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Manish Mohan M
Assistant Professor, Department of Pharmacology, Sree Gokulam Medical College & Research Foundation Venjaramoodu, Trivandrum, Kerala, India

Nirmal George
Professor, Department of Pharmacology, Sree Gokulam Medical College & Research Foundation Venjaramoodu, Trivandrum, Kerala, India

Ivy Abraham Varghese
Assistant Professor, Department of Pharmacology, Sree Gokulam Medical College & Research Foundation Venjaramoodu, Trivandrum, Kerala, India

Shobha P
Professor, Department of Pharmacology, Sree Gokulam Medical College & Research Foundation Venjaramoodu, Trivandrum, Kerala, India

Ramani PT
Professor, Department of Pharmacology, Sree Gokulam Medical College & Research Foundation Venjaramoodu, Trivandrum, Kerala, India

Corresponding Author:
Manish Mohan M
Assistant Professor, Department of Pharmacology, Sree Gokulam Medical College & Research Foundation Venjaramoodu, Trivandrum, Kerala, India

MSG unveiled: exploring preclinical and clinical findings: A literature review

Manish Mohan M, Nirmal George, Ivy Abraham Varghese, Shobha P, and Ramani PT

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Abstract
Monosodium glutamate (MSG), commonly known as China salt, is a flavor enhancer used to produce the pleasant taste sensation known as umami when added to food. Due to urbanisation, fast-food culture, and the lack of stringent government regulations, the use of MSG has increased among people of all socioeconomic statuses, with an average daily human consumption of 0.3-1 gram. The toxic effects of MSG have been demonstrated in both humans and animals, yet there is still debate regarding its safety when used in food.

Keywords: Monosodium glutamate, Chinese restaurant syndrome, metabolic syndromes, food ingredients

Introduction
Monosodium glutamate (MSG), commonly known as china salt, is one of the most widely used flavour enhancers all around the globe [1]. It is derived from L-glutamic acid, a naturally occurring amino acid in a wide variety of food products. MSG is present in a variety of foods either as a flavour enhancer or as a goof additive in the form of hydrolysed protein or used as purified monosodium salt [2]. MSG was discovered in Japan from a seaweed in 1908. During that period, glutamic acid and MSG were obtained through extraction, which was a costly and slower process [3]. Over the years, the use of MSG increased with its availability in various foods in several grocery stores and markets. Urbanisation, fast food culture and the absence of stringent regulations by the Government have increased the use of MSG by the population of all socioeconomic strata alike [2]. MSG produces a unique aroma in processed foods that is widely identified in Japanese as "umami". Apart from its flavour and promoting ability, MSG is linked to different types of toxicity; some of these are metabolic disorders, obesity, and detrimental and neurotoxic effects on the reproduction system.
MSG forms part of commercially processed foods' most widely used food flavour. As an additive enhancer, MSG releases a flavour that is never offered by other foods [3]. In 1992, the average consumption of MSG in the United Kingdom's general population was 580 mg/day and 4.68 g/day for the UK's extreme consumers. A joint inquiry by the Government of Australia and New Zealand showed that a typical 100 g Chinese restaurant meal contains 10-1500 mg MSG [4]. The expected daily average MSG consumption per individual in industrialised nations is between 0.3 to 1.0 gm; however, this could be influenced by the MSG composition in such foods and individual preference.

History of Monosodium glutamate
The history of Monosodium Glutamate dates back to over 100 years. The Umami flavour-producing MSG was discovered by Kikunae Ikeda, a Japanese chemist who derived the flavour from seaweed [1]. The chemist made a discovery that MSG had particular flavour-promoting properties [5]. Ikeda discovered that glutamate is the reason behind this "savoury" taste, and he named this unique taste sensation "Umami". But Kikunae was unaware that this intervention would lead to one of the world's longest-lasting food controversies. After that, all around the globe, MSG became an unavoidable part of food, especially in canned and frozen foods.

The negative reputation of MSG started back in the 1960s. During these periods, The New England Journal of Medicine published a publication from Robert Ho Man Kwok, a Maryland doctor. The doctor had mentioned his experience with symptoms such as headaches and flushes associated with allergic reactions after each moment he consumed food bought from a Chinese restaurant [6]. So, this prompted him to question the cause. Was the cause of the responses he felt is because of the wine he drank, or the spices used to prepare the food or the MSG? His address, collection of symptoms known as "Chinese Restaurant Syndrome," triggered several individuals to write about their experience in the journal about experiencing symptoms such as flushes or having headaches following consumption of Chinese food [7].

In 1969, an experiment was carried out by John Olney, a neuroscientist, with the injection of the MSG directly into a white mouse [8]. The obtained results from the tests revealed that MSG could result in numerous neurological complications in the subject. MSG produced brain lesions and impaired brain development in the mice in that study. However, successive laboratory tests have undone the unwanted perception of MSG. The FDA recognises MSG as generally safe. The agency states that despite several individuals acknowledging that they are susceptible to MSG, the agency's research on such people has not consistently activated reactions [9]. Still, MSG continued to be in use all over the globe despite its popularity that waned between the 1960s and 70s. Currently, MSG is available worldwide and has different consistencies in various countries. Despite its popularity and the carrying nature of its applications, MSG is still in the market and used because several people recognise its flavouring capabilities.

Chemistry of MSG

The chemical formula of MSG is C5H8NO4. Na. Pure MSG exists as a white, odourless, water-soluble powder. This compound has a molecular weight of 169.11 g/mol and a melting point of 232 °C. The PH value of MSG solution ranges from 6.7 to 7.2. It is highly soluble in water. Once MSG dissolves in the water, it generates free glutamate and sodium within the body. MSG doesn't require any enzyme to break it into active components. So, after ingestion, MSG detaches in aqueous solutions, producing the glutamate anion and an equivalent cation, for instance, Na+.

Consequently, there is no variation between the glutamate added as MSG and that which is present naturally in foods. Cations such as Mg2+, Na+, and K+ play a crucial role in enhancing the umami taste. Chemical modifications such as esterification and amide formation diminish the Umami taste[1].

Glutamic acid occurs naturally in the body and several foods. MSG is chemically differentiated from glutamate, which exists in food proteins [10]. Glutamic acid is obtained from 2-oxoglutaric acid and glutamine through glutamate synthase. The α-amino groups of glutamic acid are reassigned to other amino groups in the aminotransferase process.

Additionally, the glutamic acid carbon skeleton is the centre of arginine, γ-aminobutyric acid, and proline creation. Glutamate dehydrogenase deaminates glutamic acid, consequently resulting in 2-oxoglutaric acid and ammonia.

Sources of MSG, Natural sources of glutamate

MSG is the sodium salt that forms part of the common amino acid glutamic acid. Glutamic acid naturally occurs in the body and several food additives and foods. These foods where glutamate is available typically include examples like cheese, kelp and tomatoes [11]. Worldwide, people have consumed foods rich in glutamate. An example of such food is the authentic historical dish within the Asian community known as the "glutamate-rich seaweed broth". The initial extraction of MSG from seaweed broth was accomplished in 1908 [12]. But nowadays, instead of removing and crystallising MSG directly from seaweed broth, the flavour is produced through a fermentation process of sugar cane, starch, sugar beets, or molasses. The fermentation method resembles that applied in manufacturing vinegar, yoghurt, and wine.

Glutamate is naturally synthesised in the body and combines with other amino acids to make several structural proteins. When glutamate binds to protein molecules, it is tasteless and never produces the umami taste. However, free glutamate is ejected in the hydrolysis of proteins during fermentation, ripening, heat cooking, and ageing processes [13]. The umami taste components are also plentiful in several other foods. These include vegetables (potatoes, mushrooms, tomatoes, carrots, soybeans, Chinese cabbage, green tea), seafood, meat, and cheese. So, this contributes to the distinct tastes of these classes of foods. Subsequently, the substances linked to the umami flavour are essential in producing a distinctive taste in several natural foods.

Pharmacokinetics

After ingestion, MSG is absorbed into the body very quickly, which will spike the plasma level of glutamate. The pharmacokinetic feature of glutamate depends upon the form of glutamate, whether it is unrestricted or inbound. Inside the body, MSG dissociates into sodium ions and glutamate. MSG doesn't require any enzymes for its breakdown [14]. After its breakdown, glutamate transports across the intestinal lumen via the receptors called sodium carboxylate transporter and excitatory amino acid transporter [15]. Nearly all glutamate is metabolised in the intestinal lumen itself. The central part of its cytoskeleton will produce glutathione, alanine, arginine, lactate, etc. or may be converted to carbon dioxide. The nitrogen part in its structure produces amino acids such as proline, glutamine and branched-chain amino acids. Only the remaining little part will be absorbed in the portal vein [16]. In a previous study conducted in young volunteers, peak glutamate level was attained within 80 minutes devoid of any side effects, after administering MSG at a dose of 30 mg/kg every 20 minutes for a total duration of 220 minutes [17].

Receptors of Glutamate in the Human Body

The glutamate receptors are abundant in number and too complicated. More than twenty glutamate receptors are recognised within the mammalian central nervous system. These receptors are classified into two major classes. These are the voltage-sensitive (ionotropic) and ligand-sensitive (metabotropic) receptors [18]. Every type has numerous sub-types. The ionotropic receptors are quick-acting, and once these receptors open, they cause significant variations in the flow of current, even if the difference in voltage across the membranes is negligible. After the glutamate binding, acting as a ligand, it combines with the ionotropic receptor. After

the bond formation, the receptor's channel undertakes a conformational modification that permits an instantaneous entry of extracellular sodium into the cells and an outflow of potassium ions [19]. This produces depolarisation of the postsynaptic cell membrane enough to trigger the transmission of the signal. A central glutamate ionotropic receptor, N-methyl D-aspartate (NMDA), is highly receptive to calcium ions. Apart from the potassium and sodium ions, the calcium ions have desirable and undesirable impacts. The NMDA receptor is rare; it is considered as a coincidence detector, that is, for the channel to open, there must be a bond between the glutamate and the receptor. Consequently, the postsynaptic cells must undergo depolarisation since, at psychosomatic levels, the channel is inhibited by magnesium; hence, it only opens when depolarised.

The ionotropic receptor channels are developed through assemblies of homotetrameric or heterotetrameric sub-units of proteins. The three families of ionotropic receptors with intrinsic ligand permeable channels are Kainate, NMDA and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) [20]. After discovering these ligands, several others, whether antagonists or agonists, were successively found. Despite the variations in their properties and anatomical composition, glutamate receptors are identified for their intercessory glutamate responsibility in memory and learning processes through the modification or plasticity of the channel components. Also, these receptors promoted gene expression and glutamate neurotransmission. The NMDA receptors are significantly expressed in the astrocytes and neurons [21]. The expansive capability of the human brain for learning, memory, recovery from damage, and plasticity is linked to the enhancements of signalling of the synaptic physiology and anatomy of NMDA [22]. This mainly occurs in the hippocampus and several sections of the mammalian CNS. The primary mechanism essential for the plasticity entails the neurogenesis, pruning of synapses, and activity-reliant improvement of the synaptic strength.

Metabolism of Glutamate in the Human Body

Glutamate is the non-essential amino acid synthesised in the human body through different metabolic pathways. The metabolism of glutamate plays a crucial function in the biosynthesis of the proteins and nucleic acids [23]. This metabolism is linked to several diverse stress reactions. As an excitatory transmitter, glutamate functions as a product and substrate in several responses. The deficiency of enzymes involved in glutamate metabolism is linked to disorders such as hyperammonemia, gyrate atrophy, γ-hydroxybutyric aciduria, hemolytic anaemia, and 5-oxoprolinuria.

The metabolism of Glutamate entails numerous irreversible and reversible reactions. Specific enzymes regulate these reactions. Inhibitors and activators control the availability of these enzymes. For example, during the metabolism that converts L-glutamate to N-acetyl-L-glutamate, the N-acetyl glutamate synthase (NAGS) enzyme is activated by L-arginine [24]. At the same time, the enzyme's function is inhibited by N-acetyl-L-aspartate, succinate, N-acetyl-L-glutamate, and coenzyme A. Similarly, the conversion of glutamine into glutamate is catalysed by several proteins [25]. These include glutaminase (GLS/GLS2), glutamine-fructose-6-phosphate transaminase (GFPT1 and GFPT2), and phosphoribosyl pyrophosphate amidotransferase (PPAT). The GLS/GLS2 undergoes regulations by ammonia and inorganic phosphate as kinase proteins control the PPAT. In addition to glutamate taking part in the metabolic pathways, it regulates several neural signal pathways. This regulation is achieved through the contact ionotropic glutamate receptors like NMDA and AMPA.

Glutamate is a vital metabolic energy producer that assists highly proliferating cells in achieving the high demand for ATP, reducing agents, and biosynthetic precursors. Glutamine gains entry into the body in the form of amino acids. The glutamine then transforms into glutamate, a process in the mitochondria assisted by the deamination reaction [26]. This reaction undergoes catalysis by GLS (glutaminase). Consequently, glutamine is converted into TCA cycle transitional α-ketoglutarate (α-KG). This process is aided by alanine, glutamate dehydrogenase (GDH), or aspartate transaminases (TAs). What follows is the production of conforming amino acid and α-KG. The latter is a crucial metabolite that significantly reloads the ATP cycle intermediates and produces ATP. This process is known as anaplerosis [27]. Whenever the mitochondrial of hypoxia is dysfunctional, α-KG is transformed into citrate in a carboxylation reduction reaction process catalysed by IDH2 (Isocitrate dehydrogenase 2). This citrate is then ejected from the mitochondria to synthesise amino and fatty acids, releasing a reducing agent, cataplerosis (NADPH). Within the cytosol, glutamine releases its amide nitrogen to aid in synthesising hexosamines and nucleotides to form glutamate. The cytosolic glutamate produces glutathione, vital in sustaining redox homeostasis and guarding the cells against oxidative tension.

The safety profile of Monosodium glutamate

The daily food intake of glutamate from proteins is between 10 and 20 g, while the added MSG flavour ranges between 05 and 3.0 g [28]. Only about 5% of the orally consumed glutamate undergoes absorption into the body into the systemic circulation. The more substantial portion is utilised as an oxidative substrate in the intestinal mucosa. The plasma glutamate level hence does not increase whenever glutamate is ingested in the diet in the form of glutamate in the nutrition or as free glutamate found in the MSG. The average intake of MSG per day is estimated to be 0.3-1.0 g [29]. The Food and Drug Administration(US), the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and the European Food Safety Association considered this MSG to be a substance generally recognised as safe (GRAS) [30]. According to the WHO, the nutritional consumption of glutamate is not hazardous to health [31]. Both clinical and preclinical studies revealed the toxic effects of MSG

Experimental studies have proved that MSG is toxic for both humans and experimental animals [32]. Various adverse effects were reported in the metabolic/digestive, respiratory, cardiovascular, and nervous systems, among other systems [33].

Preclinical studies associated with MSG

1) MSG exposure with cardiac toxicity

Studies found that MSG intake increases oxidative stress within the cardiac tissue and elevates some cardiac disease biomarkers, such as lactate dehydrogenase, aspartate transaminase, and alanine transaminase [34, 30]. Another experiment in myocardial infarcted rats showed that MSG at a dose between 0.5 g/kg and 1.5 g/kg induced lethal

tachyarrhythmias by hindering AMPA receptors [35]. In another study, subcutaneous administration of MSG at a dose of 4 mg/g and 8 mg/g for six days suggested the development of MSG-induced dose-dependent oxidative stress. This study showed a significant rise in lipid peroxidation and xanthine oxidase level and a substantial reduction in superoxide dismutase and catalase activities in cardiac tissue [36]. In another survey of newborn Wistar rats, subcutaneous administration of MSG at a dose of 4 g/kg for seven days resulted in a significant increase in total cholesterol level, triglycerides level and a decrease in HDL-cholesterol level [34]. In a study conducted by Baky *et al*. intraperitoneal administration of MSG in albino rats at a dose of 4 g/kg for nine days (three times/week, for three consecutive weeks) showed a significant increase in thiobarbituric acid-reactive substances level and decreases in L-ascorbic acid, glutathione, superoxide dismutase, catalase in cardiac tissue. In addition to this, the histology of cardiac tissues reported necrotic lesions [37].

2) Metabolic syndromes

Diabetes is a vast field of research activities, and the injection of 2 mg/g of MSG in newborn mice produced glycosuria and diabetic symptoms by the end of 29 weeks [38]. In this study, the blood glucose, triglycerides, and cholesterol levels were higher in the MSG administered group than in the control group. Later, a similar study on rats confirmed that MSG is a potent chemical inducing diabetes mellitus [32]. Intraperitoneal MSG injected at a dose of 4 mg/kg for five days resulted in more betterment of obesity and triglyceride levels in Spontaneously Hypertensive Rats (SHR) when compared to Wistar Kyoto rats (WKY) rats [39]. Another experiment on adult Wistar rats showed that MSG intake could decrease beta-cell mass in the pancreas [40].

3) Hepatic complications

The liver is a significant organ that metabolises compounds that reach systemic circulation. Several studies reported that MSG could lead to hepatic complications. In a survey conducted by Onyema *et al*. on rats, MSG administered at a dose of 0.6 mg/g for ten days showed a significant increase in liver enzymes glutathione-s-transferase (GST), catalase, and superoxide oxidase and increased lipid peroxidation[41]. Another study on rats with MSG administered at a dose of 0.6 mg/g and 1.6 mg/g for two weeks showed elevated liver enzyme levels (Gamma-Glutamyl transferase {GGT} & Alanine Transaminase {ALT}). It decreased total protein, albumin, and globulin levels [32]. So, all these studies concluded that MSG intake might damage the antioxidant enzyme system and can alter the hepatic and renal functions of the body. Another study showed that subcutaneous administration of MSG (4 g/kg, Single-dose administration) within five days of their birth showed characteristic liver histopathology of nonalcoholic steatohepatitis (NASH) and metabolic syndrome-like feature [42]. In another study, MSG mixed with diet and orally given to Wistar rats at a dose of 0.04 mg/kg and 0.08 mg/kg for 42 days showed histological abnormalities such as dilatation of the central vein, cytoarchitectural distortions of the hepatocytes, and atrophic and degenerative changes on the liver [43]

4) Immune System Effects

The impact of MSG on the immune system was directly assessed in several preclinical experiments. A study conducted in neonatal rats, where MSG administration (4 mg/g, subcutaneous days 2, 4, 6, 8, and 10 of life) showed an increase in the levels of the interleukin (IL)-1β and IL-12, the IL-4, IL-10 with a lowering of IL-4, IL-10, and tumour growth factor (TGF)-β levels in the blood serum [44]. In another study using neonatal rats, second-day evaluation following MSG administration showed increased leptin, triglycerides, insulin and corticotropic-adrenal response (acute-phase response of inflammatory stress), along with impaired pro-inflammatory cytokine response. But the anti-inflammatory cytokine response remained normal [45]. A study by M Hriscu *et al*.. tested the effects of MSG on blood neutrophils phagocytic activity and phagocytic response in mice. The study showed a decline in the percentage of blood lymphocytes without influencing the regular phagocytic activity of the neutrophils [46]. In contrast, another study in neonatal rats using MSG (4 mg/g, subcutaneous, on day 4 of life) showed an elevation in the number of macrophages and their phagocytic activity as well [47].

A previous study showed that MSG administration in rats (4 mg/g, i.p., six consecutive days) influences thymocyte proliferation rate. The study concluded that MSG significantly modulates the thymocyte proliferation rate by regulating the apoptosis rate of the cells. MSG resulted in downregulating Bcl-2 protein, while Bax protein levels did not change considerably 48. Another study on rat thymus showed that MSG treatment could induce oxidative stress in thymus [49]. In another study using mice, MSG administration showed dysfunction of DTH (delayed-type hypersensitivity) effector T cells [50, 30]. A previous research study examined the effect on age-dependent natural killer (NK) cell cytotoxic (NKCC) activity after the destruction of the arcuate nucleus (AR) of the hypothalamus in newborn mice with MSG administration. This study observed a correlation between natural killer (NK) cell cytotoxicity depression and decreased numbers of large granular lymphocytes in the MSG treated mice [51]

5) CNS functions and morphology

Glutamate is a major excitatory neurotransmitter in the central nervous system (CNS). So in excess amounts, it can lead to excitotoxicity, and it is associated with chronic neurogenerative diseases such as Parkinson's disease, amyotrophic lateral sclerosis, etc. [52]. Lucas and Newhouse observed degeneration of the retina in infant mice following the subcutaneous injection of the MSG [53]. While working on intracranial lesions associated with subcutaneous glutamate injections in mice, Olney JW coined the term "Glutamate Excitotoxicity" [54]. Studies also reported that MSG intake would produce free radicals, activation of enzymes (proteases, phospholipases, endonucleases), gene toxicity and apoptotic changes in mouse and rat [55, 56]. These studies also proved that reacted oxygen species are the ones that are causing genotoxicity.

In a study by Sadek *et al*., subcutaneous administration of MSG on male Wistar rats at a dose of 5 mg/kg stated that MSG produced an increase in the levels of brain and serum cholinesterase, creatine phosphokinase and lactate dehydrogenase and indicated that it could lead to upregulation of pro-apoptotic Bax in neuronal cells. The study concluded that lycopene is effective in relieving the harmful reactions of MSG by decreasing lipid peroxidation and inducing modifications in the activity of cholinesterase and antioxidant pathways. The study results also showed that lycopene protects brain tissue by inhibiting apoptosis

signalling induced by MSG [57]. Intraperitoneal MSG at 2 g/kg for seven days in albino rats produced behavioural and physiological alterations such as precipitation of aggressiveness, decreased locomotor activity and loss of muscle strength. Histopathology showed a loss of neurons in the hippocampal region [58].

Another study revealed glutamate intoxication of MSG 4 mg/kg for 21 days resulted in albino mice, resulting in the development of a hyperalgesia state, suppression of behavioural activities, along with a significant increase in the anxiety level. Animal studies have demonstrated that the intraperitoneal (i.p.) administration of MSG for 21 days at a dose of 10 mg/kg showed an anxiolytic effect, and 80 mg/kg showed an anxiogenic effect. In addition to the behavioural changes, histological changes were also noted as a sign of neurotoxicity at doses 40 mg/kg and 80 mg/kgs, such as loss of pyramidal cells, Purkinje cells, granule neurons, and increasingly prominent astrocytes. In another study in mice, MSG at a dose of 40 mg/kg and 80 mg/kg showed a rise in plasma Glutamate and Glutamine, and histological examination of the cerebrum, hippocampus, and cerebellum showed signs of neuronal injury [59]. Another trial in which subcutaneous administration of MSG solution resulted in overactivation of glutamate receptors in the brain This study showed Behavioral changes such as screeching, tail stiffness, head nodding, and generalised convulsions altered because of the changed biochemical environment (total amino acid content) [60]. In a previous 21-day study, MSG at a dose of 80 mg/Kg produced anxiogenic behaviour [61].

6) Effects on fertility and fetal development

An important safety issue reported by preclinical studies is the effect of chronic MSG exposure on fetal development/growth. MSG at a dose of 0.04 mg/kg and 0.08 mg/kg body weight (orally) showed histological findings such as cellular hypertrophy and degenerative and atrophic changes in the ovaries of adult Wistar rats [43]. Another experiment in adult male Wistar rats with MSG at a dose of 4 g/kg (intraperitoneal, 14 days) reported changes like a decrease in testicular weight, decrease in tubular diameter, reduction in germinal epithelium height, decrease in the spermatic count and abnormalities of sperms morphology [62]. Subcutaneous administration of 2 g/kg MSG in Female Swiss Albino mice newborns for five days (second, fourth, sixth, eighth and 10th day of life) [63] and follow up histology study of the ovarian tissue after 75 days, showed an increase in the number of the primary follicle, serum prolactin, growth hormone and a decrease in the serum estradiol [64]. Here, most of the studies are of acute studies, and chronic exposure studies are required for further investigations of the effect of MSG on reproductive health.

Clinical studies on MSG Exposure

a) MSG & Energy intake:

As per previous reports, MSG increases the palatability of food in a low concentration, and we expect a reduction in satiety. But most studies reported satiety enhancement, which is the opposite effect 65. Information regarding the impact of MSG on energy is contradictory. Some studies reported no significant difference between hunger level and energy intake. A previous study compared 2 g MSG with NaCl and found that MSG produced a substantial rise in postprandial levels of circulating leucine, isoleucine, valine, lysine, cysteine, alanine, tyrosine, and tryptophan [66]. Most of the studies proved that MSG consumption increases the palatability of food and enhances satiety.

b) MSG & Obesity

Animal studies have already proved that MSG intake induces hypothalamic lesions and leptin resistance that could lead to overweight. A cross-sectional study conducted in Chinese people has confirmed that MSG intake (average intake-0.33 g/day) leads to an increased risk of overweight independent of their physical activity and calorie intake [67]. China Health and Nutrition Survey (CHNS), a prospective open-cohort, ongoing nationwide health and nutrition survey confirmed the abovesaid thing. An epidemiological study conducted in 349 Thai adults (average intake of MSG was 4.0±2.2 g/day) assessed the prevalence of obesity, weight gain, insulin resistance and metabolic syndrome. The study proved that MSG intake increases the prevalence of metabolic syndromes or obesity in a dose-dependent manner [7]. Still, there is a lot of controversy regarding the weight gain/metabolic syndromes and MSG intake. In 2008, a cross-sectional study conducted in Vietnamese adults (average MSG intake was 2.2±1.8 g/day) showed that MSG consumption did not produce significant weight gain after adjusting for age, sex, multiple lifestyle factors and energy intake [68]. So, large clinical trials are needed to understand the relationship between long-term exposure to MSG and obesity.

c) MSG Sensitivity

Till now, many studies have reported the harmful effects of MSG. Chinese restaurant syndrome (CRS) is an MSG-related symptom complex which consists of a series of symptoms such as weakness, flushing, dizziness, headache, dyspnea, numbness, muscle tightness, and syncope [69]. Previous studies reported that MSG sensitivity in the general population is 1% [70]. In MSG sensitive patients, this flavour enhancer caused mild to severe late-onset asthmatic symptoms (1-2 hr. post-ingestion) [69]. However, the studies on MSG intake and asthma exacerbation had a small sample size and questionable study design.

Contrary to this, a large number of studies conducted in Chinese adults showed no association between asthmatic exacerbations and MSG intake. Some case reports linked MSG consumption to Urticaria and allergic responses [71]. However, due to the lack of reliable studies, this is still a matter of controversy.

d) Impact on atopic dermatitis

Atopic dermatitis is a chronic skin disease common during infancy and early childhood. Some studies reported exaggerating atopic dermatitis because of MSG and other food additives ingestion [72, 73]. Since this atopic dermatitis is related to inflammatory and immune-mediated pathogenic factors, various molecules, including environmental factors, contact allergens and food additives, can aggravate the disease [74]. It is plausible that food additives may worsen the symptomatology, while an individualised, additive-free diet may benefit these patients even though a significant direct link connecting the MSG intake and atopic dermatitis has not yet been established.

e) Impact on Pain conditions

Some studies have also unveiled the effect of MSG on pain-associated conditions, but there is a lack of support from substantial clinical evidence. In a double-blinded, placebo-controlled, crossover study, MSG at a dose of 75 mg/kg reported a significant increase in headache [75], and a dose of 150 mg/kg showed an elevation of systolic blood pressure.

Another multicentric, multiphase, double-blinded, placebo-controlled crossover study (5 g MSG one day versus placebo) noted a significant increase in the frequency of headaches with the MSG [76]. In another randomised, double-blinded, placebo-controlled study conducted in patients with myofascial temporomandibular disorder (TMD), a single oral dose of MSG (150 mg/kg) showed a significant increase in the interstitial concentration of glutamate and a worsening of the intensity of spontaneous pain. Another study conducted in female patients with fibromyalgia MSG (5 g, over three consecutive days) found to cause worsening of symptoms [77]. All these studies suggest a probable relationship between MSG and pain conditions, but further studies are needed to establish a direct link between these two.

Conclusion

Due to industrialisation and urbanisation, our food culture has undergone a significant transformation. The fast-food industry in our country is rapidly expanding, leading to an excessive use of flavor enhancers, such as MSG, despite government regulations. Conducting studies to assess the potential adverse effects of chronic MSG consumption is imperative. Presently, research on the impact of MSG administration on animals and humans is limited to short-term studies. Therefore, long-term studies are necessary to explore the effects of MSG, considering that it is one of the world's most commonly used food ingredients today.

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