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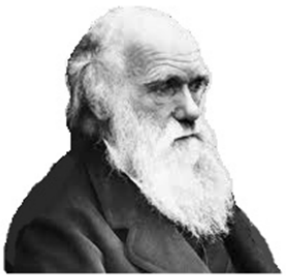

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Effect of Monosodium Glutamate on the Body System

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ABSTRACT

Worldwide, monosodium glutamate is utilized as a flavor enhancer and is composed of essential amino acids for nutrition. Numerous health issues are thought to be linked to monosodium glutamate. Studies have demonstrated that monosodium glutamate has harmful side effects, notably in animals, such as the development of obesity and diabetes as well as hepatotoxic, neurotoxic, and genotoxic consequences. According to several accounts, human subjects were becoming more ravenous, eating more, and becoming obese. Only a few human studies have been done to examine the potential genotoxic, neurotoxic, and hepatotoxic consequences of monosodium glutamate. Exploring the molecular and metabolic mechanisms relating to monosodium glutamate will need a lot of investigation.

***Keywords*:** Hepatotoxic, Obesity, Diabetes, Monosodium Glutamate

1. INTRODUCTION

Monosodium Glutamate (MSG) is the sodium salt of the non-essential amino acid glutamic acid, one of the most abundant amino acids found in nature. Glutamate is thus found in a wide variety of foods, and in its free form has been shown to have a flavour enhancing effect. Because of its flavour enhancing properties, glutamate is often deliberately added to foods – either as the purified monosodium salt (MSG) or as hydrolyzed protein. Animal proteins

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may contain about 11 – 22 % by weight of glutamic acid, with plant proteins containing as much as 40% glutamate [1]. Glutamate is thus found in a wide variety of foods, and in its free form, where it has been shown to have a flavour enhancing effect, is also present in relatively high concentrations is some foods such as tomatoes, mushrooms, peas and certain cheeses. As a result of its flavour enhancing effects, glutamate is often deliberately added to foods – either as the purified monosodium salt (MSG) or as a component of a mix of amino acids and small peptides resulting from the acid or enzymatic hydrolysis of proteins (e.g. hydrolyzed vegetable protein or HVP). Other substances, such as sodium caseinate and "natural flavourings", are also added to many savoury foods and these can also contain considerable amounts of free glutamate.

The use of added MSG became controversial in the late 1960s when it was claimed to be the cause of a range of adverse reactions in people who had eaten foods containing the additive. An ongoing debate exists as to whether MSG in fact causes any of these symptoms and, if so, the prevalence of reactions to MSG. The purpose of this assessment is to review previous considerations of the safety of MSG, as well as any more recent scientific publications, to determine if MSG has the potential to cause severe adverse reactions when ingested with food.

2. SAFETY OF MONOSODIUM GLUTAMATE (MSG)

2. 1. JECFA Safety Evaluations

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has undertaken two evaluations of the safety of MSG. The first of these was conducted in 1971 – 1974, and the second was conducted in 1987 [2].

JECFA examined acute, sub-chronic, and chronic toxicity studies in rats, mice and dogs, together with studies on reproductive toxicity and teratology. Glutamate was found to have a very low acute oral toxicity. The LD_{50} for rats and mice is about 15,000 and 18,000mg/kg body weight, respectively. Sub-chronic studies as well as chronic studies of up to two years duration in mice and rats, including a reproductive phase, did not reveal any specific adverse effects at dietary levels of up to 4%. A two-year study in dogs at dietary levels of 10% also did not reveal any effects on weight gain, organ weights, clinical indices, mortality or general 18 behaviour. Reproduction and teratology studies using the oral route of administration did not reveal any adverse effects, even at high doses.

The JECFA evaluation also addressed two other issues. These were:

i. Potential neurotoxicity, especially to the infant, and
ii. The putative role of Monosodium Glutamate in Chinese Restaurant Syndrome (CRS).

- **Potential neurotoxicity**

Examination of potential neurotoxicity was a major component of the safety evaluation, with reports from 59 separate studies in mice, rats, hamsters, dogs, rabbits, guinea pigs, duck and primates being considered. This issue was given a large amount of attention because of reports that lesions (focal necrosis) in the hypothalamus were observed reproducibly in rodents and rabbits after intravenous or subcutaneous administration of glutamate or after very high bolus doses by gavage. The neural lesions were observed within hours of administration and the mouse appeared to be the most sensitive species. Notably, most of the studies with primates

were negative with regard to hypothalamic lesions. The oral gavage doses required to produce the lesions were of the order of 1000mg/kg body weight as a bolus dose. The threshold blood levels associated with neuronal damage in the mouse are 100 – 300 μmol/dL in neonates rising to 380 μmol/dL in weanlings and greater than 630μmol/dL in adult mice. In humans, plasma levels of this magnitude have not been recorded even after bolus doses of 150 mg/kg body weight (about 10g for an adult). The oral ED50 for production of hypothalamic lesions in the neonatal mouse is about 500 mg/kg body weight by gavage, whereas the largest palatable dose for humans is about 60 mg/kg body weight with higher doses causing nausea. It was thus concluded that voluntary ingestion would not exceed this level.

- **Putative role of Monosodium Glutamate in Chinese Restaurant Syndrome (CRS).**

In consideration of idiosyncratic intolerance to MSG, most of the reports of reactions were found to be anecdotal, however a number of studies that had been undertaken with human volunteers were reviewed. Examination of these studies failed to demonstrate that MSG was the causal agent in provoking the full range of symptoms associated with CRS. It was therefore concluded that controlled double-blind crossover trials have failed to demonstrate an unequivocal relationship between CRS and consumption of MSG and also that MSG has not been shown to provoke bronchoconstriction in asthmatics.

It was concluded that the total dietary intake of glutamates arising from their use at levels necessary to achieve the desired technological effects and from their acceptable background in food do not represent a hazard to health. For that reason, the establishment of an Acceptable Daily Intake (ADI) was not considered necessary, and an "ADI not specified" was allocated to L-glutamic acid and the monosodium, potassium, calcium and ammonium salts.

It was also noted that the available evidence did not indicate that pregnant women and infants were at any greater risk in relation to exposure to glutamate than other members of the general population.

2. 2. Federation of American Societies for Experimental Biology (FASEB) Review

In response to continuing reports of adverse reactions to MSG and other glutamate-containing ingredients, the United States Food and Drug Administration (FDA) contracted the FASEB to conduct a review of reported adverse reactions to MSG. The full report of the study was released in 1995 [3]. 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 documentary evidence to indicate 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 (bolus) dose of MSG of 3g in the absence of food. The report also stated available data suggest strongly that ingestion of MSG in capsule form on an empty stomach is more often associated with occurrence of adverse reactions, than is ingestion with food.

In relation to asthma, the report concluded that the only scientifically verified adverse effects of MSG in humans that have been reported are initiations of bronchospasms in a subgroup of people with severe unstable asthma. The report stated that there appears to be a small subset of people with severe unstable asthma who respond to doses of 1.5-2.5g of MSG given in a low energy challenge vehicle e.g. a capsule, in the absence of a meal containing protein and carbohydrate.

The report recommended that to confirm the MSG symptom complex, multiple double blind, placebo-controlled challenges on separate occasions must reproduce symptoms with the ingestion of MSG and produce no response with placebo. The Expert Panel suggested that five separated challenges would be necessary to conclude that subjective symptoms (e.g. headache, chest tightness, numbness, etc.) are secondary to MSG in highly suggestible individuals, whereas only three would be necessary for those individuals not considered highly suggestible. In individuals with objective findings (e.g. bronchospasm, vomiting etc.), a single double blind challenge was considered sufficient. The Expert Panel recognized that the use of capsules ensures the greatest control over dose and blinding, however, they also noted that the use of capsules obviates the potential role of the oral cavity and oesophagus in the precipitation of potential adverse effects. The Expert Panel suggested that the use of capsules versus liquids would depend on the goal of the study. For example, if the goal is to study the potential for adverse effects of MSG ingestion under conditions of normal use, a liquid vehicle would be most appropriate. The Expert Panel also noted the results of a study where administration of MSG in capsules resulted in a 3 to 4-fold attenuation of peak plasma glutamate levels [4].

2. 3. Monosodium Glutamate as a trigger factor for asthmatic attacks

Asthma is a relatively common disorder that can have serious consequences for the sufferer, including death and therefore is a significant public health problem. In Australia, asthma affects between 22 – 24% of children and 13% of adults [5,6], although the prevalence of food-induced asthma is somewhat lower and has been estimated to affect 0.24% of adults and 11% of children [7].

The causes of asthma are complicated and can vary from patient to patient, however inflammation of the bronchial airways is the characteristic finding in the majority of asthmatic patients [8]. Multiple trigger factors can activate asthma attacks in asthmatic patients already afflicted with inflammation of the bronchial tree and these factors will vary from patient to patient but are important because identification and avoidance of such trigger factors can substantially improve the quality of life of asthmatic individuals [9].

A possible association between MSG and the triggering of asthma attacks was first suggested in 1981 [10]. Since then a small number of studies have been conducted to investigate this association but have produced conflicting results. Five of these studies did not demonstrate MSG-induced asthma attacks [7, 11-14], whereas three have concluded that some people with asthma do get MSG-induced attacks [15-17].

The study by Allen et al (1987) recruited 32 subjects, including two subjects who were the subject of the original case report [10]. Of the 32 who were studied, 14 gave a history of asthmatic attacks after consuming a Chinese meal, with the other 18 having unstable asthma and a reported sensitivity to other chemicals (aspirin, benzoic acid, tartrazine, and sulphites). All subjects underwent single blind oral challenges with MSG (0.5, 1.5, and 2.5g in capsules) followed by Peak Expiratory Flow (PEF) measurements for 12 hours after each challenge. PEF measures how fast a subject can blow air out of their lungs. A positive response was defined as a 20% decline in PEF. Some of the challenges were conducted in the morning and some in the afternoon. Subjects followed a specific exclusion diet (specific details not provided) beginning 5 days before challenges. Some asthma medications (theophylline) were ceased prior to the challenges. One subject was reported to react to all three doses, another to the 1.5g dose only and 12 to 2.5g only. Thirteen subjects were thus concluded to have experienced an MSG-induced asthma attack.

This study has been criticized for a variety of reasons, including: a lack of blinding of observers, that is, the study used a single blind, rather than a double blind protocol; inadequate procedures for establishing baseline and control data; the use of effort-dependent PEF, which can be influenced by subject bias; the cessation of anti-inflammatory and bronchodilator medications just prior to the challenge sequence making it hard to judge whether an asthmatic attack is due to the challenge substance, rather than simply a result of the withdrawal of therapy; and no measurements of immunologic inflammatory markers or changes in airway responsiveness were taken.

The study by Moneret-Vautrin (1987) used a single blind, placebo-controlled challenge protocol to study 30 asthmatic patients undergoing oral challenges with 2.5g MSG [16]. The authors did not report the MSG history of the test subjects. No specific diet control was exercised during the course of the study. Declines in PEF were used as an indicator of a positive response, with PEF measurements being taken hourly for 12 hours after challenge. All treatment with corticoids was ceased 21 days prior to challenge, and treatment with theophylline was ceased three days prior to challenge. Two out of the 30 subjects were reported as having a positive reaction to MSG 6-10 hours after challenge.

This study has been criticized for the following reasons:

- ✓ The two positive reacting subjects were not re-challenged in a double blind protocol;
- ✓ Both subjects exhibited wandering baseline 21 PEF values during their placebo challenges, therefore differences between placebo and MSG PEF measurements would have been difficult to detect; and
- ✓ Bronchodilator therapy was discontinued three days before challenge, which could have led to airway instability, particularly as 7 of the 30 subjects tested were reportedly allergic to house dust.

Schwartzstein et al (1987) studied a total of 12 mildly asthmatic subjects using a double blind, placebo controlled protocol [13]. The study was an outpatient study so the authors were not able to supervise diets with respect to MSG content. Six of the subjects did not require asthma medication and the other six were able to discontinue their medication for 12 hours without any change in lung function measurement. One subject had a positive history of asthmatic attacks following ingestion of a Chinese meal. Challenges were done with 1.5g MSG and used Forced Expiratory Volume in one (1) -second (FEV1) measurements plus the occurrence of asthma symptoms as indicators of whether an asthma attack had occurred. FEV1 is an effort-independent measurement, which measures how much air can be blown out in one second of a forced manoeuvres. FEV1 measurements were taken hourly for 4 hours after challenges with placebo or MSG. No subjects in the study were reported as having an MSG-induced asthma attack.

The criticisms of this study include: only one subject with a positive MSG history was recruited; the total study population was considered too small; the largest challenge dose used may have been too low (1.5g, compared to the 2.5g used in previous studies); lack of dietary supervision; and lung function measurements were only performed for up to 4 hours after challenge, compared to 12 hours for previous studies.

Germano et al (1991) studied 13 non-asthmatics and 30 asthmatics using a single blind oral challenge protocol with MSG administered in capsules containing increasing doses at 30-minute intervals for a total dose of 7.6g [11]. Two of the subjects had a positive history of reacting to food containing MSG. Subjects were maintained on their asthma medications

throughout the study. The study was an outpatient study and it is not known if any diet control was used. A positive reaction was defined as >20% fall in FEV1 following MSG challenge. One of the subjects exhibited a significant drop in FEV1 following MSG challenge. This subject was re-challenged using a double blind placebo controlled protocol with no change in FEV1 being observed.

This study has been criticized for the following reasons: only 2 of the subjects used in the study had a history of bronchoconstriction after a Chinese restaurant meal; and the study was only reported in abstract form and therefore few experimental details are available.

Altman et al (1994) recruited 47 subjects for a study using a double blind placebo controlled protocol, although only eight of these were reported as having asthma [12]. It is unknown whether the subjects were subject to any diet control during the course of the study or whether any changes were made to the asthma medications of any of the asthmatic subjects. The study was conducted in two phases. In phase I, three doses of MSG (1.5g, 3.0g, 6.0g) and three placebo does in a liquid vehicle were administered after an overnight fast in random order on different days. The subject recorded symptoms in a 24-hour diet/symptom diary. Phase II repeated the challenge using self-administered capsules at home. Eleven out of the 26 people who completed Phase I reported symptoms after both MSG and placebo, and two after placebo only. Six reported no symptoms after any dose and seven after MSG only. In two of these cases, symptoms were reported at 3g but not at 6g. Ten out of the 16 subjects, who completed Phase II, reported no symptoms after any dose. Symptoms that were reported were of short duration and did not affect daily activities. None of the subjects that had asthma were reported as having any asthmatic symptoms following MSG challenge.

This study has been criticized for the following reasons: the study was reported in abstract form only and therefore contains very little experimental detail; only a small number of asthmatic subjects were used and it is not known if any of these had a history of reacting to MSG; self-reported asthma symptoms were used rather than objective measures of asthma status; the study was funded in part by the International Glutamate Technical Committee and therefore has been considered by some to not be independent.

The Hodge et al (1996) study was designed to compare two different methods of testing for asthma reactions, however one of the substances used was MSG [17]. A total of 11 asthmatic subjects were tested using a double blind placebo control challenge protocol. One of the two methods being tested required subjects to comply with a specific diet. All subjects continued to use their usual asthma medications. FEV1 measurements were taken for two hours following each challenge. Graded doses from 1.2g up to 4.8g MSG were administered in capsule form. One of the subjects was reported as having and MSG-induced asthma attack.

The main criticism of this study is that its main aim was not to explore MSG-induced asthma therefore it is difficult to fully interpret the MSG results.

Woods et al (1998) undertook an outpatient study using 12 subjects with clinically documented asthma and a perception of MSG-induced asthma [7]. Usual bronchodilator medications were continued and subjects complied with strict diet avoidance of MSG during the study. A randomized, double blind, placebo-controlled challenge protocol was used with subjects being administered with 1g and 5g MSG in capsule form (placebo used was 5g lactose). After challenge, subjects were monitored using FEV1 measurements for 8 hours and then sent home for self-monitoring for the next 4 hours using a PEF monitor. The study also measured bronchial hyper responsiveness and soluble inflammatory markers. No immediate or late asthmatic reactions were apparent in any of the subjects after oral challenge with 5g MSG.

This study has been criticized for the following reasons: as an outpatient study, the reliability of the dietary program could not be supervised directly; during the last 4 hours of the post-challenge observation period, patients were at home performing unsupervised PEF measurements; and the study only looked at a small number of subjects.

Woessner et al (1999) recruited 100 subjects, 30 of whom had a history of Chinese restaurant asthma attacks and the remaining 70 subjects had suspected aspirin-sensitive asthma and did not have a perceived sensitivity to MSG [14]. Subjects were admitted to an in-patient facility on the day prior to commencement of the challenges and remained in the facility for the duration of the study. The study used a single blind, placebo-controlled challenge protocol. Subjects followed a "low" MSG diet throughout the study. FEV1 baseline measurements were taken prior to commencement of the study. Placebo challenges (2.5g sucrose capsules) were given in the morning and afternoon on the first day of the study followed by hourly FEV1 measurements for a total of 12 hours. This was followed on the second day with MSG challenges (2.5g capsules) if during the placebo challenge, FEV1 values varied by less than 10% over the course of observation. Again, hourly FEV1 measurements were taken for a total of 12 hours.

The criteria used for a presumptive MSG-induced asthma attack was a 20% decline in FEV1 values from baseline with or without accompanying symptoms. If there was a 20% drop in FEV1 value, serum tryptase levels were determined and the subject underwent two double blind placebo-controlled MSG challenges on days 3 and 4. Only 1 of the 30 subjects with a history of asthma attacks following a Chinese restaurant meal experienced a 20% decline in FEV1 values during the single blind screening challenge with MSG. The subject was without asthma symptoms throughout the MSG challenge and serum tryptase levels were normal. Subsequent double blind placebo-controlled MSG challenges in replicate were negative, with the post-MSG changes in FEV1 values of less than 1%. No other subjects had a significant fall in FEV1 value or the development of asthma symptoms during the MSG challenge. The mean change in FEV1 with MSG challenge was no different from that of placebo challenge. For 15 of the 30 subjects who had previously perceived themselves to be MSG sensitive, causes other than MSG were identified as the trigger factor for their asthma attacks following a Chinese restaurant meal.

3. FOOD ALLERGIES

Food allergies are an abnormal response by the body's immune system to certain components of foods, usually specific proteins. True food allergies may involve several types of immunological responses [18]. The most common food allergy reactions are the immediate hypersensitivity reactions, which are mediated by allergen specific Immunoglobulin E (IgE) antibodies. Symptoms of IgE-mediated allergic reactions, such as acute urticaria or anaphylaxis, can occur immediately after ingestion of the offending food, depending on the dose ingested but they may be delayed by several hours in other cases, such as atopic dermatitis. Although all humans have low levels of circulating IgE antibodies, only individuals predisposed to the development of allergies produce IgE antibodies that are specific for and recognize allergens. The IgE-mediated response is divided into two stages:

i. Sensitization; and
ii. The allergic reaction.

Exposure to a food allergen elicits the formation of specific IgE antibodies by the B-lymphocytes.

The IgE antibodies attach with exceptionally high affinity to receptors on the surface of tissue mast cells and blood basophils (immature red blood cells). At this point the individual is sensitized to the allergenic substance but has yet to experience an allergic reaction. Subsequent exposure to the allergen will result in the crosslinking of the allergen to the IgE molecules on the mast/basophil cell surface. The crosslinking triggers the mast/basophil cells to release various chemical mediators, such as histamine and cytokines. The release of these mediators results in various inflammatory reactions that may occur in the skin, gastrointestinal tract or the respiratory tract. In extreme cases, food allergens can cause anaphylactic shock resulting in the rapid and potentially life threatening collapse of the cardio-respiratory system. IgE-mediated food allergies affect between 1 and 2% of the population [19,20], however, infants and young children are more commonly affected with the prevalence in children under three years of age being between 5 and 8%. True food allergies also include delayed hypersensitivity reactions, the mechanisms of which are less clear. Such reactions include cell-mediated mechanisms involving sensitized lymphocytes in tissues, rather than antibodies [21]. In cell-mediated reactions, the onset of symptoms occurs more than 8 hours after ingestion of the offending food.

The prevalence of food-induced, cell-mediated reactions is not known [22] but the reactions are well documented in infants and typically occur following exposure to milk and soybeans. The most common cell-mediated hypersensitivity reaction affecting all age groups is coeliac disease, also known as gluten-sensitive enteropathy.

Coeliac disease results from an abnormal response of the T lymphocytes in the small intestine to the gluten proteins in cereals and affects genetically predisposed individuals. The T cells have specific markers on their surface that recognize the allergen deposited at a local site such as the gastrointestinal mucous membrane, resulting in an inflammatory reaction affecting the epithelium of the small intestine.

3. 1. Food Intolerances

Food intolerances can be described as any form of food sensitivity that does not involve an immunological mechanism. They can be classified according to their mechanism e.g., enzymatic, pharmacological or undefined [23,24], or alternatively can be defined in terms of the reactions they elicit e.g., metabolic food disorders, anaphylactoid reactions or idiosyncratic reactions [25]. Food intolerances usually produce less severe symptoms than food allergies, and affected individuals can usually tolerate some of the offending food in their diets. The best-known examples of metabolic food disorders are lactose intolerance and favism both of which involve the inherited deficiency of an enzyme.

In the case of lactose intolerance the reaction is due to an inherited deficiency of the enzyme lactase in the gut of the affected persons. Favism is intolerance to consumption of faba beans or inhalation of pollen from the Vicia faba plant. Reactions are due to an inherited deficiency of the enzyme, erythrocyte glucose-6-phosphate dehydrogenase. Most metabolic food disorders are genetically acquired and both lactose intolerance and favism occur at much higher frequencies in certain ethnic groups [25]. Anaphylactoid reactions have symptoms similar to those of anaphylaxis, but are triggered instead by non-immunological mechanisms, which directly lead to the release of chemical mediators from mast cells. To date, no specific substances in foods causing this response have been identified, with the majority of cases being associated with the administration of certain drugs or the radio-contrast dyes used for X-ray

studies. Idiosyncratic reactions refer to adverse reactions where the mechanism is undefined. One example is sulphite-induced asthma, which has been estimated to affect 1 – 2% of all asthmatics.

3. 2. Adverse reactions to food additives

Sensitivity to most food additives is believed to occur in only a small minority of the population [26,27], with most adverse effects due to various pharmacological and other non-immunological mechanisms [28], rather than being true allergic reactions.

Exacerbation of asthma is one of the adverse effects most typically reported as being associated with food additives. Although 23 to 67% of people with asthma perceive that food additives exacerbate their asthma (Dawson et al 1990, Abramson et al 1995), various double blind, placebo-controlled trials report a prevalence rate of less than 5% [29,30].

3. 2. 1. Reported reactions

In 1968, a letter was published in the New England Journal of Medicine describing a syndrome, which began 15 to 30 minutes after eating in certain Chinese restaurants, and lasted about 2 hours with no lasting effects. The symptoms were described as “numbness at the back of the neck, gradually radiating to both arms and the back, general weakness and 10 palpitation” [31]. The author noted that the symptoms simulated those he has had from hypersensitivity to acetylsalicylic acid, but were milder. The author suggested numerous possible causes for the symptoms, including alcohol, salt and MSG used in cooking. The term “Chinese Restaurant Syndrome (CRS)” was coined to describe the symptom complex.

Since that time numerous other case reports have appeared in the literature, with the focus mainly on MSG as the causative agent in CRS. An increasing number and variety of symptoms have also subsequently been added to the list of manifestations of CRS. In 1995, the Federation of American Societies for Experimental Biology (FASEB), who had been commissioned by the United States Food and Drug Administration (FDA) to undertake a review of reported adverse reactions to MSG, reported that the following symptoms are considered representative of the acute, temporary, and self-limited reactions to oral ingestion of MSG [3]:

- Burning sensations in the back of the neck, forearms, 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.

3. 2. 2. Prevalence of reactions

A small number of studies have been conducted to try and determine the true prevalence of CRS and these have produced conflicting results. While one survey has classified CRS as

very common, putting its prevalence at 25% [32], another survey has estimated its prevalence to be much lower, at between 1 to 2% of the general population [33]. The conflicting results appear in part to be due to the way the studies have been conducted and also the way various symptoms have been characterized by the different investigators.

The survey [32], which estimated the prevalence of reactions to be 25%, has been criticized as having several inherent biases and therefore is considered to represent an exaggerated estimate of the true prevalence [34-36]. The main criticisms relate to methodological problems, such as demand bias in the questionnaire where leading questions such as "Do you think you get Chinese restaurant syndrome?" were asked, and population bias, where the surveyed population was not considered representative of the general population and had a higher than average awareness of CRS prior to the survey. Another major criticism is that the clinical criteria used for selecting reactors from non-reactors were quite broad and thus could have led to an overestimate of CRS prevalence in the population group studied.

A slightly later survey [33], which reported an estimated prevalence for "possible CRS" of between 1 and 2%, attempted to redress some of the biases inherent in the first survey, and thus is considered a more reliable indicator of the true prevalence of reactions. This survey was conducted using the National Consumer Panel of the Market Research Corporation of America, and therefore should have avoided any population bias. Efforts were also made to avoid demand-biased questions in the questionnaires used. The most problematic of these is that numerous symptoms have been associated with CRS and many of these symptoms are ambiguous and imprecise. The various clinical presentations thus make it difficult to accurately diagnose CRS and this is likely an important confounding factor in questionnaire surveys.

3. 2. 3. Proposed mechanisms

Numerous mechanisms have been proposed for CRS. While some of the proposed mechanisms postulate an involvement for MSG, others do not.

It has been suggested that CRS resembles an immediate hypersensitivity reaction in that the symptoms typically occur within a few minutes to several hours after eating the offending food. However, no evidence for an IgE-mediated reaction exists [35], although the possibility of an anaphylactoid reaction cannot be discounted. Other non-allergenic mechanisms that have been suggested as the cause of CRS include acetylcholinosis, vitamin B6 deficiency, reflux oesophagitis, and histamine toxicity.

Ghadimi et al (1971) suggested that CRS was the result of an increase in acetylcholine caused by the ingestion of MSG in large doses with the glutamate being converted to acetylcholine via the tricarboxylic acid (TCA) cycle [37]. A similarity between the symptoms of CRS and those occurring after injection of acetylcholine (flushing, feeling of warmth, throbbing in the head, palpitations, and substernal constriction) was noted and it has also been 12 observed experimentally that in humans there is a 28% decrease in cholinesterase after MSG is ingested. The symptoms of CRS were also found to be capable of modulation using drugs affecting the cholinergic mechanisms.

Folkers et al (1984) have suggested that the reactions experienced by MSG-sensitive individuals are a result of vitamin B6 deficiency [38]. They found that when MSG responders received supplemental B6, CRS symptoms were prevented.

Kenney (1986) has suggested that the symptoms seen in CRS are caused by MSG but are not a neurological/physiological reaction [39]. He has suggested that CRS is actually a case of reflux oesophagitis, with MSG acting as an oesophageal irritant. The symptoms and regions of

the body affected by CRS were noted to be similar to those of pain referred from the upper oesophagus. Studies have shown that a variety of seemingly unrelated substances such as coffee, orange juice and tomato juice, ingested via oesophageal infusion, can cause similar types of symptoms [40]. Adding weight to this hypothesis are the results of studies suggesting that individuals reacting to MSG may react to concentration rather than dose and that the same dose taken in capsules is associated with fewer reactions.

Chin et al (1989) suggested that there are similarities between CRS and scombroid poisoning, caused by naturally occurring histamine in foods and they therefore undertook assays of several common Chinese restaurant dishes and condiments for histamine content [41]. It was concluded that while the histamine content of most of the foods assayed was not sufficient alone to cause histamine toxicity, in certain situations histamine intake over the course of an entire meal could approach toxic levels.

To date, very little research has been done to investigate any of these proposed mechanisms further. The FASEB report (1995) found that a major constraint in identifying mechanisms has been the inability to make connections between studies of adverse effects and those of metabolic response to oral MSG challenges. The former lack data on any objective measures of response, in particular, blood glutamate concentrations, and the latter focus on blood glutamate data without evaluation of adverse effects.

4. PHYSICAL AND CHEMICAL PROPERTIES OF MONOSODIUM GLUTAMATE (MSG)

Monosodium Glutamate (Molecular Weight: 187.13) is typically marketed as a white crystalline powder and is readily soluble in water but sparingly soluble in ethanol. MSG is not hygroscopic and is considered quite stable in that it does not change in appearance or quality during prolonged storage at room temperature. MSG does not decompose during normal food processing or cooking but in acidic conditions (pH 2.2-2.4) and at high temperatures it is partially dehydrated and converted into 5-pyrrolidone-2-carboxylate [42]. The chemical structure of MSG is shown in Figure 1 below.

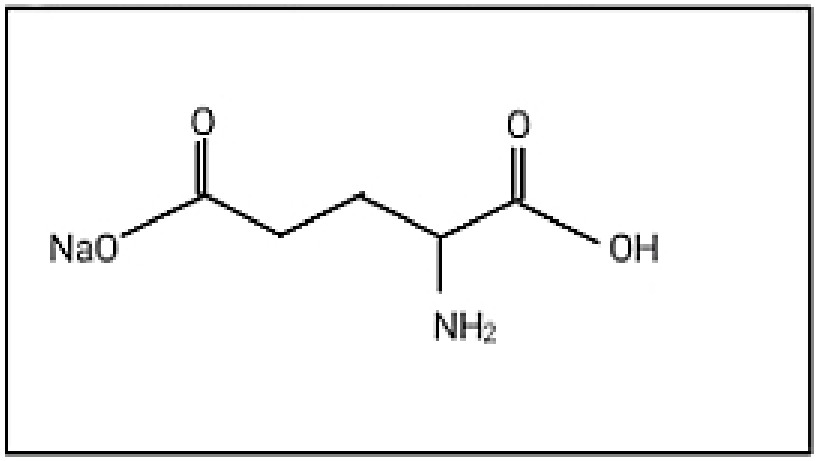

Figure 1. Chemical Structure of MSG

MSG is produced today through fermentation processes using molasses from sugar cane or sugar beet, as well as starch hydrolysates from corn, tapioca etc. Prior to the development of the fermentation process, MSG was produced by hydrolysis of natural proteins, such as wheat gluten and defatted soybean flakes.

MSG is a taste active chemical and is said to impart a unique taste. The characteristic taste of MSG is a function of its stereo-chemical structure with the D-isomer having no characteristic taste. The MSG taste is readily identified in Asian cultures as being distinct from the four basic tastes (sweet, sour, salty, bitter) and has been called "unami". Roughly translated, "unami" means "savoury deliciousness". Western cultures have had difficulty in describing this taste and thus have not identified it as unique. More recently however "unami" has gained widespread acceptance as a fifth basic taste [43].

The optimal palatability concentration for MSG is between 0.2 – 0.8% and its use tends to be self-limiting as over-use decreases palatability. The largest palatable dose for humans is about 60 mg/kg body weight [44].

4. 1. Sources and Occurrence

As an abundant amino acid, glutamate is found in a virtually all foods, including meat, fish, poultry, breast milk and vegetables. In general, protein-rich foods such as breast milk, cheese and meat, contain large amounts of bound glutamate, while most vegetables contain relatively low amounts. However, despite their lower protein contents, vegetables tend to contain proportionally higher levels of free glutamate, especially peas, tomatoes, and potatoes. The typical glutamate content of various foods is given in Table 1. The free glutamate content of other foods such as traditional seasonings, packaged foods and restaurant food is presented in Table 2.

Table 1. Naturally occurring Glutamate in various foods [42].

Food	Bound Glutamate (mg/100g)	Free Glutamate (mg/100g)
Milk/dairy products:		
Cow's milk	819	2
Human milk	229	22
Parmesan cheese	9847	1200
Poultry products:		
Eggs	1583	23
Chicken	3309	44
Duck	3636	69
Meat:		
Beef	2846	33
Pork	2325	23

Fish:		
Cod	2101	9
Mackerel	2382	36
Salmon	2216	20
Vegetables:		
Peas	5583	200
Corn	1765	130
Carrots	218	33
Spinach	289	39
Tomatoes	238	140
Potato	280	180

Table 2. Free glutamate content of traditional seasonings, various packaged foods and restaurant meals [45,46].

Food type	**Free glutamate content (mg/100g)**
Concentrated extracts:	
Vegemite	1431
Marmite	1960
Oyster sauce	900
Soy sauce:	
China	926
Japan	782
Korea	1264
Philippines	727
Fish sauce:	
Nampla	950
Nuoc-mam	950
Ishiru	1383
Bakasang	727

Condensed soups	0 – 480
Sauces, mixes, seasonings	20 – 1900
Chinese restaurant meals	<10 – 1500
Italian restaurant meals	10 – 230
Western restaurant meals	<10 – 710

5. KINETICS AND METABOLISM

5. 1. The role of Glutamate in Metabolism

Glutamate performs a myriad of essential roles in intermediary metabolism and is present in large amounts in the organs and tissues of the body. The daily turnover of glutamate in the adult human has been estimated as 4800mg [47]. Some of the important metabolic roles of glutamate include:

- A substrate for protein synthesis – as one of the most abundant amino acids present in nature, comprising between 10 – 40% by weight of most proteins, L-glutamic acid is an essential substrate for protein synthesis. Glutamic acid possesses physical and chemical characteristics which make it a principal contributor to the secondary structure of proteins, namely the α-helices [48].
- A transamination partner with α-ketoglutarate – L-glutamate is synthesized from ammonia and α-ketoglutarate (an intermediate of the citric acid cycle) in a reaction catalyzed by L-glutamate dehydrogenase. This reaction is of fundamental importance in the biosynthesis of all amino acids, since glutamate is the amino group donor in the biosynthesis of other amino acids through transamination reactions [49].
- A precursor of glutamine – glutamine is formed from glutamate by the action of glutamine synthetase. This is also an important central reaction in amino acid metabolism since it is the main pathway for converting free ammonia into glutamine for transport in the blood. Glutamate and glutamine are thus key links between carbon and nitrogen metabolism in general and between the carbon metabolism of carbohydrate and protein in particular [50].
- A substrate for glutathione production – glutathione, a tripeptide composed of glutamic acid, cysteine and glycine, is present in all animal cells and serves as a reductant of toxic peroxides by the action of glutathione peroxidase. Glutathione is also postulated to function in the transport of amino acids across cell membranes [49].
- A precursor of N-acetylglutamate – an essential allosteric activator of carbamoyl phosphate synthetase I, a key regulatory enzyme in the urea cycle, ensuring that the rate of urea synthesis is in accord with rates of amino acid deamination [5].
- An important neurotransmitter – glutamate is the major excitatory transmitter within the brain, mediating fast synaptic transmission and is active in perhaps one third of central nervous system synapses [52]. Glutamate is also a precursor to another neurotransmitter GABA.s
- An important energy source for some tissues (mucosa) – intestinal tissues are responsible for significant metabolism of dietary glutamate, where it serves as a

significant energy yielding substrate [48]. A net effect of the extensive intestinal metabolism of dietary glutamate is a relatively stable plasma glutamate concentration throughout fasting and fed periods.

5. 2. Kinetics and metabolism of dietary glutamate

Humans are exposed to dietary glutamate from two main sources – either from the digestion of ingested dietary protein, or from the ingestion of foods that contain significant amounts of free glutamate (either naturally present, or added in the form of MSG/hydrolyzed protein).

Glutamate is absorbed from the gut by an active transport system specific for amino acids. This process is saturable, can be competitively inhibited and is dependent on sodium ion concentration [53]. Glutamic acid in dietary protein is digested to free amino acids and small peptides, both of which are absorbed into mucosal cells where peptides are hydrolyzed to free amino acids and some of the glutamate is metabolized. Excess glutamate appears in the portal blood, where it is metabolized by the liver.

A number of early studies with dogs [54], and later, studies conducted in rats [55,56], demonstrated that the vast majority of dietary glutamate is metabolized by the gastrointestinal tract. In fact, very little dietary glutamate enters either the systemic or the portal blood supply [48], indicating it is almost exclusively utilized by the intestinal tissues.

The process of dietary glutamate utilization by the intestinal tract has recently been extensively studied using enteral infusions of [13C5] glutamate in rapidly growing piglets consuming diets based on whole-milk proteins [50,57]. The results showed that 95% of dietary glutamate presented to the mucosa was metabolized in first pass and that of this, 50% appeared as portal CO_2, with lesser amounts as lactate and alanine. This indicates that glutamate is the single largest contributor to intestinal energy generation. The studies also indicated that about 10% of dietary glutamate is incorporated into mucosal protein synthesis, with the remainder being used for the synthesis of proline, arginine and glutathione. In fact, all three substances – proline, arginine and glutathione – are derived almost exclusively from dietary glutamate, rather than the vast in vivo pool of glutamate.

As a consequence of the rapid metabolism of glutamate in intestinal mucosal cells, with any excess glutamate being metabolized by the liver, systemic plasma levels are typically low, even after ingestion of large amounts of dietary protein [47,58]. Human plasma is reported to contain between 4.4 – 8.8 mg/L of free glutamate [35].

Studies on the effects of food on glutamate absorption and plasma levels have been done in mice, pigs and monkeys as well as humans. When infant mice were given MSG with infant formula or when adults were given MSG with consommé by gastric intubation, peak plasma glutamate levels were markedly lower than when the same dose was given in water, with the time to reach peak levels being longer [59]. Similar effects of food on glutamate absorption and plasma levels have been observed in humans. Only slight rises in plasma glutamate have been observed following ingestion of a dose of 150 mg/kg body weight to adults with a meal, with human infants, including premature babies, also demonstrating the same capacity to metabolize similar doses given in infant formula [60].

Human plasma glutamate levels were much lower when large doses of MSG were ingested with meals compared to ingestion in water. In general, foods providing metabolizable carbohydrate significantly attenuate peak plasma glutamate levels at doses up to 150 mg/kg body weight [61-68].

In reviewing all the evidence in relation to the effect of MSG ingestion on plasma glutamate levels, the FASEB Expert Panel concluded that the composition of the dosing vehicle as well as the conditions of administration of the dose can significantly impact on changes in circulating glutamate in response to oral ingestion [69]. Overall, the evidence indicates that the extent of the rise in plasma concentrations of glutamate is affected by a number of factors including the size of the dose (increases with increasing dose); the nature of the dosing vehicle (e.g. water causes greater rise than a mixed meal); the temporal proximity of food consumption (fasted subjects exhibit a greater response than those dosed with a meal); and macronutrient composition of the concurrent food (carbohydrate and mixed meals have an attenuating effect compared with fasting or protein).

Breast milk concentrations of glutamate are quite high and are also influenced only modestly by the ingestion of MSG [70,71]. Of the twenty free amino acids in human breast milk, glutamate is the most abundant, accounting for >50% of the total free amino acid content [72]. Up to 540mg glutamate/L has been found in human milk, whereas cow's milk contains 10-20 mg/L [73].

The placenta is considered virtually impermeable to glutamate [74]. Studies with both sheep and humans have shown the placenta removes glutamate from foetal circulation, while concurrently supplying glutamine into the foetal circulation in very large amounts [75,76].

Although glutamate is an important neurotransmitter in the brain, the blood brain barrier effectively excludes passive influx of plasma glutamate. In guinea pigs, rats and mice, brain glutamate levels remained unchanged after administration of large oral doses of MSG which resulted in plasma levels increasing up to 18-fold [61, 77-80]. Brain glutamate increased significantly only when plasma levels were about 20 times basal values following an oral dose of 2g MSG/kg body weight [61].

The majority of the glutamate used by the brain is derived from local synthesis from glutamine and TCA cycle intermediates and a considerable fraction is also derived from the recycling of brain protein [81].

6. CONCLUSION

On balance, and taking into account the design and methodological flaws evident in many of the studies as well as the conflicting results that have been produced, the evidence for Monosodium Glutamate (MSG) induced asthma attacks is inconclusive. More recent studies suggest MSG may not be a 24 significant trigger factor. Further challenge studies, conducted along the lines of the Woessner et al (1999) study, would be useful to help resolve the ongoing debate about whether MSG is a trigger factor for asthmatic attacks. The evidence suggests that ingestion of large amounts (≥3g) of MSG may be responsible for causing symptoms similar to CRS in a small subset of individuals.

These symptoms, although unpleasant, are neither persistent nor serious and appear more likely to occur when MSG is ingested in the absence of food. As MSG would always be consumed in the presence of food, an important question that remains unanswered by the scientific literature is what 28 effect consumption with food would have on the incidence and severity of symptoms. The pharmacokinetic evidence suggests food, particularly carbohydrate, would have an attenuating affect.

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