

REVIEW ARTICLE

An Overview on Monosodium Glutamate: Its direct and indirect effects

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ABSTRACT:

Monosodium glutamate (MSG) is basically used to develop the flavour of variety food items all over the world. The interest of using MSG has been growing rapidly with respect to food processing industry since last 30 years. Many researchers have identified MSG as the most controversial food ingredients for its negative impact towards the animal and human. The present review is nothing but a detail study on MSG, its historical background, chemical characters, commercial importance, use as food additives and its direct and indirect negative impacts on health. This specific study has pointed out how some common diseases like epidemic obesity, diabetes and cardiovascular disease are increasing rapidly day by day in the Indian continental area, linked with excess intake of processed food among the people. Thus, MSG intake also creates several lifestyles related disorder indirectly. The aim of this review is to aware people about the role of MSG on human health.

KEYWORDS: Monosodium glutamate, flavour enhancer, Umami, excitotoxin, obesity and diabetes.

1. INTRODUCTION:

The term widespread and silent killer is so familiar to all of us now-a-days. That is monosodium glutamate (MSG) which is actually more harmful for our health than nicotine, alcohol and numerous other drugs that are lurking in the kitchen cabinets. MSG, is a simple monosodium salt of glutamic acid [1]. Glutamic acid is a 'non-essential' amino acid which can be synthesized in our body. It is found naturally in our body. Besides our body, it is also found in tomatoes, broccoli, mushrooms, cheeses, seaweed, nuts, legumes, meats, most dairy products and protein bound foods [2]. Only the free form of glutamate can enhance the flavour of foods which is found naturally in very fractional ratio. Flavour-enhancing special effects of tomatoes, yeast extracts, fermented soy products, and fermented or hydrolyzed protein products are due to the existence of free glutamate ions. On the other hand, glutamate is the building blocks of protein and glutamic acid plays crucial role, not only in our metabolism system but also act as neurotransmitters [3] to help us in learning and remembering [4].

Apart from that sodium salt of glutamic acid is famous for its artificial flavour enhancing property to the industrial food processing [5]. MSG is one of the cheapest, common food additives which is available in the market [6] and is used widely in crackers, instant nodules, canned soups, barbeque sauce, processed meats and salad dressings etc. Pure white crystal salts of MSG can easily mix with many foods to make it more popular among chefs to make their food tastier. Now-a-days MSG is also used in animal feeding in a little volume. It can also be found in our local supermarkets and restaurants in the name of 'Ajinomoto' [7] and even found in baby foods too. Most of the cases MSG are mainly used in the fries and drinks to enhance the flavour. Thus, MSG has mingled into our daily life food chart either as a hidden ingredient labels or listed under other trade names. However, the intake of glutamate salt in excess amount, especially in the form of artificial food additive like MSG, may causes neurotoxicity and creates numerous side effects [8]. Free glutamate is introduced 'Umami' flavour to the foods. After the 19th century, multinational 'food brand' entered into the Indian market as a part of the globalisation. As a result, 'fast food' and processed food industry becomes one of the fastest growing industry. Now, we are very familiar with this western food culture and include them as a part of our daily diet. Now a huge numbers of urban peoples finished either their breakfast or lunch or dinner with this high calorie 'Fat food'; such as pizza, pasta, burger, fried

chicken, instant noodles, chips, canned food and other processed foods. Industrialization, urbanisation and changing of lifestyle enforces us to intake such kind of readymade food. It is now well established that most of the packed food items contain significant amount MSG. A joint report was published by the government of Australia and New Zealand in 2003 indicated that all types of Chinese based meal contain excess amount of MSG (10 to 1500 mg/100 gm) [9]. This is the main reason that the Chinese food and other processed food attract us, especially children. But one thing we never tried to understand that excess intake of this fast food without regular workout converted us into obese. The rate of this obesity has increased almost double among the Indian population compared to past decade. On the other hand, obesity is connected with various diseases regarding to our daily lifestyle. It has been well known that excess consumption of glutamate ion for a 'MSG sensitive persons' may be dangerous. It may damage our nerve system and it has indirect effect to generate obesity and obesity related diseases. Many other symptoms are observed due to the regular consumption of MSG such as flushing, headache, chest pain, numbness or burning in or around the mouth, sense of facial pressure or swelling, sweating etc. Recently some studies on it indicate that India will be the biggest 'hub' of the Diabetes Mellitus (type –II) in the Asia within 2020 [10]. So, in this situation it is the biggest challenge for the India as well as for Indian people, to fight against the obesity as well as several related diseases. Thus, it is the high time to restrict the use of MSG in the food items. Though, the related research has been carried out since long time but there has no significant review. This overview represented the details discussion with respect to food and science. This overview does not mean to be exhaustive but rather aims to present a snapshot of the area in as brief a manner as possible. We hope that the discussions will be helpful both for the new comers who are new to this field as well as for those who already well-versed in the topics under consideration.

2. Chemical Identity:

MSG is a white crystallized, odourless sodium salt of glutamic acid (molecular formula: $C_5H_8NNaO_4$, molecular mass 169, density of $1.538g/cm^3$ & melting point $225^\circ C$). It can exist as neutral zwitterionic structure in the solid state or mild acidic condition. In physiological pH in between 7.35–7.45 both the carboxylic groups loses protons and exist as the glutamate anion ($^-OOC-CH(NH_3^+)-(CH_2)_2-COO^-$). Structure of glutamic acid depends on the p^H of the medium. Free glutamic acid is less soluble in cold water but more soluble in hot water and it is almost insoluble in acetone, ether and acetic acid as well as in ethanol and methanol. It undergoes sublimation at $200^\circ C$ and decomposed at $247^\circ C-249^\circ C$. It is optically active and

optical rotation being $(+37- (+)38.9 (25^\circ C)$. There are two optical isomers of Glutamic acid: D(-) and L(+)

3. Historical Background:

People around the world of different countries have eaten glutamate-rich foods during the history [11]. It became commercially available in United States in early 1950 and since then its uses increases rapidly in restaurant industry and it became popularise worldwide within a short time. The substance was revealed and recognized in the year 1866, by the German chemist Karl Heinrich. Glutamic acid was synthesised at first by treated gluten of wheat in sulphuric acid [12].

In 1908, Japanese professor Kikunae Ikeda of the Tokyo Imperial University was able to extract glutamate from the seaweed broth. Prof. Ikeda also identified that brown crystal of glutamic acid is responsible for the undeniable flavour of many foods, especially in seaweed. However he named this special flavour 'Umami'. Professor Ikeda then filed a patent [13] and thus the commercial production of MSG started from the year 1909. Now-a-days, instead of extracting and crystallizing of MSG from seaweed broth, it can also be produced by the fermentation of starch, sugar beets, sugar cane or molasses. This fermentation process is similar to the process of making yogurt, vinegar and wine. The Kyowa Hakko Kogyo Company developed the industrial fermentation process to produce L-glutamate [14].

4. Process of Production:

The manufacturing method of glutamate has been shifted from the extraction method to the fermentation method in the 1960s. To make this preparation of MSG by the fermentation process, '*Corynebacterium glutamicum*', is used as a microorganism [14]. The extracted sugar, after adding fermented microorganism and processed, glutamate is accumulated, concentrated and then crystallised via generic bioprocess flow. The most relevant factors influencing L-glutamate formation are the ammonium concentration, i.e. control of p^H and oxygen concentration of the medium. Although, in total, a huge amount of ammonium is necessary for sugar conversion to L-glutamate, a high concentration is inhibitory to growth as well to the production of L-glutamate. Therefore, ammonium is added in a low concentration at the very beginning of this fermentation process and is then monitoring continuously during the course of the fermentation. The oxygen concentration is also controlled, since under conditions of insufficient oxygen, the production of L-glutamate is poor and lactic acid as well as succinic acid accumulates, whereas with an excess oxygen supply the amount of α -ketoglutarate as a by-product accumulates. The fermentation method has the advantage of making mass production at low

cost, which was the great impetus for expanding the amino acid market.

Brazil is the world's top producing country of sugar cane which is the main raw material of MSG. Thus, several MSG production company was build up in that region. Japan based company 'Ajinomoto' claims that they have almost 30 per cent share of the market; whereas the China-based Fufeng Group is the largest producers of MSG and 'Meihua' are the second largest producers.

5. MSG and Umami taste:

Professor Ikeda identified that glutamate provides the savoury taste to the soup and this is called 'Umami', which means 'tasty' in Japan. He gave the product to an iodine manufacturer who created more from it and marketed it with the name of 'Ajinomoto' [7], which means 'essence of taste'. This taste is significantly different from others. However, after 1985 the scientific community included Umami as 'fifth basic taste'. Umami is the feeling that we experience when receptors were subsequently found in the sensory cells in taste buds on the surface of the tongue meet the glutamate rich food [15]. Just as sweet is perceived as the 'taste of carbohydrates', Umami is perceived as the 'taste of proteins' [16]. To get this 'sensational taste' MSG is added into various processed foods. Actually, MSG helps to bring out the best natural flavours in various foods such as meat, poultry, seafood, and vegetables. Soups, casseroles, gravies, and sauces are some examples of dishes that can be tastier by the addition of MSG.

6. MSG and Glutamate in Food:

The glutamate in MSG is chemically indistinguishable from glutamate that is present in food proteins. Only a fraction of the glutamate in foods remains as "free" form, and these are responsible for increasing the flavour of foods. Out of the two isomers, only the L-glutamate has exclusively flavour-enhancing properties [17]. 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 fermented naturally-occurring foods. Our bodies ultimately metabolize both sources of glutamate in the same way. Glutamate occupies a central position in human metabolism [18]. It comprises between 10–40% by weight of most proteins, and can be synthesised in vivo. The concentration of glutamate in breast milk is only modestly influenced by the ingestion of MSG because glutamate is virtually impermeable through placenta. On an average, adult consumes approximately 13 grams of glutamate each day from the protein in food, while intake of added MSG is estimates at around 0.55 grams per day.

7. Glutamate - Protein Building Block and Excitatory Neurotransmitter:

Glutamate is the most predominant excitatory neurotransmitter in the body, being present in over most of the nervous tissue [19]. Glutamate is also used by the brain to synthesize GABA (γ -Aminobutyric acid), the main inhibitory neurotransmitter of the mammalian central nervous system [20].

Overstimulation of glutamate receptors causes neurodegeneration and neuronal damage through a process called excitotoxicity [21]. Excessive glutamate, or excitotoxin acting on the same glutamate receptors, over activate glutamate receptors (specifically NMDARs), causing high levels of calcium ions (Ca^{2+}) to influx into the postsynaptic cell [22]. High Ca^{2+} concentrations activate a cascade of cell degradation processes involving proteases, lipases, nitric oxide synthase, and a number of enzymes that damage cell structures often to the point of cell death [23]. Ingestion of exposure to excitotoxin that act on glutamate receptors can induce excitotoxicity and cause toxic effects on the central nervous system [24]. This becomes a problem for cells, as it feeds into a cycle of positive feedback cell death.

Glutamate excitotoxicity triggered by overstimulation of glutamate receptors also contributes to intracellular oxidative stress [25]. When the glutamate concentration around the synaptic cleft cannot be decreased or reaches higher levels, the neuron kills itself by a process called apoptosis. Excessive extracellular glutamate concentrations reverse glutamate antiporter, so glial cells no longer have enough cystine to synthesize glutathione (GSH), an antioxidant [26]. Lack of GSH leads to more reactive oxygen species (ROSs) that damage and kill the glial cell, which is unable to uptake and process extracellular glutamate (Nicholls, 2009). This is another positive feedback in glutamate excitotoxicity. In addition, increased intracellular Ca^{2+} concentrations activate nitric oxide synthesis (NOS) and the over-synthesis of nitric oxide (NO). High NO concentration damages mitochondria, leading to more energy depletion, and adds oxidative stress to the neuron as NO is a ROS [27]. Excitotoxicity due to excessive glutamate release and impaired uptake occurs as part of the ischemic cascade and is linked with stroke [27], autism [28] some forms of disability, and diseases such as amyotrophic lateral sclerosis and Alzheimer's disease [27]. On the contrary, decreased glutamate release is observed under conditions of classical phenylketonuria [29] leading to developmental disruption of glutamate receptor [30].

8. Global food processed market and MSG:

Zion Research has published a report regarding global market analysis of monosodium glutamate and food Processing Industry. According to the report, the global monosodium glutamate market was valued at USD 4,500.0 million in 2014, and is expected to generate revenue of USD 5,850.0 million by end of 2020, growing at a CAGR of 4.5% between 2015 and 2020 [31]. Thus, it is clear that MSG market is highly increasing due to rising demand for flavouring agents. The demands for MSG coming from restaurants and institutional food service providers as well as household consumption are also expected to grow at moderate pace in the years to come. The global monosodium glutamate market is mainly driven by strong growth of food processing industry across the world. However, rising health issues with the consumption of MSG and various regulatory policies regarding use of MSG in food products is expected to limit the growth of this market.

Food processing industry (snacks, canned food, frozen food, others), restaurants and institutional food service are some of the major application markets for MSG. Food processing industry is the largest segments of monosodium glutamate market. The demand for Chinese food products and fast food is unexpectedly high in Asia pacific region. Restaurants and institutional food service providers is also an important application segment of MSG and expected to witness significant growth in the years to come. Strong demand for MSG from India, China, Vietnam, Indonesia, Thailand, Japan, Taiwan, etc. is mainly responsible for rapid growth of this industry in the region. Change in lifestyle, and food habit is primarily responsible for the growth of MSG market in this region. Thus, increasing MSG market around the India also reflected the changing the food habit and lifestyle in that region. Thus, higher growth rate of processing industry in India indicates higher demand of commercially ready- to- eat packed food. Much more packed food means much more intake of MSG. So, we are consuming more and more flavour enhancer and as a result it can cause so many health hazards 'silently'.

9. Why MSG is bad for human health?

The harmful effects of glutamate on the central nervous system (CNS) were first observed in 1954 by T. Hayashi, a Japanese scientist who noted that direct effects of glutamate to the CNS caused seizure activity, though this report went unnoticed for several years. In 1957 D. R. Lucas and J. P. Newhouse, noted that single doses of 20-30 gm of sodium glutamate in human life does not affect any permanent illness, but it destroyed the neurons in the inner layers of the retina in newborn mice [32]. In April 1968, Robert Ho Man Kwok, Chinese American doctor wrote a letter to the *New England Journal of Medicine*, & coining the term

"Chinese restaurant syndrome"(CRS) [33]. In this letter he claimed that he has faced some strange syndrome i.e. numbness at the back of the neck and general weakness and palpitation after eaten out the Chinese food within 20-30 mins. He pointed out that it may happen due to presence of excess of MSG in the food. This syndrome is often named as 'Chinese food syndrome' and 'monosodium glutamate symptom' complex [34]. In 1969, Professor John Olney published his remarkable work in 'Science' and revealed that the 'negative effect' of MSG was not restricted to the mice retina only, but occurred throughout the brain, and coined the term 'excitotoxicity' [35]. According to his research, MSG can also overexcite the cells at the point of damage or death, causing brain damage to other disabilities [36]. Studies have shown free glutamic acid is the neurotransmitter of brain, nervous system and there are glutamates responsive tissues in other parts of body as well. However abnormal function of glutamate receptors [37] has been linked with certain neurological diseases such as Alzheimer's disease and Huntington's chorea [38, 39].

According to the Olney experiment, 'newborn mice subcutaneous injections of monosodium glutamate induced acute neuronal necrosis in several regions of developing brain including the hypothalamus' [40]. As adults, treated animals showed stunted skeletal development, marked obesity, and female sterility. Pathological changes were also found in several organs associated with endocrine function' [35]. Subsequent research by Mark Mattson provided evidence for the involvement of excitotoxicity in Alzheimer's disease, and other age-related neurodegenerative conditions that involve oxidative stress and cellular energy deficits [1]. Recently scientific study also confirmed that MSG exposures to the young rat develop 'anxiogenic' and depressive like behaviours [41]. Thus harmful effects of MSG are quite clear, It's ingesting can cause diabetes, adrenal gland malfunction, seizures, high blood pressure, excessive weight gain, stroke and other health problems. It has been reported that MSG is 'neurotoxin' resulting in brain cell damage, retinal degeneration, endocrine disorder and some pathological conditions such as addiction, stroke, epilepsy, brain trauma, neuropathic pain, schizophrenia, anxiety, depression, Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis [42]. Thus, if someone takes MSG containing food and experiences any of these conditions, then he or she immediately needs to eliminate MSG from his or her diet.

10. Adverse Effect of MSG:

Most food additives act either as preservatives or as enhancer of palatability. The effect of monosodium glutamate was studied extensively and the model study

shows its harmful effects. It can initiate severe headache, burning sensation, increase the rate of obesity, increases the asthma and affects the male fertility. It also affects the Kidneys of adult Wistar rat and investigation suggested that the functions of the kidney could have been adversely affected due to the distortion of the cyto-architecture of the renal cortical structures and cellular necrosis associated with the kidney [43]. Although there is no such strong evidence that MSG is sole responsible element for the different diseases.

11. Side Effects & Safety Steps:

In 1959, the U.S. Food and Drug Administration (FDA) labelled MSG as "Generally Recognized as Safe" (GRAS), and it has remained that way ever since. However, almost after 10 years later it started showing numerous side effects. From numbness to heart palpitations were experienced by the people after eating MSG and called it "Chinese Restaurant Syndrome" or more appropriately called "MSG Symptom Complex", (FDA) identifies it as "short-term reactions" to MSG. Although the FDA continues to claim that consuming MSG in food does not cause these ill effects, many other experts say otherwise. Then the FDA admits that "short-term reactions" known as 'MSG Symptom Complex' can occur in certain groups of people, mainly those who have eaten "large doses" of MSG or those who have the problem of asthma. According to the FDA, 'MSG Symptom Complex' has some more symptoms such as: Numbness, burning sensation tingling, facial pressure or tightness, chest pain or difficulty breathing, headache, nausea, rapid heartbeat, drowsiness and weakness. 'MSG symptom complex' may be appeared within one hour, after eating 3 grams of MSG or more than it on a empty stomach or without other food. This reaction becomes more serious when the MSG is eaten in a large quantity or in a liquid form, such as clear soup. Due to the consistent research on the excitotoxic effects of MSG on the brains of young animals in the 1960s, researchers testified before the U.S. Congress about the danger of using MSG in baby food. As a result, MSG was voluntarily removed from baby foods in 1969. However, under current regulations of FDA (1995), when MSG is added to a food, it must be identified as 'monosodium glutamate' in the label's ingredient list.

12. Keeping MSG Out of the Diet:

The best way of avoiding MSG toxin is to avoid processed food as much as possible and take more and more fresh foods. On the other side, such as is in restaurants, we should order MSG-free menu items, or request them to serve MSG free meal. We should also know what ingredients to be added or watch out for on packaged foods and lookout for many hidden names of MSG. At last, it is very important to become self-conscious and to distribute the proper knowledge of

health consciousness to the middle and lower-class people in India who are really unknown to this fact.

13. CONCLUSION:

Monosodium glutamate (MSG) is used in a large area as 'most controversial' flavour enhancer, which can be found in most of the processed food items. The result of rapidly growing food processed industry in India with the help of MSG, will converted India into the biggest hub of diabetes mellitus (type -II) within the year of 2050. MSG is an excitotoxin, causing brain damage, and as well as 'neurotoxin'. Federation of American Societies for Experimental Biology (FASEB) examine the safety of MSG in the 1990s. The FASEB report identified some short-term, transient, and symptoms, such as headache, numbness, flushing, tingling, palpitations, and drowsiness that may occur in some sensitive individuals who consumes 3 grams or more of MSG without food. MSG can excite brain cells to death, creates brain lesions, causes leptin insensitivity, contributes to obesity, linked to sudden cardiac death, implicated in strokes, promotes cancer cells growth. Thus, to keep us healthy we have to avoid MSG contain food items from our daily routine. This is only possible if food manufactures can specify the complete list of constituent's and strictly follow the guideline as provided by FASSI (Food safety and standard authority of India). Awareness campaign of 'not to use MSG contain food items' among the consumers have to be increased so that they can actually realise the 'toxic effect' of artificial food additive used in packed food. Moreover, regular random sampling should be continued by the authorised government organisation throughout the year to watch out whether the food is safety or not. If any kind of contamination, malpractices noticed at any stage of manufacturing, packing or as well as during the supply of commercially available food materials, must be taken action in 'strong hand'. Now this is the time to scrutinise the role of MSG as food enhancer in large scale and further research in that field should be encouraged more and more.

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