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Review Article

Effects of monosodium glutamate on human health: A systematic review

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ABSTRACT

Monosodium glutamate (MSG) is one of several forms of glutamic acid found in foods, in large part because glutamic acid (an amino acid) is pervasive in nature. MSG is used in the food industry as a flavor enhancer with an umami taste that intensifies the meaty, savory flavor of food, as naturally occurring glutamate does in foods such as stews and meat soups. MSG has been used for more than 100 years to season food, with a number of studies conducted on its safety. Under normal conditions, humans can metabolize relatively large quantities of glutamate, which is naturally produced in the gut by exopeptidase enzymes in the course of protein hydrolysis. The median lethal dose (LD_{50}) is between 15 and 18 g/kg body weight in mice and rats, respectively, five times greater than the LD_{50} of salt (3 g/kg in rats). The use of MSG as a food additive and the natural level of glutamic acid in foods are not toxicological concerns in humans. The U.S. Food and Drug Administration have given MSG it's generally recognized as safe (GRAS) designation. A popular belief is that large doses of MSG can cause headaches and other feelings of discomfort, known as 'Chinese Restaurant Syndrome' (CRS), but double-blind tests fail to find evidence of such a reaction. The European Union classifies it as a food additive permitted in certain foods and subject to quantitative limits.

Keywords: MSG, Chinese restaurant syndrome, oxidative stress, appetite enhancer, oral care

INTRODUCTION

Foods have two main functions, i.e. they provide nutrition and an occasion for a pleasurable social event. Both functions are fulfilled only if a food is actually consumed. A food composed of the nutritional elements required for an optimal diet that is unattractive and thus not consumed provides no nutrition. Flavouring systems are of vital importance in savoury food manufacturing. Many industrially prepared foods are particularly attractive to potential consumers primarily because of their typical flavours. Therefore it's no surprise that the food industry dealing with these product segments shows great interest in the use of food or food ingredients carrying the typical umami taste and flavour enhancement systems. Flavourings can play an important nutritional role, particularly in foods that are not very flavourful, by providing the needed appeal. Monosodium glutamate (MSG) is the sodium salt of the amino acid glutamic acid. Glutamic acid or glutamate is one of the most common amino acids found in nature. It is the main component of many proteins and peptides, and is present in most tissues. It is made commercially by the fermentation of molasses, but exists in many products made from fermented proteins, such as soy sauce and hydrolyzed vegetable protein. Glutamate is also produced in the body and plays an essential role in human metabolism [1]. It is a major component of many protein-rich food products such as meat, fish, milk and some vegetables. However, only the free form of glutamic acid or glutamates has an effect on the glutamate receptors. When bound to other amino acids in a protein, it does not stimulate glutamate receptors. They become partially free during processing, thereby accentuating their characteristic flavor properties [2, 3]. The two isomers of monosodium glutamate are L-glutamate enantiomer and D-glutamate enantiomer. Only the L-glutamate enantiomer has flavor-enhancing properties. Manufactured monosodium glutamate contains over 99.6% of the naturally predominant L-glutamate form, which is a higher proportion of L-glutamate than found in the free glutamate ions of naturally occurring foods [4].

HISTORY

Glutamic acid was discovered and identified in 1866 by the German chemist Karl Heinrich

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Ritthausen, who treated wheat gluten with sulphuric acid [5]. Kikunae Ikeda of Tokyo Imperial University isolated glutamic acid as a taste substance in 1908 from the seaweed *Laminaria japonica* (Kombu) by aqueous extraction and crystallization, calling its taste umami. Ikeda noticed that dashi, the Japanese broth of katsuobushi and kombu, had a unique taste not yet scientifically described (not sweet, salty, sour, or bitter) [6]. To verify that ionized glutamate was responsible for *umami*, he studied the taste properties of glutamate salts: calcium, potassium, ammonium, and magnesium glutamate. All these salts elicited *umami* and a metallic taste due to the other minerals. Of them, sodium glutamate was the most soluble and palatable and the easiest to crystallize. Ikeda called his product 'monosodium glutamate', and submitted a patent to produce MSG; the Suzuki brothers began commercial production of MSG in 1909 as *Aji-no-moto* (essence of taste) [5, 7]. The level of glutamates and free amino acids increases considerably after ripening or seasoning of certain foods. Especially certain cheeses due their taste and texture to long ripening, which increases the presence of amino acids. These products are often used to enhance the flavor of meat dishes (**Table-1**).

Table 1: Natural glutamate content of fresh food -the values is expressed in mg/100g food [8].

Types of Foods	Bound glutamate	Free glutamate
Milk/Milk products		
Cow	819	2
Human	229	22
Parmesan Cheese	9.847	1200
Poultry products		
Eggs	1.583	23
Chicken	3.309	44
Duck	3.636	69
Meat		
Beef	2.846	33
Pork	2.325	23
Fish		
Cod	2.101	9
Mackerel	2.382	36
Salmon	2.216	20
Vegetables		
Peas	5.583	200
Corn	1.765	130
Beets	256	30
Carrots	218	33
Tomatoes	238	140

PROPERTIES OF MSG

Monosodium glutamate (MSG, also known as sodium glutamate; IUPAC name- Sodium 2-aminopentanedioate) is the sodium salt of glutamic acid, one of the most abundant naturally occurring non-essential amino acids (**Fig. 1**). The tongue is sensitive to five flavors- salt, sweet, bitter, sour, and umami in the Japanese language, the taste of MSG. 'Umami' is used by the Japanese to describe the taste of MSG as well as the meaty taste of certain fish and broth [9]. The substances which constitute the umami taste can be divided in two main groups.

- One is the □-amino acid group, represented by monosodium glutamate.
- 5'-nucleotid group, represented by inosine 5'-monophosphate (IMP) and guanosine mono phosphate (GMP) and their derivatives [10].

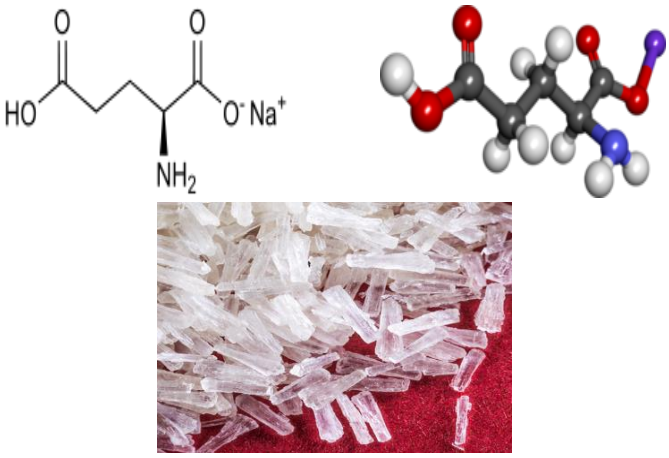

Figure 1: Chemical structure of Monosodium Glutamate

Food palatability increases with appropriate concentrations of MSG [11]. The basic sensory function of MSG is attributed to its ability to enhance the presence of other taste-active compounds. Ideal serum levels of Glutamine to Glutamate appear to be 9 parts Glutamine to 1 part Glutamate, which is mediated by enzymatic conversion in various parts of the body as required by fluctuating levels. When enzyme function is depressed or electrolytes are deficiency-stressed in the presence of too much glutamate to too little glutamine the optimal ratio fails to support aerobic metabolism. This is the reason why athletes need to read the labels and consider reducing MSG from their diet. 'Monosodium Glutamate' appears on labels as "MSG", 'contains glutamate', 'hydrosolated', or simply a processed protein that contains "Glutamate", should be limited. Simplified summary of glutamic acid, glutamate, and glutamine pathway [2].

AMMONIA + GLUTAMINE
↓
GLUTAMINE SYNTHASE ENZYME
↓
GLUTAMATE GLUTAMINE (BRAIN) CONVERSION
↓
GABA or GLUTAMATE
↓
ENERGY + GLUTATHIONE + NIACIN GLUTAMINE SYNTHASE
↓
GLUTAMATE OR GABA
↓
GLUTAMINE [SCAVENGES AMMONIA]
↓
GLUTAMINE
↓
GLUTAMATE
↓
GABA
↓
GLUTAMINE

EFFECTS OF MONOSODIUM GLUTAMATE (MSG)

MSG on oxidative stress: More recent studies have examined other metabolic and toxic effects of MSG, with a number of the reports showing that showing the induction of oxidative stress in different tissues of experimental animals after administration of chronic doses of MSG [12-14]. Glutamic acid has been suggested as one of the amino acids utilized by the kidney during gluconeogenesis since the net uptake of important gluconeogenic precursors such as lactate, glycerol, glutamate, glutamine and other amino acids by the kidney accounts for the turnover of glucose by the kidney [15]. Increased influx of substances into the kidney has been associated with various changes and oxidative stress [14]. This has been corroborated in more recent reports in which hyperglycemia caused oxidative stress in the kidney via the formation of free radicals and altered the antioxidant reactions catalyzed by ROS scavenging enzymes [16]. Hyperglycemia is also known to increase glucose auto-oxidation and labile glycation or intracellular activation of the polyol pathway, with the subsequent oxidative degradation of the glycated protein enhancing the production of reactive oxygen species [16].

Monosodium glutamate causes obesity: MSG may influence you to overeat, leading to obesity. Researchers from the University of North Carolina did a study among people in rural China to examine the effects of MSG. They chose that region because most people there prepare their meals at home without processed foods but still use a lot of MSG. Those who used the most MSG were also the most likely to be overweight, regardless of how their total calories and levels of physical activity

compared with those who used the least. In other studies, mice are injected with MSG for the very purpose of causing them to become obese. Scientists think MSG causes lesions in the brain and interferes with its processing leptin [17, 18]. Leptin is a hormone that signals to the brain that you have had enough to eat, and it shuts off your appetite and increases your calorie-burning. Problems with leptin signaling, called leptin resistance, are factors in obesity.

Monosodium glutamate and cancer: According to the American Institute for Cancer Research, studies to uncover MSG's potential ill effects began in the late 1960s. At that time, some people began to believe that the additive in dishes they ate at Chinese restaurants made them sick. Since that time, scientists have looked and have not found a link between monosodium glutamate and cancer [19]. Katherine Zeratsky, a registered and licensed dietitian with Mayo Clinic, says that people's complaints about monosodium glutamate vary. Some say they develop headaches or nausea while others feel flushed after eating it. Accelerated heartbeat, chest pain and weakness also are some of the reactions individuals associate with MSG. There also are those who say they begin to sweat or feel a certain pressure or numbness in the face when exposed to the food additive. The U.S. Food and Drug Administration requires manufacturers to indicate on the label that a product has MSG. Read the list of ingredients before buying canned and other processed goods. If you have a history of reacting to monosodium glutamate, do not buy anything that lists it as an ingredient.

Monosodium glutamate poisoning: Other terms for MSG are Chinese restaurant syndrome, glutamate-induced asthma, hot dog headache and MSG syndrome. The term 'Chinese restaurant syndrome' was first used in the 1960s to describe the symptoms experienced by some people after eating in Chinese restaurants. Monosodium glutamate poisoning refers to a cluster of symptoms recognized as an adverse reaction to MSG. The symptoms include headache, sweating, flushing, heart palpitations, weakness, chest pain and nausea [20]. Other symptoms are tightness in the face and burning, numbness and tingling in the face and neck.

MSG on pregnant and lactating women: It is common practice for expectant women to eat a varied and well-balanced diet and consume enough calories to ensure a healthy pregnancy. To facilitate fetal growth and development, most amino acids are actively transported across the placenta. Research indicates that amino acid concentrations are higher in the fetus, regardless of what the mother consumes [21]. Both the placenta and fetal liver play important roles in amino acid (and specifically glutamate) transport and metabolism important for fetal development [22]. In rodent studies, researchers investigated effects of dietary intake of MSG on reproduction and birth. The study looked at three generations of mice that were fed a daily intake of up to 7.2 g/kg of MSG. No adverse effect was observed in each generation, nor was there evidence of any incident of brain lesions in the neonates.

Besides research on the fetus, scientists also investigated the effect of MSG ingestion on lactation and breast-fed infants. Upon examination of lactating women who consumed MSG at 100 mg/kg of body weight, researchers noticed no increase in the level of glutamate in human milk, and no effect on the infant's intake of glutamate. According to Baker and colleagues, a newborn infant, through breastfeeding, ingests more free glutamate per kilogram of body weight than during any other period of its life. American Academy of Pediatrics Committee stated that MSG has no effect on lactation and poses no risk to the consuming infant [23].

MSG on children: It has been speculated that children would metabolize oral MSG more slowly than adults. However, research conducted by Stegink and colleagues at the University of Iowa showed that children as young as one year old metabolize glutamate as effectively as adults. In the study, infants were fed beef consommé providing MSG at various dosage levels of 0, 25 and 50 mg/kg of body weight. Researchers measured the infant's plasma glutamate levels and, after comparing the children's plasma levels to those of adults, found no higher plasma glutamate values for children [24]. Additionally, scientific evidence has not implicated MSG in attention deficit hyperactivity disorder or other behavioral problems in children. For the general population, MSG does not pose a health risk [25]. Based on the scientific evidence upholding the safety and efficacy of MSG, the Select Committee on GRAS Substances (SCOGS) concluded in 1980 that there is no evidence that demonstrates reasonable grounds to suspect a hazard to the public when glutamic acid or its salts are used at current levels and manners now practiced [26].

MSG and neurological effects: MSG is a well-known compound in research circles used to fatten up rats for experimentation, because it dramatically increases insulin production. According to 'Contemporary Nutrition,' the food additive industry readily admits that MSG has addictive properties and can cause people to gain weight, but

they justify its use by claiming that this can be beneficial to elderly persons who are sometimes malnourished. Glutamate, the main component of MSG, is the primary excitatory neurotransmitter in the brain, and it has been linked to neurological symptoms when taken in excess [27, 28].

Neurotransmitters, such as glutamate, are important for chemical communication in the brain, where they are very carefully balanced and managed. Excessive quantities of a neurotransmitter, however, can cause it to become an excitotoxin, a substance that over-excites cells to the point of damage, when the balance of glutamate is upset this substance can become neurotoxic, leading to enzymatic cascades resulting in cell death [29]. Neurological conditions that some researchers claim may be associated with MSG include migraines, seizures, autism, attention deficit disorder, hyperactivity, Alzheimer's disease, Lou Gehrig's disease, multiple sclerosis and Parkinson's disease. However, according to a 2007 issue of the 'European Journal of Clinical Nutrition,' an international team of experts concluded that MSG was "harmless for the whole population." They declared that 16 mg/kg of body weight per day was the safe limit for MSG consumption [30].

MSG as an appetite enhancer: MSG is used extensively throughout the world as a flavor enhancer. It improves such specific flavor characteristics of food as continuity, mouth fullness, mildness, and thickness of food. It also improves the overall preference for food. In the elderly, there is a general decrease in the sensitivity of the senses, including taste. Several such reports have described the taste threshold to MSG in elderly people in Western countries; however, few data have evaluated changes in elderly people in Asian countries [31]. A recent study reported the sensitivity and preference for L-glutamate (umami taste) in middle-aged and elderly Japanese women. Similar to findings in Western individuals, the threshold and preferred concentrations of L-glutamate were significantly higher in elderly Japanese women than in middle aged Japanese women [32]. L-Glutamate (umami taste) preference varies under different physiologic conditions. The preference for umami is affected by nutritional status. For example, poorly nourished subjects prefer foods with a higher MSG concentration than do well-nourished subjects [11]. It was reported that umami taste sensitivity is correlated with the protein preference score, suggesting that the taste threshold for umami predicts one's liking as well as preference for high-protein foods.

Oral care effect of MSG: Eating is one of the great pleasures in life. Optimal nutrition, appetite satisfactions are of paramount importance in the elderly. When food is ingested, saliva acts not only as a solvent that allows tastants to be extracted from foods but also as a glue and lubricant for masticated foods that permits safe swallowing. Furthermore, saliva is important for the dental health (lubrication and mineralization), immune function, and prevention of microbial growth [33]. Salivary secretion is provoked by mechanical (mastication and speech) and gustatory stimuli, as well as the autonomic nerves [34]. Kawamura et al and Horio and Kawamura reported that umami taste stimuli increase salivary flow in healthy adult subjects. According to one study, next to sour taste, umami taste is the most potent taste stimulus of saliva secretion from the parotid gland. In addition, of the 5 basic tastes, the increase in salivary secretion produced by umami is the most long lasting [35]. Schiffman and Miletic have measured the influence of umami taste on the amount of immunoglobulin A in the saliva (sIgA) secreted by elderly subjects ingesting food. The ingestion of a food containing added MSG was observed to produce significantly more saliva secretion than occurred after ingesting the same food with no added MSG. Salivary sIgA concentration was not different; hence, the oral cavity experienced a greater total exposure to secreted sIgA when MSG was present in the food [36]. The ability of umami to increase salivary flow may therefore have clinical potential in the elderly, who frequently experience dry mouth and its complications.

CONCLUSION

It is apparent that there is no shortage of research conducted on this ubiquitous ingredient and its potential health effects. Because MSG is one of the most intensely studied food ingredients in the food supply and has been found safe, the Joint Expert Committee on Food Additives of the United Nations Food and Agriculture Organization and World Health Organization placed it in the safest category for food additives. United States food and drug administration (FDA) concluded that MSG is safe when 'eaten at customary levels' and, although a subgroup of otherwise healthy individuals develop an MSG symptom complex when exposed to 3 g of MSG in the absence of food, MSG as a cause has not been established because the symptom reports are anecdotal. International and national bodies governing food additives currently consider MSG safe for human consumption as a flavor enhancer.

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