Adverse effects associated with monosodium glutamate consumption: A brief review

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SUMMARY

Monosodium glutamate (MSG) is a widely used flavour enhancer, first patented as a food additive in 1908. Although the compound has been recognized as safe for human consumption by regulatory bodies, there exist medical and anecdotal reports and beliefs that consuming MSG can elicit a variety of adverse effects. In this work, the known biologic effects of glutamate, the active compound in MSG, are first briefly discussed, followed by a summary of existing literature on adverse effects of human consumption of MSG. Overall, based on the current state of evidence, it is argued in this work that although the constellation of symptoms, now referred to as MSG symptom complex, have not reliably been reproduced in controlled study conditions and are thus often dismissed, some evidence points to possible effects of MSG on human physiology; gaps in the literature persist that warrant further study, such as better controlled studies involving MSG consumption with food.

REVIEW OF EXISTING LITERATURE

INITIAL REPORTS OF ADVERSE EFFECTS OF MSG

Monosodium glutamate (MSG) is a food additive first patented as a flavour enhancer in 1908. The active component of MSG is glutamate, which produces the taste known as umami (Sano, 2009). Adverse effects of consuming monosodium glutamate were first notably reported by Kwok in 1968. In a letter to the editor in the *New England Journal of Medicine*, Kwok coined the term "Chinese restaurant syndrome" to describe the collection of symptoms he had repeatedly experienced after eating at a Chinese restaurant, including numbness at the back of the neck with radiation to the arms and neck, generalized weakness, and palpitations. He further described similar experiences from friends of Chinese descent after eating at some Chinese restaurants. Notably, Kwok did not specifically implicate MSG as the responsible agent, but rather mentioned it in a list of speculative causes including soy sauce, cooking wine, and sodium (Kwok, 1968).

Following Kwok's publication, many further anecdotal letters were published, and a variety of investigations were conducted into the cause of this constellation of symptoms (Anon., 1968). This included a double-blind study with three participants consuming wonton soup (Schaumburg and Byck, 1968), and a single-blind cross-over study with thirty-five participants consuming tomato juice (Ambos, et al., 1968). These small initial studies concluded that MSG was the responsible agent by showing that participants reported experiencing adverse effects when they consumed test food items containing MSG, and not when they consumed the food item without MSG. However, both studies had a small sample size, were conducted solely on participants who self-reported as being susceptible to the symptoms, and neither included well-described protocols or detailed results.

STUDIES BY REGULATORY AGENCIES

In the following years, several further studies were conducted. In particular, the issue was examined by various food regulatory groups, which conducted literature reviews to reach their conclusions. In 1980, a committee of the Federation of American Societies for Experimental Biology (FASEB) concluded that MSG may cause adverse reactions in a portion of the population that is susceptible to its effects, but that evidence was not strong because some studies showed that symptoms could be elicited without MSG. It further noted that MSG levels in use in processed foods were less than those used in the experiments that elicited symptoms. The average daily MSG intake was estimated at the time to be around 550 mg/day (He, et al., 2011), while experiments typically used amounts in the range of 1 to 12 grams in a single dose. Therefore, it was concluded that levels in use in processed foods were acceptable and posed no risk of harm. No comment was made regarding MSG levels in home- or restaurant-prepared foods, as this fell outside of the committee's scope (Federation of American Societies for Experimental Biology, 1980). A joint Food and Agriculture Organization and World Health Organization report in 1987 similarly concluded that levels required for the intended effect of flavour enhancement did not pose a risk, but suggested caution regarding taking large amounts in a single dose; it did not specify what constituted a "large" dose (World Health Organization, 1987). A further review of MSG by the FASEB in 1995 suggested the less pejorative name "MSG symptom complex" and concluded that evidence suggested that causality for MSG and reported side effects had been established for a subset of the general population, noting reactions as described by previous reports to oral MSG boluses ≥ 3 g without food, and more frequently if taken on an empty stomach. However, despite the abundance of reports on these symptoms, the quality of much of the literature available at the time was deemed to be poor (Federation of American Societies for Experimental Biology, 1995). Food Standards Australia and New Zealand reviewed the safety of MSG in 2003 and concluded that many earlier studies had methodological flaws. However, they agreed that the ingestion of large amounts of MSG (≥ 3 g) without food did provoke symptoms in a small population of people. It was also noted that the literature did not adequately address whether consumption of MSG with food would alter the effect on participants (Food Standards Australia New Zealand, 2003).

RECENT CLINICAL STUDIES

Various double-blind placebo-controlled (DBPC) trials have been conducted. One trial with 61 participants suggested that statistically significant increases in headache ($p < 0.023$), muscle tightness ($p < 0.004$), numbness/tingling ($p < 0.007$), general weakness ($p < 0.040$), and flushing ($p < 0.016$) could be elicited when participants consumed 5 g MSG disguised in in a citrus-flavoured beverage (Yang, et al. 1997). A subsequent multicentre study with 130 participants used a similar protocol, but included further phases of testing on susceptible individuals, one of which included consumption of MSG with food (Geha, et al., 2000). As in the study by Yang and his colleagues, it was noted that subjects responded to higher doses of MSG; however, with later rounds of testing, it was found that subjects did not respond consistently to MSG challenge. More recently, Baad-Hansen, et al. (2010) found increases in headache, pericranial muscle tenderness, and systolic blood pressure with MSG intake in sugar-free soda versus placebo. Studies using a similar oral MSG-soda challenge have also concluded that MSG intake leads to sensitization of the masseter muscle and increased blood pressure (Shimada, et al., 2013; Shimada, et al. 2015), as well as increased susceptibility in individuals with temporomandibular disorder (Shimada, et al., 2016). However, these studies used a fairly high dose of 150 mg MSG/kg body weight.

DISCUSSION

It is currently widely believed by the public that MSG does not cause adverse effects, and that studies have definitively shown that the MSG symptom complex is not reliably reproduced in laboratory settings. Based on the review of the current literature, it is argued in this work that a more nuanced and balanced position would be more appropriate. It is argued here that:

1. MSG consumption in large amounts without food have been shown to elicit uncomfortable but non-life-threatening symptoms

2. One well-conducted double-blinded placebo-controlled trial (Geha, et al., 2000) showed that the symptoms elicited were not consistently reproduced

3. There is a paucity of well-designed studies addressing MSG consumption in large amounts with food, and the fact that both food and the pattern of MSG consumption during a meal is expected to affect the dynamics glutamate absorption

4. Arguments asserting that the average daily consumption of MSG do not exceed recommended maximum acceptable doses have only addressed MSG consumption from processed food and home cooking, and not the MSG content of restaurant food; thus, further research should be conducted in this regard
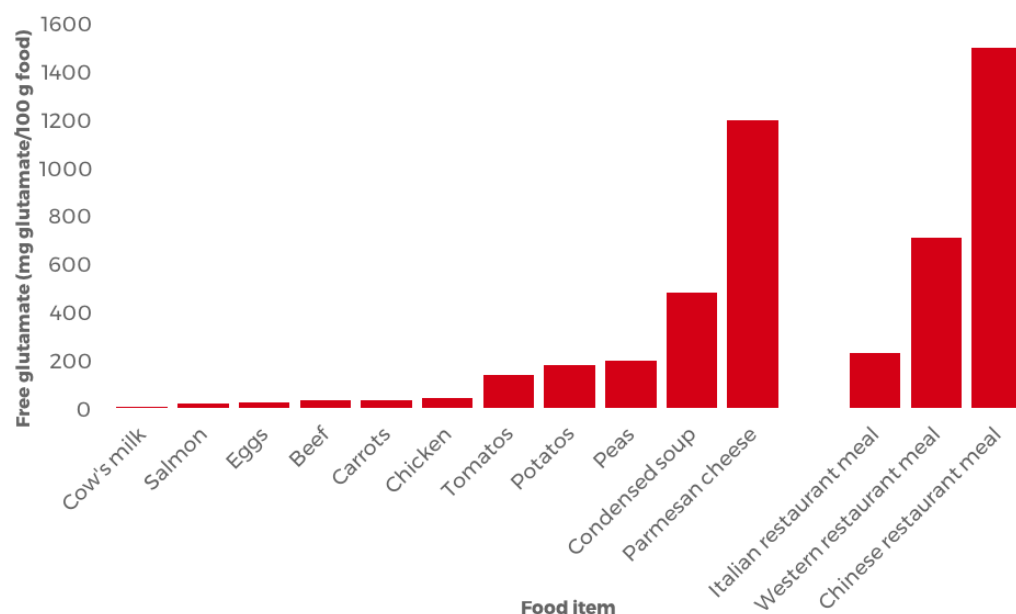
Figure 1: Comparison of free glutamate levels in various food items and restaurant meals. Values obtained from Yamaguchi and Ninomiya (1998, cited in Food Standards Australia New Zealand, 2003) and Nicholas and Jones (1991, cited in Food Standards Australia New Zealand, 2003); maximum values were selected for those with ranges provided.

Of particular note, food regulatory agency reports have acknowledged that large doses of MSG consumed without food appear to elicit temporary adverse effects that are not life-threatening. Double-blinded placebo-controlled studies agree with this conclusion, but have shown that symptoms are not elicited consistently. The literature review conducted for this work did not find any major DBPC since that of Geha, et al. (2000); we argue it would be prudent to replicate this study given the relatively low number of participants that were tested in the later phases of their study, which precluded statistical analysis (12 participants in Protocol C, and 2 for Protocol D). Furthermore, following the work of Geha, et al. (2000), in which MSG consumption with food was assessed in Protocol D, no further DBPC with MSG with food were located. It has previously been asserted that consumption with food may affect absorption of glutamate; it has also been noted that consumption of MSG in food may occur in a variety of temporal patterns over the course of the meal. Studies should therefore evaluate MSG consumption with food to better elucidate possible adverse effects of consuming MSG in real-life situations.

The basis of several assertions of MSG's safety includes the argument that MSG is not consumed in amounts as high as those used in studies. However, these assertions are either based on the claim that high consumption of MSG does not occur because it is not required for its intended flavour-enhancing effect (World Health Organization, 1987), or based on calculations and surveys of processed foods and home cooking (Rhodes, et al., 1991; He, et al., 2011; Henry-Unaeze, 2017). Given that MSG symptom complex was originally associated with eating restaurant food containing MSG, it is unclear whether MSG consumption amounts as previously estimated from processed food and home cooking, ranging from 0.6 to 1.5 g/day (Henry-Unaeze, 2017), apply to restaurant food. One estimate of MSG content in restaurant food reported up to 1500 mg free glutamate/100 g food (Nicholas and Jones, 1991 cited in Food Standards Australia New Zealand, 2003) (Figure 1). It has also been estimated (although, without justification or reference) that a highly seasoned restaurant meal may contain as much as 5 g MSG (Yang, et al., 1997), which falls within the range of MSG levels consumed in experiments. It may be reasonable to systematically survey restaurant food for its MSG content to more accurately inform MSG with food studies; new protocols have been developed that may facilitate this, such as the liquid chromatography-tandem mass spectrometry used by Cebi, et al. (2018).

In conclusion, evidence currently suggests that ingestion of large amounts of MSG without food may trigger symptoms consistent with MSG symptom complex in susceptible individuals. However, there is currently a lack of studies regarding the adverse effects of MSG consumption with food, and estimates of MSG consumption are currently based on processed and home-cooked foods, not restaurant foods. Therefore, it is argued that further DBPCs challenging participants with MSG in food, informed by better quantification of MSG in restaurant foods, should be conducted before dismissing the possibility that MSG may produce adverse effects when consumed.

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