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TOXIC EFFECTS OF MONOSODIUM GLUTAMATE ON HUMAN: A REVIEW

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Abstract

Monosodium glutamate is one food enhancer which enhance flavor, originally used for meat and savory dishes, however these days it's used in a wide array of foods or 'food like' products. Its toxic effects have been shown in numerous animal studies, however in most of them, the method of administration and the doses were not similar to human MSG intake, in this paper the review is highly focused on the side effects of MSG which affect CNS, causes abnormalities in liver, gastric problem, obesity, increased ROS in cell and effects on reproductive organs were discussed.

Introduction

In 1908, in Japan, Kikunae Ikeda invented the food ingredient, "mono-sodium glutamate" who identified the natural flavor, enhancing substance of seaweed, however, today's MSG is completely man made and there is nothing natural about it. About one year later, with a partner, he formed a company, Ajinomoto, to produce the product. Mono-sodium glutamate did not appear in the United States to any degree until the late 1940s, following the Second World War. During the war, it had been noted that Japanese soldiers' rations tasted better than the rations used by our soldiers. The difference was believed to be "mono-sodium glutamate." Today, "mono-sodium glutamate" or its reactive component, "processed free glutamate acid," is found in almost all the processed foods that are manufactured in the United States [1]. Monosodium Glutamate (MSG) is one of the world's most extensively used food additives which is ingested as part of commercially processed foods. As a flavor enhancer, MSG increases the sapidity of food. MSG produces a flavor that cannot be provided by other foods. It elicits a taste described in Japanese as umami, which is translated to ''savory'' (Birks 2005). Monosodium glutamate (MSG) was discovered in the early 19th century in Japan

and is extensively used in Chinese, Japanese and Thai cuisine. This compound is widely used all over the world as a flavor enhancer in food and spices. MSG was located by biochemist Kikunae Ikeda (Japanese biochemist), and later perfected in many laboratories. In 1968, the New England Journal of Medicine, asked for help in determining why he and his friends suffered reactions shortly after eating in some Chinese restaurants, though he never experienced such reactions when he lived in China. The journal titled the letter "Chinese Restaurant Syndrome," and researchers from around the country wrote the journal to suggest that Dr. Kwok and his friends' problem was intolerance to MSG. One letter indicated that 30% of the population reacted to MSG [2]. In 1991, the average intake of MSG in United Kingdom was 580 mg/day for general population individual and 4.68 g/day for extreme users (3). The estimated average daily MSG intake per person in industrialized countries is 0.3–1.0 g, but it depends on the MSG content in foods and an individual's taste preferences (4). In the past, MSG was extracted from foods rich in protein such as algae. Currently, MSG is produced by an industrial fermentation process. It is a flavor enhancer that we find in the enamel, most of the Asian dishes, sauces, soups, spices, etc. In fact, MSG is a brain stimulating neurotransmitter that stimulates appetite and, in large quantities, can cause symptoms that vary according to the ingested dose and the sensitivity of the individual: from a simple discomfort (generally 1-2 days after ingestion) to syncope (sudden, temporary or definitive cessation of heart function, breathing disruption and loss of sensitivity and voluntary movements). It can also pose problems for people suffering from asthma (5). studies providing the evidence of MSG toxic effects have raised the increasing interest in MSG intake as flavor enhancer. Neurotoxic effects in brain, obesity and metabolic defects, Chinese restaurant syndrome" and detrimental effects on sex organs are the most discussed in the connection with MSG intake. We briefly review the studies about MSG effects and its potential pathological influence on different systems in humans.

Central Nervous System

Glutamate is the excitatory neurotransmitter in the mammalian central nervous system (CNS) playing an important role in both physiological and pathological processes (6). Glutamate receptors include three families of ionotropic receptors (NMDA - N-methyl-D-aspartate, AMPA - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and kainate) and three

groups of metabotropic receptors (mGluR) (Meldrum 2000). They are dispersed throughout the central nervous system including amygdala, hippocampus and hypothalamus where they regulate many vital metabolic and autonomic functions (Collison et al. 2012). MSG is used as an agent which in high doses causes neuronal necrosis in hypothalamic arcuate nuclei in neonatal rats (7). However, MSG effects are more extensive and not limited to hypothalamic area. MSG (4 mg/g, subcutaneously, on postnatal days 1, 3, 5 and 7) led to prefrontal cerebral cortex changes, including fewer neurons, shorter and less ramified dendritic processes (8) and loss of cortical cell number from postnatal day 8-14 compared to control rats (9). The same dose of MSG injected subcutaneouslyon days 2, 4, 6, 8, and 10 of postnatal life resulted in 30% and 40% reduction of pituitary weight in ages of 6 and 12 months respectively (10). Pituitary weight affection seems to be connected with its function derangement. Increased proopiomelanocortin mRNA levels and adrenocorticotropic hormone concentration in the adenopituitary have been found in neonatal MSG-treated rats compared with controls (4 mg/g, 5 administrations intraperitoneally) (11). Furthermore, numerous studies have shown that neonates treated with MSG exhibited neuronal cell death with reduction of photoreceptor and glial cells (12). Although the toxic effects of MSG on the CNS have been shown in previously mentioned animal studies, there are problems to apply these results` to human MSG intake. Subcutaneous or intraperitoneal MSG administration in rats can be hardly compared with peroral intake of MSG. FAO/WHO Expert Committee on Food Additives (JECFA) in 1988 noted that blood levels of glutamate associated with lesions of the hypothalamus in the neonatal mouse were not approached in humans even after bolus doses of 10 g MSG in drinking water (13). No pathological changes in the hypothalamic arcuate nuclei of pregnant and lactating female rats and their fetuses, sucklings, and weanling mice were observed after MSG intake in diet (14.0, 42.8 or 42.0 g/kg) (14). This can be explained by the results of the study in pigs which has shown that less than 5% of ingested glutamate was absorbed from the gut into the portal blood (15). However, contradictory results in different brain areas have been found in male albino rats fed by a lower dose of MSG (3 g/kg/day) mixed with their foods for 14 days. Histological examination of cerebellar cortex showed degenerative changes as pyknotic Purkinje and granule cells with areas of degeneration surrounded by inflammatory cells in granular layer (16). Inconsistency in above mentioned results requires further research to

elucidate the mechanisms of MSG action in the CNS after absorption in humans. Moreover, the ingested glutamate effects on CNS must be researched also in its connection with signalling from the gastrointestinal tract. In rats, activation of both the gastric and the celiac branches of the vagus nerve led to the activation of the insular cortex, limbic system, hypothalamus and nucleus tractus solitaries. Furthermore, as a result of postingestive effects, MSG was able to induce flavor-preference learning (17).

Obesity and Metabolic Disturbances

Data from animal studies, in which neonatal administration of MSG provides a model of obesity with impaired glucose tolerance and insulin resistance led to concerns about obesity in humans using MSG in food. More hypotheses have proposed the mechanisms of MSG influence on metabolism. The potential link between MSG and obesity includes the MSG effect on energy balance by increasing palatability of food and by disrupting the hypothalamic signaling cascade of leptin action (18). The inflammatory basis of MSG-induced obesity was demonstrated in the 19^{th} weeks old rats which were treated by subcutaneous injections of 2 mg/g of MSG on postnatal days 2 and 4 and by subcutaneous injections of 4 mg/g on postnatal days 6, 8 and 10. MSG increased mRNA expression of interleukin-6, tumor necrosis factor-alpha, resistin and leptin in visceral adipose tissue, it increased insulin, resistin and leptin levels in serum and it also impaired glucose tolerance (19). As liver transaminases were severely depressed, authors hypothesized that MSG could induce liver injury likely as a consequence of incipient nonalcoholic steatohepatitis, contributing to inflammation (20). The associations of liver alterations with adipose tissue metabolism in nonalcoholic steatohepatitis after dietary MSG have been also shown at 32 weeks of age C57BL/6J mice which mothers were fed by low-dose dietary monosodium glutamate (0.64 g/l; 97 mg/kg) throughout gestation and were weaned onto the same diet. MSG increased the expression of several genes implicated in adipocytes differentiation, elevated serum free fatty acids, triglycerides, insulin and bile synthesis (21).

Chinese Restaurant Syndrome

The Chinese restaurant syndrome "(CRS) was for the first time described more than 40 years ago. The original description of symptoms having their onset about 20 minutes after

starting the meal included numbness or burning at the back of the neck, radiating into both arms and sometimes into the anterior thorax, which was associated with a feeling of general weakness and palpitation ('Chinese restaurant syndrome' 1968). The symptoms of flushing, dizziness, syncope, and facial pressure were described later (22). Monosodium glutamate was widely believed to be associated with CRS, however reviews of relevant studies have proposed that the studies which associated MSG with CRS did not have the robust experimental design, results were inconsistent and the frequency of responses to MSG intake was not high enough to bring evidence that MSG is the trigger of CRS (23). Thus there appears to be little reason to embark on an extensive workup and treatment regimen with a presumptive diagnosis of MSG intoxication (24). Headaches or other symptoms after Chinese food intake could be rather associated with exceptionally high concentrations of fat and sodium typical for Chinese restaurant meals (25). After 40 years of research we can conclude that the symptoms of CRS have not been proved to be associated with MSG compound in Chinese food and the prevalence of the typical symptoms is very low. In a questionnaire survey in 1979 including 3222 respondents only 1-2% reported symptoms characteristic for CRS and only 0.19% associated the characteristic symptoms with consumption of Chinese food (26)

Reproductive Organs

The effects of MSG on the reproductive system are documented in a smaller number than the effects previously mentioned and to our best knowledge they are limited only to animal studies. In male Swiss Albino mice subcutaneous administration of MSG at a dose of 2 mg/g during the perinatal period at the 2nd, 4th, 6th, 8th and 10th days of life lead to the increase in the number of the pachytene stage of primary spermatocyte at the 75th day of life compared to controls (27). The double dose (4 mg/g) of MSG administered at the same time to newborn rats resulted in the decreased weight of pituitary glands and testes and lowered testosterone level in 4 months oldsexually mature male rats (28). In female Swiss Albino mice, subcutaneous injection of MSG (2 mg/g) at the same perinatal period (2nd, 4th, 6th, 8th and 10th day of life) led to increased number of the primary follicles without any increase in number of Graffian follicles in ovarian tissue at the 75th day of life (29).

Monosodium glutamate excitotoxicity increase reactive oxygen species

Glutamate excitotoxicity increases superoxide through activation of the arachidonic acid pathways and increase NO production through activation of nNOS enzyme. Mitochondria play a pivotal role in ROS production during glutamate excitotoxicity. Mitochondria are not only ATP producers through oxidative phosphorylation but also are regulators of intracellular Ca2+homeostasis (30). After intracellular Ca2+overload induced by glutamate excitotoxicity, mitochondria attempt to buffer the Ca2+concentration in the cytosol by uptake Ca2+through the mitochondrial Ca2+uniporter (31). This process maintains the cytosolic Ca2+ concentrations temporarily. Entry of high amount of Ca2+into the mitochondria attenuates the mitochondrial membrane potential, leading to the opening of mitochondrial permeability transition pores which release cytochrome c that induce apoptosis. Mitochondrial Ca2+ overload increases ROS production (32) and impairs the mitochondrial antioxidant roles with reduction in ATP synthesis which makes the cell more vulnerable to death insults (33).

Conclusions

Monosodium glutamate (MSG) is one of the world's most widely used food additives which enhances the flavor of food. MSG toxic effects on central nervous system, adipose tissue, hepatic tissue and reproductive organs were shown in numerous animal studies, however the method of administration and the used doses in most of them were not comparable with human MSG intake MSG intake in human studies was associated with increased levels of several circulating amino acids, however no changes in the postprandial glucose and insulin were found, which was in contradiction to animal studies` results, Chinese restaurant syndrome and asthma were not proved to be associated with MSG intake. Vitamin C, vitamin E, quercetin and diltiazem had protective effects on MSG-induced toxic changes.

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