History of the MSG debate

"NO MSG SERVED HERE," read many signs lining the windows of competing Chinese restaurants and other establishments serving ethnic, particularly Asian, cuisine. Such claims have enjoyed increasing popularity in recent years, as Americans have become more health conscious. As residents of LA, and as medical students who order our share of take-out (especially around exam season), we have a vested interest in getting to the bottom of this issue: What is the big hubbub about MSG?

Monosodium L-glutamate (MSG) is the sodium salt of glutamic acid, which is a widely-used flavor enhancer in Chinese food. Added during the cooking process, it is supposed to bring out the subtle flavor inherent in the food itself. Only after 1950 did MSG become available in the U.S., the average daily intake being estimated at 0.3 to 1 gm. Still, the bulk of American dietary MSG comes from high seasoned restaurant meals, which may contain as much as 4 to 6 gm.

Since then, MSG has been implicated in symptoms ranging from numbness, flushing, drowsiness, lacrimation, syncope, headache, urticaria, abdominal pain, atopic dermatitis, neuropathy, orofacial granulomatosis, neuropsychiatric disorders, and ventricular tachycardia to bronchospasm in induced asthmatic attacks. The first reported case in the literature dates back to 1968, when Dr. Robert Kwok described his personal experience of "numbness at the back of the neck, gradually radiating to both arms and the back, general weakness and palpitation" after eating at a Chinese restaurant (4). He suggests, after eliminating soy sauce and cooking wine, the high sodium content of Chinese food as a possible cause, and implicates monosodium glutamate because of its high dissociation constant.

In the years following, quite a few articles have been published debating this hot question. While many reports have been anecdotal in nature (154 letters as of July 1, 1994), some attempts at well-designed scientific studies have been made. Results are inconclusive so far, but the culprit seems to have shifted from the sodium content to glutamate, which is an excitatory neurotransmitter in the CNS.

Chinese restaurant syndrome

The so-called Chinese restaurant syndrome (CRS) consists of a characteristic triad of symptoms – facial pressure, chest pain, and a burning sensation (or flushing), particularly of the head and upper trunk – following a Chinese meal. An early, though poorly designed trial, by Gore, et al., found that following oral ingestion of varying concentrations – 1.5, 3, and 6 gm – of MSG dissolved in cold tap water after an overnight fast, 13.9% of randomized participants reported reaction to MSG versus only 4.2% responded to placebo. While this difference was statistically significant, the symptoms recorded did not correspond to the classic triad which had been anecdotally known. The symptoms noted most often in this trial were headache, nausea, hypersalivation, and fullness (2).

Another early trial by Kenney, et al. involved the administration of varying concentrations of MSG in 150 ml of tomato juice (to cover the taste), and evaluation of the effect by giving a questionnaire. This study uncovered a potential dose-response relationship, "particularly marked in the case of stiffness and tightness symptoms and somewhat less obvious in the case of pressures, warmth, and tingling, which exhibited a clear threshold for their appearance at the 2- to 3- gm level" (3). Higher doses of MSG seemed to correlate with a longer duration of symptom experience, even though the cause remained elusive.

As recently as last year, a more rigorously designed two-phase study by Yang, et al., sought to confirm the existence of a MSG-symptom complex (6). This trial involved oral challenge of MSG in a citrus-tasting beverage (to mask the flavor) in self-identified MSG-sensitive subjects. If the initial 5 gm challenge was positive for 2+ symptoms, the subjects were then retested in random sequence with 1.25, 2.5, and 5 gm doses of MSG (or placebo). The initial challenge did not give a significant statistical difference in positive responses between MSG and placebo (36.1% vs. 24.6%), with the placebo response being remarkably high. However, a more detailed analysis revealed a sequence effect for the placebo (i.e. placebo recipients tended to report symptoms more often if the placebo was given first than if given second), that was absent for MSG. The average severity of symptoms in response to MSG was nevertheless greater, particularly with flushing.

Yang designed the 2nd phase of the trial to reveal differences that the placebo sequence bias may have masked. Upon rechallenge, they found a clear dose-dependence of symptoms, and an apparent threshold dose of 2.5 gm, thus confirming Kenney's results. More specifically, CRS-associated symptoms such as headache, muscle tightness, numbness/tingling, general weakness, and flushing occurred more frequently after MSG , all with P-values well below the .05 level of significance (6). While the self-selection of the candidates prevents this study from offering information about the general population, it does serve as a useful pilot study to examine effects of MSG on a sub-population which may harbor genetic or nutritional predisposition to MSG-sensitivity.

In summary, the scientific studies suggest that there exists a subgroup of healthy individuals in the population that responds to an oral bolus >3 gm in the absence of food, by exhibiting dose-dependent symptoms generally associated with the MSG symptom complex. Researchers acknowledge that the effects of MSG on serum glutamate levels may be more profound on an empty stomach than with a meal, but at least these studies identify what types of symptoms might be caused by MSG (5).

MSG-provoked asthma

Unlike many of the other, more subjective, symptoms experienced after MSG ingestion, asthmatic attacks can be severe and life-threatening. Asthma is the only documented predisposing medical condition linked to adverse health effects of MSG (5). Allen's 1987 study entailed challenging 32 subjects with asthma (some with history of severe attacks after Chinese food), with 500 mg capsules of MSG, in a hospital, after an overnight fast

(1). They monitored peak expiratory flow rate as an objective measure of bronchodilation. In addition to subjective symptoms such as headache, chest tightness, warmth & sweating, itch, nausea, patients responded in a dose-response fashion to the 0.5,1.5, and 2.5 gm MSG challenges with progressively lower respiratory flow rates.

Thirteen of the 32 patients displayed a positive challenge, although the delay of asthma onset varied anywhere from 1-12 hours. On the same patient, the study was able to demonstrate reproducibility of delay of asthma onset, despite administration of the MSG dose at different times of day. This landmark study, which was corroborated by other studies, seems to indicate a strong link between ingestion of MSG and induction of an asthma attack, at least in a subgroup of responders to MSG. Despite a careful design, this study still possesses a potential flaw. The patients' corticosteroid medications were continued, but theophylline doses were stopped prior to the challenges. Either continuation of drugs might prevent MSG-precipitated attacks, or discontinuation of drugs may lead to an increased non-specific susceptibility which happened to be triggered by MSG (5). Somehow, future studies need to rule out an "off-drug" phenomenon.

The cause of predisposition and provocation is unclear, although the underlying mechanism may be intimately linked to CRS once it is better understood. Evidence does support the existence of a subgroup of asthmatics who respond to MSG challenge. The up-to-12-hour delay in symptomatic onset after MSG ingestion is clinically relevant, as it makes for difficult recognition by the patient and diagnosis by the physician.

Potential mechanisms of MSG

Glutamate levels has been suspected as a culprit for MSG-associated symptoms, because MSG is both neuroexcitatory and neurotoxic in animals and man at high doses. Kenney's group was one of the first to actually measure glutamate concentration in the venous blood. While the plasma glutamate levels following MSG was significantly high than after placebo ingestion ($P < 0.01$) "neither 'resting' level of blood glutamate nor the level achieved after MSG ingestion served to predict reaction or non-reaction" (3). Nevertheless, the sensations of CRS described as pressure, warmth, burning, and tingling suggest the involvement of subcutaneous free-nerve chemoreceptors.

A similar mechanism may govern the dose-dependent response of MSG-sensitive asthmatics as well. Allen proposes that the "development of asthma in close association with the onset of CRS symptoms suggests a peripheral neuroexcitatory effect, such as stimulation of irritant receptors in the lung, leading to reflex bronchoconstriction" (1). As a corollary to this, the 1-12 hour delay of the asthmatic attacks might be explained as a central augmentation of the lung's reflex activity.

Early on, scientists postulated that a possible allergic reaction to MSG might cause the observed symptoms. Yang discounted the involvement of any IgE- or mast cell-mediated mechanism, because no allergy-suggestive symptoms such as rhinoconjunctivitis, urticaria, angioedema, or anaphylaxis were found (6). While asthma may, in some cases,

involve an allergic mechanism, it now seems that the glutamate explanation covers that base as well.

More studies need to be done to elucidate the mechanism, the majority of symptoms may well be mediated by MSG interaction with either central or peripheral glutamate receptors. Many hypotheses are being thrown around. Glutamate excitotoxicity by free radical action may be one possibility. CNS effects arise from stimulation of glutamate receptors that activate neuroendocrine systems, mediate pain, inflammation, blood pressure regulation and respiration. In the periphery, likewise glutamate receptors linked with gastrointestinal motility, respiration, and the endrocrine system may be stimulated (5).

If serum glutamate levels are responsible for the symptoms, then it is the total of naturally occurring free glutamate plus the added MSG which must be considered by MSG-sensitive patients. Savory foods such as cheeses, tomatoes, and mushrooms are high in free glutamate (1). However, as long as MSG is not added to a meal which boosts the glutamate level significantly, natural levels of glutamate in food are not likely to induce asthma.

Recent research in animal models also point to MSG effects on pituitary and hypothalamus, particularly in the developmental stage. These seem to work by MSG stimulation of hypophysiotropic neurons to release either release or release-inhibiting neurohormones into the hypophyseal portal circulation (5). The link may be a specific excitatory neurotransmitter receptor; so far, the NMDA receptor is an attractive candidate. However, little research has been done on humans in this area, so no conclusions can be drawn.

Areas for further research

As little good research has been done on MSG, especially in humans, there are several areas which warrant further investigation. The literature reports two cases of cardiac arrhythmia in conjunction with CRS symptoms, after ingestion of wonton soup, which has a high MSG content. These were never properly followed up on.

In addition to asthmatics, it is believed that certain subpopulations are prone to MSG sensitivity. Possible predisposing conditions include: vitamin B-6 malnutrition, infants (in utero and newborns), women taking oral contraceptives, and individuals with affective disorders (5). Epidemiological studies need to be done to determine the prevalence of CRS in the general population and MSG-sensitive asthmatics within the asthmatic population. This would also help to identify the predisposing factors and the size of the subgroups involved.

Finally, it behooves researchers to confirm or refute proposed glutamate mechanisms. The key is to establish connections between studies of symptomatic effects and those of metabolic response (i.e. serum glutamate levels). A carefully controlled clinical trial can help link the relevant subjective and objective reactions to MSG. Tests on each patient

should include complete medical history, neurological exam, blood tests (for amino acid levels, vitamin B-6 levels, standard parameters), psychometric assessments, and possibly functional imaging techniques such as PET.

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