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Monosodium glutamate (a food additive): a review on its Cytogenetic toxicity

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Abstract- Monosodium glutamate (MSG) is a umami substance, made up of nutritionally indispensable amino-acids. It is used worldwide as flavour enhancer that intensifies the savoury flavour of food, as naturally occurring glutamate does in foods such as stews and meat soups. Although it is generally recognized as being safe by food safety regulatory agencies, several studies have questioned its long-term safety. Literature showed that under normal conditions, humans can metabolize relatively large quantities of glutamate which is naturally produced in the gut in the course of protein hydrolysis by exopeptidase enzymes. The use of monosodium glutamate as a food additive however was found to be associated with adverse side-effects particularly in animals including induction of obesity, cardiotoxicity, hepatotoxicity, diabetes, neurotoxicity, low-grade inflammation, metabolic disarray, premalignant alterations along with behavioural changes. Furthermore, studies have also reported several cytotoxic and genotoxic consequences of MSG in various test systems including *Allium cepa, Vicia faba, Drosophila* as well as rat and human lymphocytes. These studies, however, have limited relevance for extrapolation to dietary human intake of MSG for risk assessment because of flaws in the methodology and dosing level. Hence, further intensive research with an appropriate design is required to explore the mutagenic potential of MSG, its causes and the preventive strategy for reducing the MSG-mediated genetic defects.

Keywords: Monosodium glutamate, flavor enhancer, toxicity, cytotoxicity, genotoxicity.

INTRODUCTION

Many industrially prepared foods that contain certain food additives are attractive to consumers because of their typical flavours.[1] Therefore, the food industry dealing with these products shows great interest in the food ingredients that carry the typical taste and flavour enhancement system. Monosodium glutamate (MSG), the sodium salt of glutamic acid ($C_3H_8NNaO_4$, Sodium 2-aminopenta nedioate) is one of the flavour enhancers most frequently used in heterogeneous group of foods as food additive either in the form of hydrolysed protein or as purified monosodium salt.[2] It is an odourless white crystalline solid, usually available in form of a monohydrate. It has high water solubility and also has a high melting point which keeps it stable during normal food processing. It is, however, produced commercially by the fermentation of molasses where bacteria release glutamic acid as a by-product, and finally converting to its sodium salt.

Glutamate, one of the most abundantly found natural amino acids, is also produced in our body, and is the main component of many proteins and peptides.[3] L-Glutamic acid was discovered and identified in 1866 by the German chemist Karl Heinrich Ritthausen.[4] Later, Kikunae Ikeda isolated glutamic acid as a taste substance in 1908 from

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the seaweed *Laminaria japonica,* calling its taste "Umami", (means "savoury"), a unique taste (not yet scientifically described) which falls outside the four classic tastes (sweet, salty, sour and bitter).[5] Ikeda named his product as 'monosodium glutamate' (MSG), and submitted a patent to produce MSG. The Suzuki brothers began commercial production of MSG in 1909 as Aji-no-moto (means "essence of taste"), the world's first umami seasoning[4]. China is one of the top producer, consumer and exporter of MSG worldwide.

Adverse Health Effects

The adverse health effects produced by eating food, especially Chinese food heavily seasoned with MSG, have been collectively referred as 'Chinese Restaurant Syndrome' (CRS). It commonly characterized by headache, flushing, sweating, numbness / burning sensation in mouth and throat, nausea and fatigue.[6] The symptoms developed after eating MSG include abdominal discomfort, urticaria (skin rashes), ventricular arrhythmia (abnormal heart rhythms in ventricles), asthma, neuropathy (dysfunction of peripheral nerves causing numbness and weakness), and atopic dermatitis (inflammation of skin resulting in itchy, redness, swollen and cracked skin). Although these symptoms are reported to vary depending on the concentration and duration of exposure but prolonged use of MSG has been linked to several pathological conditions[7] which include several metabolic disorders such as dyslipidemia[8], cardiovascular disease[9], respiratory problems[10] and even neuro-endocrine defects including Alzheimer's disease[11] and Parkinson's disease.[12]

MSG also causes reproductive system damages resulting from diminished testosterone levels.[13,14] Further, MSG causes elevation in the marker enzymes for liver damage[15], and also induces dermal allergic reactions such as dermatitis, itching, rashes, urticaria and cracked skin.[16] Moreover, numerous animal studies have indicated that MSG performs a potent role in inducing obesity in mice.[17-19] MSG users have increased weight as compared to non-user, which is a finding independent of physical activity and total energy intake.[20]

Genotoxicity Studies

Among the adverse effects of MSG, genotoxicity is of particular concern. 'Genotoxicity' refers to ability of a substance to cause adverse effects to the genetic components of the cell (DNA/Chromosomes). The genotoxic agents induce damage to the nuclear components by multiple pathways which direct attacking directly on nucleus and / or indirectly by producing chemical metabolites that have affinity to DNA or by increasing the production of free radicals.[21] The changes on the genetic set-up, if not corrected, may lead to several health ailments which particularly include neurological disorders, metabolic diseases and even cancer.[22] The study to determine the genotoxic potential of the compound, therefore, assumes its importance since the defects not only occur in the present generation but also can be inherited to the future generation as well.[23]

A number of in vivo and in vitro studies have already been carried out to assess the cytotoxic and genotoxic effects of MSG which have reported that MSG exposure can induce marked damages in the nuclear components of the cells, leading to genotoxicity.[24-26]

1. Studies on Plant systems

a) Using *Alium cepa* root tip cells

Application of *A. cepa* assay is considered as one of the most efficient and cost-effective approaches to explore the genotoxic potential of a chemical substance because of its high degree of sensitivity as well as good correlation with the results in mammalian test system.[27]

Khatab and Elhaddad (2015)[28] have found that MSG at its selected concentrations (1, 3, 5 and 7g/l) is capable of inducing chromosomal aberrations (bridges, fragments, stickiness and other morphological abnormalities) and mitodepression in the treated root tip cells of *Allium cepa*.

The cytogenotoxic effects of MSG were, however, found to be annulled by the extracts from two medical plant species, *Origanium majorana L. and Ruta chalepensis,* restore the mitotic index and reduce the chromosomal aberrations.

Prasath *et al.* (2013)[29] have also reported the cytogenetic toxicity of MSG when roots of *A. Cepa* were grown at its exposure level of 50, 100 and 500mg/l inducing chromosomal aberrations. Similar findings have also been observed by Renjana *et al.* (2013)[30] using *A. cepa* assay where the percentage of aberrations induced by MSG was found to increase in a dose and time dependent manner. In another study, the effects of different flavour enhancers (monosodium glutamate, monopotassium glutamate, calcium glutamate, monoammonium glutamate and magnesium diglutamate) on *A. cepa* were investigated. These chemicals were found to increase the frequency of chromosome aberrations with subsequent decrease in mitotic index of cells.[31]

MSG mediated similar cytotoxic and genotoxic effects on the root tip cells of *A. cepa* have further been shown by Adeyemo and Farinmade (2013)[32] when grown at its different concentrations (1,3,5 and 7 g/l). Stickiness of chromosomes at telophase was most common aberration in all the test concentrations.

One more investigation on onion root tip cells with MSG also suggested significant induction of chromosomal damage and reduction in mitotic index.[33] This result therefore indicated that MSG has the potential to induce both genotoxicity as well as cytotoxicity in *Allium cepa.*[28,33,34]

b) In *Vicia faba* seedlings

Several data have showed that exposure to MSG in the seedlings of *Vicia faba* inhibited the cell division with reduction in mitotic index, and also produced an increase in the genomic template stability tested by using RAPD-PCR.[32] The analysis therefore indicates that MSG has significant genotoxic potential, causing damage/alterations in DNA.

2. Studies on *Drosophila*

The study on the *Drosophila melanogaster* indicated that MSG exposure could produce changes in the wing development due to changes in the integrity of chromosome and transcription of genes, suggesting that MSG can induce mutations which alter phenotypes in *Drosophila.*[35] Moreover, MSG can inhibit the formation of spindle fibres which interferes with the separation of chromosomes at anaphase.[36]

The nuclear fragments (micronuclei) were observed by *in vivo* micronucleus test which suggests the induction of direct nuclear damage by MSG.[37] The comet assay further exhibits the extent of damage in the DNA upon exposure to MSG where formation of an extended tail is an indicative of severity of DNA damage.[38] Additionally, an increase in the DNA tail length (TL), DNA tail intensity (TI) and DNA tail moment (TM) have been observed upon exposure to MSG.[39] MSG also reported to increase the DNA breaks, making the super-coiled loops of DNA to relax more and cause large fraction of DNA to move.[40]

3. Studies in Mammalian system

a) On Rat

Farombi and Onyema (2006)[35] have observed that MSG treatment in rats significantly induced micronucleus formation in the polychromatic erythrocytes. They further exhibited that co-treatment with antioxidants (vitamin C, E and quercetin) inhibited the MSG induced formation of micronucleated polychromatic erythrocytes, suggesting the role of oxidative stress in MSG mediated genetic toxicity. Ismail (2012)[41], using the comet assay, reports that MSG is capable of inducing DNA damage in rat testis. El-makawy *et al.* (2016)[39] have further reported that genotoxicity could be mediated through the expression of DNA damage marker gene, gadd45b.

b) On human lymphocyte

Exposure to MSG in human lymphocytes causes structural aberrations in chromosomes (breaks, exchanges, fragments, unions and even formation of dicentric chromosome) as well as numerical anomalies (polyploidy and endoreduplication).[42-45]

MSG has also been found to increase MN formation in human lymphocytes.[46-48] RAPD-PCR test further exhibits both increase and decrease in band intensity as well as gain or loss of bands, the molecular biomarker of induced alterations. Comet assay also revealed occurrence of significant DNA damage, thus indicating that MSG might possess the genotoxic potential in the isolated human peripheral lymphocytes also.[49]

CONCLUSION

MSG, one of the most intensely studied food ingredients, is extensively used as a flavour enhancer in many food items including those from food industry and common household. No doubt, it is wonderful in taste and induces urge to eat more food but its regular intake for a longer period of time may be injurious, leading to a number of adverse effects cumulatively known as Chinese Restaurant Syndrome. Moreover, MSG not only has the potential to induce the nuclear damages in the cells but also inhibits formation of spindle fibres and anaphase separation of chromosomes/chromatids. Further, alterations in the levels of proteins encoded by of Bcl 2 and Bax proteins followed by increase in the expression of gadd45, NF-kB, TNF-α and p53 genes have also been found linked to the genotoxic effects of MSG[50]. In this study, male adult rats daily fed with MSG (8,600 and 1600 mg/kg bw) revealed the induction of genotoxic stress through exponential increase in Bax protein accompanied with decrease in Bcl_2 protein in the liver. The comet assay also revealed the occurrence of dose dependent increase in the tail length, tail intensity and tail movement of cells. The results further showed the increase in the expression

of DNA damage marker gene, gadd45b, in the liver of rats. This up-regulatory effect of MSG on the gadd45b gene expression might have been achieved via TNFα-NF-kB path way[51] where NF-kB binds to the promoter of gadd45b which, in turn, activates its transcription[52].

The studies reporting adverse effect of MSG, however, appear to have limited relevance because of methodological flaws as these are based on excessive dosing that does not meet with the level normally consumed by humans through food products. Hence, these results cannot be extrapolated to dietary human intake of MSG for risk assessment. The Joint Expert Committee on Food Additives of the United Nations Food and Agriculture Organisation and World Health Organization placed it in the safe category of food additives but the Food and Drug Administration (FDA) declared it safe for limited usage and enlist several potential side-effects linked to increased MSG consumption. FDA concluded that MSG is safe when 'taken at customary levels'. Therefore, more detailed and intense research is further needed to explore the genotoxic potential of MSG at its appropriate exposure levels using a suitable test system.

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