Introduction

The addition of monosodium L-glutamate (MSG) as a food ingredient, particularly in Asian cuisines, is not a new phenomenon. MSG is the sodium salt of glutamic acid and is added to foods either as a purified monosodium salt or along with other amino acids and peptides. It has been postulated that MSG is responsible for the fifth gustatory sensation, termed umami (meaning tasty), by binding to a specific metabotropic glutamate receptor different from the receptors for sweet, salty, sour, and bitter. Aside from being synthesized as a food additive, MSG is found in natural foods, such as tomato and cheese (13). The average daily intake ranges from 0.3-1.0 g in industrialized countries and can significantly vary depending on individual food intake and taste preferences (2).
Despite its long history as an effective flavor enhancer, there remains an ongoing debate over MSG's safeness and whether it is responsible for numerous adverse reactions, including asthma, urticaria, atopic dermatitis, ventricular arrhythmia, neuropathy, abdominal discomfort, and the MSG symptom complex. The MSG symptom complex, originally known as the Chinese Restaurant Syndrome (CRS), refers to a triad of symptoms that was first reported in 1968 after ingestion of a Chinese meal. The symptoms experienced were described as "numbness at the back of the neck and arms gradually radiating to both the arms and the back, general weakness, and palpitations"(2). Since this report, scientific interest turned to studying MSG and defining its biochemical mechanism, possible adverse effects, and potential neurotoxicity. A great deal of research has led to our current understanding of the tasty compound. This paper seeks to re-evaluate the safety of monosodium glutamate based on findings from well-designed scientific experiments.

The Chinese restaurant syndrome re-examined

The first published papers describing adverse reactions to MSG were mostly anecdotal. These reports alleged MSG as the cause of the Chinese restaurant syndrome (numbness, weakness, and palpitations). Other reported symptoms included headache, migraine, tightness, aching, flushing, sweating, fasciculation, lacrimation, syncope, dizziness, shudder attacks, paresthesias, arrhythmias, tachycardia, burning facial pressure, and chest pain (2). Because many of these allegations were subjective and based on experiments designed with low degree of rigor, double-blind, placebo-controlled studies were needed to determine whether MSG was the culprit.
The first of these high-caliber experiments was performed in 1993 by Tarasoff et al. using a randomized, double-blind crossover design treating 71 subjects with placebos and MSG before a standardized meal. Tarasoff et al. advantageously used capsules and specially formulated drinks to mask the MSG taste to ensure that subjects were blinded, thus to reduce subject bias. The study found that subjects did not respond to placebos and MSG treatments differently and that food could significantly negate the effects of high MSG doses (9). Another well-designed experiment further proved that MSG does not produce the symptoms as described by early anecdotal reports. In 2000, Prawirohardjono et al. did an assessment of adverse reactions to MSG in a randomized, double-blind, crossover, placebo-controlled study involving 52 Indonesian participants. After treating subjects with capsules of placebo or MSG (1.5 and 3.0 g) along with a standardized

Indonesian meal, researcher found no significant differences in blood pressure, pulse, and respiratory rates between the controlled group and the treatment group. They further concluded that when MSG taste was masked, no difference in symptoms was reported (6).

What would happen if MSG were ingested without food? More rigorously designed studies had been performed to verify the existence of the MSG symptom complex. In 2000, Geha et al.(1) performed a multicenter, double-blind, placebo-controlled, multiple-challenge, crossover study involving 130 self-identified MSG-sensitive subjects. As in the 1997 experiment by Yang et al.(14), the purpose of the study was to determine whether there was a statistically significant difference in the incidence of specific symptoms after 5-g treatment of MSG as compared with placebo. Strengths of this particular study included reduction of subjective bias by masking of the MSG taste with a citrus-tasting beverage and the double-blind fashion in which it was conducted. In addition, subjects must experience at least 2 of 10 predefined symptoms in order to be considered as a positive responder. (These 10 predefined symptoms included characteristics of the Chinese restaurant syndrome.) To confirm that a subject experiences MSG symptoms, he must reproduce 2 or more symptoms in four separate challenges. The reason behind the 4 challenges was to demonstrate that any responses were consistent and reproducible, as recommended by the 1995 Federation of American Societies for Experimental Biology (FASEB) report. Geha et al. found that there was a significantly higher frequency of response to MSG than to placebo at dosage of 2.5 and 5 g. Only 1.8% (2/110) subjects, however, presented a positive response (2 or more symptoms) after 4 consecutive oral challenges. Neither of the two subjects could reproduce the same symptoms reported in previous challenges. Therefore, MSG ingestion in the absence of food might induce more symptoms than a placebo but such response was inconsistent and not replicable during subsequent challenges (1).

In consideration of the three well-designed studies described above, MSG could not be demonstrated as the causal agent of the MSG symptom complex. When ingested with meals, MSG did not elicit the adverse reactions initially reported in 1968. Geha's study suggests that there may be a minority of individuals who are sensitive to >2.5 g of MSG when ingested in the absence of food. Because of failure to duplicate consistent responses on retesting, the causal relationship between MSG consumption and MSG symptom complex could not be established.

MSG associated with asthma?

In 1987, a study performed by Allen et al. drew great interest because they concluded that MSG was responsible for asthmatic reactions experienced by 14 out of 32 patient after ingestion of 2.5 g of MSG. Upon further inspection, the design of the experiment was found to be flawed in a number of critical areas. In Allen's study, the effort-dependent flow meters were used for measurements rather than the more accurate flow volume measurement. Eighteen of the subjects were sensitive to nonsteroidal anti-inflammatory drugs (NSAIDs). In addition, theophylline treatment was discontinued and beta-agonists were administered to some unidentified subjects. Because the reported decline in peak expiratory flow rates (PEFRs) in the 14 subjects could occur as late as 12 hours after MSG ingestion, the asthmatic reaction could very likely be "a reflection of spontaneous

variation in lung function" rather than a result of MSG consumption (12). Furthermore, the positive asthmatic responses could be due to NSAID-sensitivity and/or theophylline withdrawal. Indeed, more rigorously designed studies would be needed to verify the relationship between MSG and asthma, if any. In 1998, Woods et al. conducted a randomized, placebo-controlled, double-blind study involving 12 subjects, who self-defined to have MSG-induced asthma. Unlike Allen's study, subjects were allowed to continue anti-inflammatory and brochodilator medications, and conventional spirometric measurements were used. The researchers were unable to demonstrate MSG-induced asthma based on forced expiratory volume-1 (FEV1) and PEFRs data. Venous blood samples showed no significant soluble inflammatory marker activity or difference in bronchial hyperresponsiveness. Since the association between MSG and bronchoconstriction could not be proven, the small sample size was not critical (13). To further investigate the possible existence of MSG-induced asthma, Woessner et al. performed a single-blind, placebo-controlled study by challenging asthma subjects with 2.5 g of MSG with meals. Out of 100 subjects (30 of which reported MSG-sensitivity), there was no statistical difference in the change in lowest FEV1 values between placebo challenges and MSG challenges. In agreement with the study by Woods et al. (13), the relationship between MSG consumption and asthmatic reaction could not be established (12).

MSG effects on the brain

Because it is the sodium salt of glutamate, an excitatory neurotransmitter, there has been question on potential neurotoxicity by MSG. The studies conducted as of now have only demonstrated serious neurotoxicologic from MSG on animals. In 2000, Park et al. found that single intraperitoneal injection of 4.0 mg/g bodyweight of MSG caused significant damage to hypothalamic neurons in the arcuate nucleus and impaired memory retention in adult mice (5). Gonzalez-Burgos et al. found that subcutaneous administration of 4.0 mg/g bodyweight of MSG to male neonate rats induced excitotoxicity, leading to cell death in prefrontal cerebral cortex (3). As early as January of this year, Martinez-Contreras et al. reported administration of 4.0 mg/g body weight of MSG caused reactivity of astrocytes and glial cells in the fronto-parietal cortex, including hyperplasia and hypertrophy (4). While MSG's similarity to glutamate might be the reason for its neurotoxicity, it is important to note the extremely high dosage administered in these animal studies. To cause neuronal damage in animals, MSG plasma level needed to be 100-130 mumol/dl in neonates and >630 mumol/dl in adults. Such high plasma levels could not be reached in humans even after bolus doses of 150 mg/kg bodyweight of MSG (10). To recall, the average daily MSG intake ranges from 0.3-1.0 g (2). In conclusion, the plasma glutamate concentration after MSG ingestion would not reach the level that would pose medical risk in humans.

Conclusion

In light of the findings from recent studies, there is no evidence that monosodium glutamate is associated with MSG symptom complex, asthma, or neurotoxicity. Results from the well-designed experiments described above contradict and appear to invalidate

the adverse effects reported in poorly conducted studies. Still, there is a need for further examination of MSG effects on humans. As Geha et al.(1) suggested, there might be a group of individuals who are MSG-sensitive. Perhaps, there are genetic or environmental conditions that contribute to MSG-sensitivity. Rigorously conducted, placebo-controlled, double-blind experiment would be needed to further investigate the biochemical mechanism of action of MSG.

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