 h after ingesting MSG and concluded that their study suggests 'MSG is not safe for some individuals with asthma'. However, important limitations of this study have been noted [2, 28, 29]. First, use of PEFR as the sole means of determining a positive reaction is considered unreliable. PEFR is effort dependent and subject to wide but clinically insignificant variations [31]. In addition, the timing of challenge administration varied, with some occurring during the day and others at night, thereby introducing the possibility that diurnal variation in PEFR contributed to the observations [32]. Second, the maintenance bronchodilator, theophylline, was discontinued 1 day before the challenges, and at least some patients received an inhaled β-agonist 3 h before the first challenge. It is highly likely that the observed decreases in PEFR following MSG challenges were due to cessation of the pharmacologic effects of these bronchodilators rather than due to MSG. Third, single-blinding, rather than double-blinding, fails to account for unspoken signals of concern or apprehension that may be exhibited by those administering challenges. Thus, on the basis of this study, meaningful conclusions regarding the possibility that MSG may induce bronchial reactions in some asthmatics cannot be made.

Moneret-Vautrin reported the results of a series of single-blind, placebo-controlled 2.5 g MSG challenges in 30 asthmatics. A positive bronchospastic response,

defined as a 15% decline from baseline in PEFR, occurred in two subjects [33]. Use of single-blind challenges, sole reliance on PEFR, and potential destabilization of asthma by pre-challenge withdrawal of maintenance corticosteroids and theophylline are three key limitations of this study as well. Schwartzstein et al. [34] found no MSG-sensitive asthmatics in their study of 12 mild asthmatics given DBPC challenges with 1.5 g capsules of MSG. A study published only in abstract form by Germano et al. identified one of 30 asthmatics who showed a $>20\%$ decline in forced expiratory volume in 1 s (FEV_1) after ingesting 7.6 g of MSG in a single-blind challenge. A double-blind placebo-controlled challenge in this patient was not associated with a significant decrease in FEV_1 [35]. Both groups of investigators concluded that MSG was unlikely to be a significant contributing factor to adverse respiratory events in asthmatics.

To further assess the possibility that MSG induces bronchospasm in asthmatics who perceive that they are sensitive to MSG, Woods et al. [36] conducted DBPC challenges with 1 and 5 g of MSG in 12 asthmatics who perceived that MSG might be responsible for worsening of their asthma symptoms. None of the subjects experienced significant decreases in FEV_1 or PEFR. A larger study by Waessner et al. [29] included 30 asthmatics who believed that MSG ingestion exacerbated their asthma and 70 asthmatics who did not. Seventy-eight subjects had confirmed aspirin-exacerbated respiratory disease (AERD), a population identified by Allen and Baker [30] as being at a high risk for MSG-induced bronchospasm. Controller therapy with inhaled and systemic corticosteroids was continued, but β-agonists were withheld. The study design included an entire day of single-blind placebo dosing to establish the degree of pulmonary function variability. The following day, subjects with $<10\%$ FEV_1 variability received single-blind 2.5 g MSG challenges. Asthma symptoms and spirometry were assessed for 24 h. Subjects with $>20\%$ decreases in FEV_1 underwent two additional blinded MSG challenges. Only one of the 30 self-identified MSG-sensitive asthmatics had a positive initial challenge, which was not reproduced with subsequent challenges. None of the 78 asthmatics with AERD had positive challenges. The authors concluded that MSG failed to induce signs or symptoms of asthma in subjects with and without a perceived sensitivity to MSG.

To summarize, the bulk of the studies examining the potential role for MSG as a trigger of attacks of bronchospasm in asthmatics have failed to demonstrate an association. To date, no DBPC challenge-confirmed MSG-sensitive asthmatic has been reported. The few studies that, at first glance, appear to identify a small number of MSG-sensitive asthmatics have significant design flaws that leave the significance of their findings in question. Thus, strong evidence that MSG can induce bronchospasm in asthmatics is lacking and further research is needed before MSG should be considered as a possible asthma trigger.

Monosodium glutamate and urticaria/angio-oedema

As reports suggesting an association between MSG ingestion and asthmatic bronchospasm began to surface, a number of investigators began to examine the possibility that MSG might also trigger cutaneous reactions in the form of urticaria and/or angio-oedema. Most of these studies were performed in patients with a diagnosis of chronic idiopathic urticaria undergoing oral challenges with a number of food additives, including MSG. Early studies had a number of design flaws that preclude drawing any conclusions about an association between MSG and urticaria. In 1985, Genton et al. [37] published the results of their food-additive challenge study in 19 adult subjects with chronic idiopathic urticaria. Fourteen days before the challenges, all patients were asked to discontinue antihistamine medications and begin a food additive-free diet. Challenges were then performed to placebo and escalating doses of five food additives including MSG (1, 10, 100, and 200 mg). Only one additive was given per day and at least 2 days separated challenges with different additives. While the challenges were considered single-blind, no attempt was made to conceal the taste of any of the additives. Four of 19 subjects were noted to have urticaria within 6 h of receiving a dose of MSG. The authors concluded that MSG was the likely cause of urticaria in these reactors, but undoubtedly the subjects knew when they were receiving MSG. Furthermore, the possibility that 'reactions' were actually a recurrence of chronic Urticaria unmasked by withdrawal of antihistamines cannot be excluded.

Supramaniam and Warner [38] examined the possible role of MSG and seven other food additives in 36 children with urticaria with or without angio-oedema. Participants were required to have recurrent or persistent urticaria for at least 2 months with a noticeable improvement in symptoms after 4–6 weeks on a diet free of artificial food additives. Double-blind challenges with capsules containing placebo, MSG 100 mg, or one of seven other food additives were conducted at 4-h intervals. Three of the 36 children had a positive reaction, which was defined as the appearance of urticaria or angio-oedema within the 4-h interval between challenges. A case series by Botey et al. describes four children with a history of urticaria who developed urticaria or pruritic cutaneous erythema 1–12 h after an uncontrolled oral challenge with 50 mg of MSG. In the latter two studies, the authors fail to mention whether medications were discontinued before challenges or whether challenges were performed during periods of disease activity or quiescence. In addition, the 4-h interval utilized by Supramaniam and Warner [38] may not have been long enough to exclude the possibility that reactions

were caused by agents tested 8–12 h previously. Thus, these studies fail to clarify whether MSG was in fact responsible for the appearance of urticaria in these subjects.

In an attempt to further clarify the possible relationship between MSG and urticaria, Simon [40] conducted food-additive challenges in 65 patients with active chronic urticaria, including four who gave a history of MSG-induced urticaria. Before the challenges, antihistamine doses were tapered to the minimum effective dose for controlling hives. Baseline urticaria was assessed using a scoring system that involved the 'rule of nines' in which the skin surface of the body is divided into areas of 9% and a 'severity' score from zero to four (zero = no urticaria; one = urticaria involving up to 25% of that surface area; two = up to 50% of that area; three = 75%; and four = diffuse urticaria). A positive challenge was defined as an increase in the total skin score of $>30\%$ or nine points. Subjects initially underwent single-blind challenges with 2.5 g MSG challenges, and those with positive challenges underwent DBPC challenges at least 2 weeks later. Two subjects had positive single-blind challenges to MSG but neither reacted to double-blind placebo-controlled challenges. The author concluded that sensitivity to MSG likely accounts for 0–3% of the chronic urticaria population.

Perhaps the most compelling support for MSG sensitivity as a possible, albeit extremely rare, cause of urticaria comes from a rigorous evaluation of a single patient with a 12-year history of chronic urticaria by Asero [41]. After multiple negative series of skin prick tests (SPT) for airborne and food allergen sensitization, the patient was placed on an additive-free diet, which was associated with a significant decrease in urticaria severity and a need for antihistamines. An open challenge consisting of a 3-week unrestricted diet was associated with increased urticaria severity, followed by improvement once again on resumption of the additive-free diet. Two separate DBPC challenges with a relatively low dose of 100 mg of MSG were positive, with the appearance of 'severe urticaria' within 45 min of administration of MSG on both occasions (but not placebo). A single case of angio-oedema without urticaria apparently induced by MSG has also been reported by Squire [42]. A 50-year-old man reported recurrent attacks of angio-oedema of the face and extremities temporally related to ingestion of a soup base containing MSG. An open challenge with the soup base, a blinded challenge with the soup base, and a single-blinded placebo-controlled challenge with MSG 250 mg all resulted in angio-oedema within 16–24 h. Dietary avoidance of MSG was associated with an extended remission of attacks.

In contrast to the case for MSG as a cause of asthmatic bronchospasm, there does appear to be some evidence to suggest that MSG may be a rare cause of urticaria, and possibly angio-oedema. It is worth noting, however, that the bulk of the studies suggesting such a relationship have been limited by inadequate blinding, small sample sizes, and potentially confounding withdrawal of antihistamines before MSG challenges.

Monosodium glutamate and rhinitis

In recent years, the possibility that MSG may induce acute rhinitis symptoms and contribute to chronic rhinitis has been raised. In two separate reports, Asero has described three patients with chronic rhinitis symptoms attributed to dietary MSG ingestion, two patients with perennial rhinorrhoea, nasal itching, and episodes of sneezing paroxysms and one patient with chronic rhinosinusitis with nasal polyposis, associated anosmia, and obstructive nasal symptom [43, 44]. Evaluation for specific IgE sensitization to common airborne allergens (as measured by SPT) was negative in all three patients. Physical examination and sinus imaging failed to show alternative anatomic or infectious aetiology of the nasal symptoms. All three patients experienced marked and sustained improvement in nasal symptoms following the initiation of an 'additive-free' diet, relapse of nasal symptoms within a few days of the resumption of an unrestricted diet, and a second remission of symptoms with re-institution of the elimination diet. DBPC challenges with 100 mg capsules of MSG induced 'severe' rhinitis symptoms within 4–24 h of MSG ingestion and lasted 1–2 days in all three patients. Administration of placebo and seven other food additives was not associated with nasal symptoms. A second DBPC challenge confirmed these results in two of the patients. While these two case reports suggest a possible relationship between ingestion of MSG and the development of rhinitis, further studies will be required before conclusions can be made regarding the possible association between dietary MSG consumption and acute or chronic rhinitis symptoms.

Conducting monosodium glutamate challenges

Given the concerns raised by various reports of MSG-induced illness in the lay and medical literature, allergists and other clinicians may be called upon to perform oral challenges with MSG. While the current literature does not lend support to the concept that routine use of oral MSG challenges is likely to be helpful in the evaluation of all patients with asthma, urticaria/angio-oedema, or rhinitis, this diagnostic modality may be particularly helpful in excluding MSG as a cause of symptoms in patients suspecting themselves to be MSG sensitive. Recommendations and considerations for oral MSG challenge protocols for suspected 'Monosodium glutamate symptom complex' and MSG-induced asthma and urticaria have been published [14, 45, 46]. The authors of these protocols emphasize avoiding a number of pitfalls raised by the studies

discussed in this review. In the case of MSG challenges for suspected MSG-sensitive asthma, continuation of asthma medications, monitoring with FEV_1 (rather than PEFR), and use of placebos with administration of placebos and MSG on different days in single-blind, followed by double-blind challenges are recommended [46]. Recommendations for conducting oral MSG challenges in patients with chronic idiopathic urticaria include: withholding of antihistamines, or for patients with intractable chronic symptoms, tapering to a minimally effective dose; elimination of MSG from the diet for at least 1 week before the challenge; use of objective, quantitative grading scales for determination of positive reactions; use of placebo controls; adequate blinding; and MSG doses that are likely to be encountered in the patient's typical diet [47].

Conclusion

Since the initial description of the 'Chinese restaurant syndrome' by Kwok in 1968, the controversial concept that dietary ingestion of MSG might be responsible for a variety of clinical conditions including the 'Monosodium glutamate symptom complex', asthma, urticaria, angio-oedema, and rhinitis, has received a great deal of attention from investigators, clinicians, and the general public. While there is some evidence to suggest that large doses of MSG (>3 g) ingested on an empty stomach without concomitant food ingestion may elicit some of the symptoms of the 'Monosodium glutamate symptom complex', it would be inappropriate to conclude that MSG consumed as part of a typical western diet would be likely to induce such symptoms. The case for MSG as a clear cause of asthma, urticaria, angio-oedema, or rhinitis is much less convincing. In the case of asthma in particular, critical analysis of the methods and experimental design of virtually all the studies purporting to demonstrate that MSG causes asthmatic bronchospasm shows a number of limitations that preclude concluding that such a link exists. In addition, more scientifically rigorous studies (such as those involving DBPC challenges) have demonstrated that the possibility that MSG consumption plays a role in the provocation of asthma is unlikely, even in self-identified MSG-sensitive subjects. In contrast, the series of studies examining the possible role of dietary ingestion of MSG as a provoking factor for urticaria and angio-oedema suggests that it may be a rare cause, likely accounting for $<3\%$ of cases of urticaria, but the overall quality of the evidence supporting such a relationship is less than ideal. The evidence for MSG as a cause of rhinitis is limited to two suggestive case reports. Further investigations into the relationship between MSG and these conditions must include DBPC challenges and careful attention to medication dosing so as to eliminate the possibility that withdrawal of pharmacologic effects is resulting in false-positive reactions. In short, the current evidence does not suggest that MSG is a significant contributor to asthma, urticaria, angio-oedema, or rhinitis.

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