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Study of the Toxic Effectsof Monosodium Glutamate on the Central Nervous System

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Abstract
Background:Monosodium glutamate (MSG) is one of the most common food additives used in commercial foods and has been over-used over time. It is found in many processed foods found in every market. Monosodium glutamate adds a special aroma to processed foods.This taste sensation is called "umami" in Japanese or "savoury".Its toxic effects have been shown in several animal studies, however in most of them, the method of administration and the doses were not similar to human MSG intake.MSG is called in many countries "China salt" but besides its flavor-enhancing effect, MSG has been associated with more than one different form of toxicity.MSG has been associated with obesity, metabolic disorders, neurotoxic effects, harmful effects on reproductive organs, and Chinese restaurant syndrome.Monosodium glutamateresults in an elevated glutamate level which leads to excitatory toxicity that may cause severe neurological damage and other complications to the central nervous system.
Keywords:Monosodium Glutamate (MSG),Toxicity, Central nervous system.

1. Monosodium Glutamate:

Monosodium glutamate (MSG) is a salt originally derived from the herb, commonly marketed as a flavor enhancer. Trade names of monosodium glutamate include Ajinomoto, Vetsin, Accent, and Chinese salt. This compound is usually available as a white, odorless, crystalline powder. It is freely soluble in water, but it is insoluble in common organic solvents. It dissociates in solution to glutamate and sodium ions **(1).**

There are three methods for MSG production, the old methods either by hydrolysis of vegetable proteins with hydrochloric acid to disrupt peptide bonds or by direct chemical synthesis with acrylonitrile, and the recent method by bacterial fermentation (Corynebacterium species) which secretes amino acids into a culture from which L-glutamate is isolated. The product then undergoes many processes as filtration, concentration, acidification, and crystallization **(2).**

Monosodium glutamate (MSG) had become a household word when hydrolyzed protein products were frequently used like vegetable proteins and sodium caseinate in 1960. These products contain processed free glutamic acid with the same neurotoxic properties and flavor-enhancing of free glutamic acid present in MSG. Monosodium glutamate was replaced with hydrolyzed vegetable proteins in baby food but remained in infant formula because it was responsible for increasing temperature and affect the fat deposition and the body mass when used at an early age in 1970. Nowadays, MSG becomes extensively used in canned tuna, frozen entrees, crackers, processed meats, and dietary supplements. It is also found in soaps, cosmetics, infant formula, and vaccines

(3).

Glutamate is the foremost excitatory neurotransmitter in the body. Multiple human and animal studies proved that glutamate was widely oxidized in the gut. Numerous transporters and receptors for glutamate are found in gastrointestinal tract and nervous system. The intestine is the main site for catabolism of amino acids especially nonessential ones like glutamate **(4).**

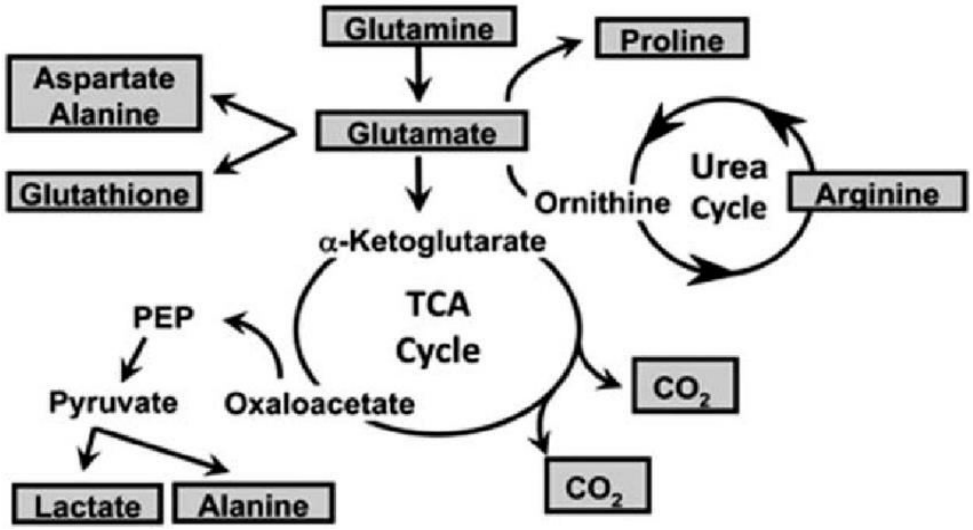

Figure (1): Metabolic cycle of dietary glutamate in the intestine **(5).**

Glutamic acid is a class of chemicals known as excitotoxins. The young and the elderly are most at risk from MSG as the blood-brain barrier is not fully developed in the young and can be damaged by aging or disease in the elderly. A Canadian study demonstrated that ingredients that contain MSG are used in baby formula, allowing neurotoxins to be more accessible to the brain which is not well developed than the case in healthy adults **(6).**

Chinese restaurant syndrome (CRS) was reported as the initial occurrence of side-effects after ingestion of Chinese meal with MSG in 1968 and the symptoms included numbness at the back of neck and arms, weakness, and palpitations. Animal studies showed an increase in blood glucose, triglycerides, and cholesterol levels as compared with control animals. Monosodium glutamate also proved to be a strong chemical for obesity and diabetes induction **(7).** Moreover, MSG can cause hepatic and renal function disorders by increasing oxidative stress and decreasing the actions of antioxidant enzymes. The liver enzymes including ALT and GGT were increased, while serum total protein, albumin, and bilirubin levels were decreased **(8).**

Monosodium glutamate (MSG) acts as an excitatory amino acid, increase the level of MSG in the synaptic cleft region resulting in excessive glutamate receptor activation with persistent depolarization (excitotoxicity) producing metabolic and functional exhaustion of the affected neurons leading to neural necrosis, cerebellar damage, and motor function deterioration **(9).** The most common disorders of neurotoxicity include ischemia and traumatic brain injury, chronic conditions like multiple sclerosis, and Parkinson's disease. It affects the chemical composition of the hippocampus and activates neurodegenerative pathways **(10)**. Similarly, the toxic effects of MSG on the cerebellar cortex **(11).**

The representing symptom of the toxic effects of MSG is ataxia. This debilitating disease is caused by sustained high concentrations of MSG. Moreover, the increased levels of glutamate lead to increased calcium entry, internal oxidative stress with the generation of free radicals, mitochondrial dysfunction, and eventually necrosis **(11)**.

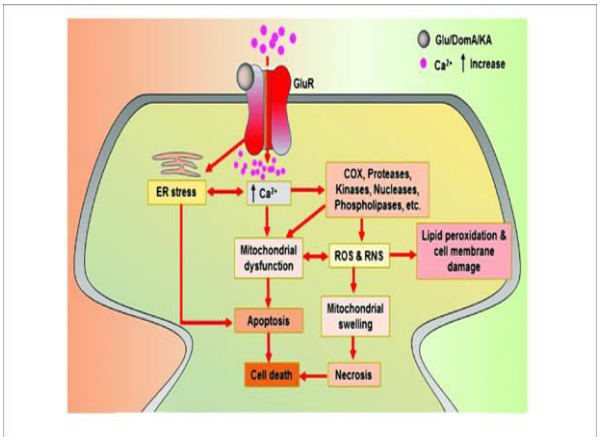

Figure (2): Metabolic glutamate receptor-mediated neurotoxic actions of glutamate, domoic acid, and kainic acid. Upon binding to glutamate receptors, all toxins produce an agonistic reaction that leads to cell death. Glu: Glutamate; KA: Kainic acid; DomA: Domoic acid; COX: Cyclooxygenase; ROS: Reactive oxygen species; and RNS: Reactive nitrogen species **(12).**

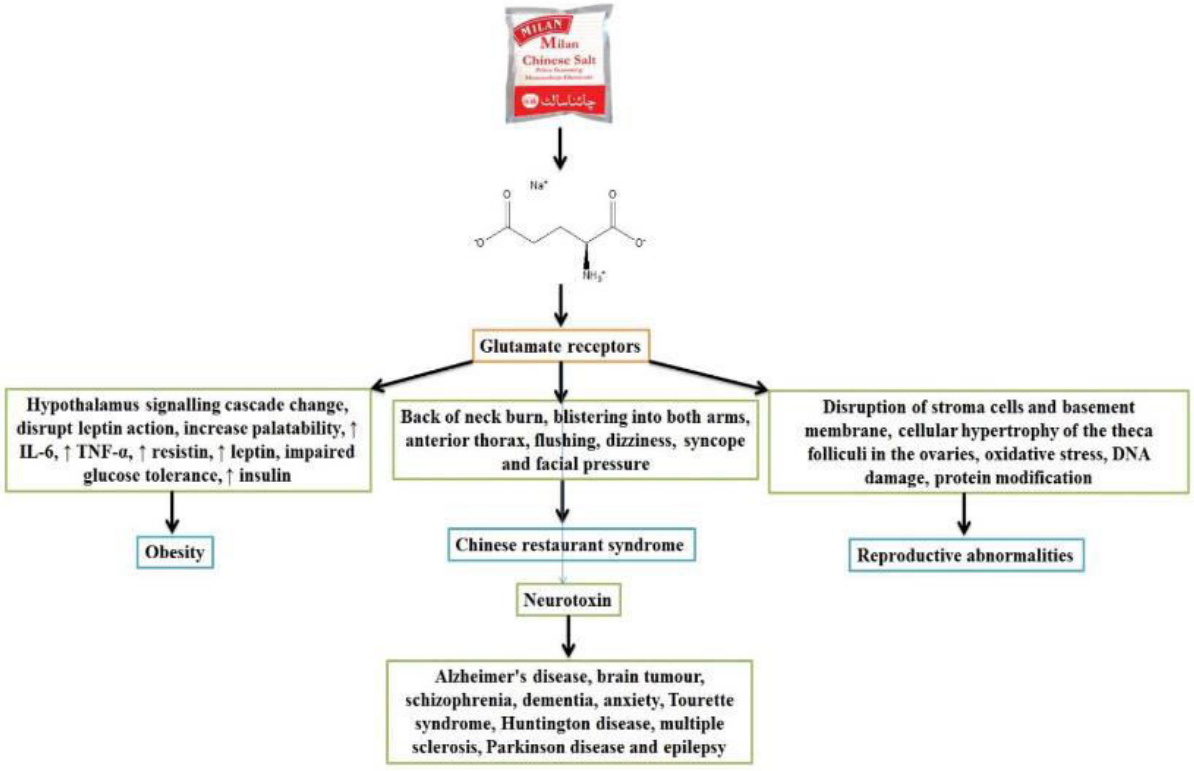

Figure (3): MSG toxicity leads to different disorders**(13)**.

2. Effects of MSGon 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 **(14).** 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 **(15).**

MSG is used as an agent which in high doses causes neuronal necrosis in hypothalamic arcuate nuclei in neonatal rats **(16)**. 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 and loss of cortical cell number from postnatal day 8-14 compared to control rats **(17).** 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 **(18).** Pituitary weight affection seems to be related to its function derangement. Increased proopiomelanocortin mRNA levels and adrenocorticotropic hormone concentration in the a denopituitary have been found in neonatal MSG-treated rats compared with controls (4 mg/g, 5 administrations intraperitoneally. Furthermore, numerous studies have shown that neonates treated with MSG exhibited neuronal cell death with reduction of photoreceptor and glial cells **(19)**.

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 **(20).** 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) **(21).** 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 **(22).** 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 **(13).**

The next important difference between rodent and human MSG intake is a period of life with regard to neuronal development. It was suggested that MSG excitotoxicity occurs only when the blood–brain barrier is vulnerable, for example in neonates **(23)**. JECFA in 1988 suggested that ingestion of MSG was not associated with elevated levels in maternal milk and glutamate did not readily pass the placental barrier **(24).** Also, the Consensus meeting in 2007 noted that glutamate did not trespass into fetal circulation, even in high doses **(25)**. However, the opposite findings have been shown in animal studies and the glutamate neurotoxicity in newborns with the behavioral effects rather than structural or histological changes remains in question. Kunming filial mice which mothers treated with MSG (2.5 mg/g or 4.0 mg/g body weight) per os in 17-21 days of pregnancy had significantly impaired Y-maze discrimination learning in the 60.day, although the neuronal damage of the periventricular organs or the hypothalamus was not observed **(26).**

Effect of MSG on Spinal Cord:

In A recent study done by **(27),** they examined oxidative stress in the spinal cord and different brain regions of rats administered with MSG in the first days of life or in post-natal day (PND) 90. In this study, the neonatal administration of MSG reduced only the activity ofsuperoxide dismutase(SOD) and did not alter all other assessed parameters of oxidative stress, in the spinal cord of rats at PND 3.

Because SOD is the first detoxification enzyme and the most powerful antioxidant in the cell, this result may indicate the onset of oxidative stress, which possibly develops with subsequent administrations of MSG. As a limitation of this study,they acknowledged that only malondialdehyde(MDA) levels were evaluated as a marker of oxidative damage; however, other markers could be already altered in rats administered with MSG. Interestingly, MSG caused oxidative stress in the spinal cord and thermal nociception in the tail immersion test in rats only at PND 3. The behavior of tail withdrawal is widely recognized as a spinal reflex **(28)**, which could indicate that the effects of MSG involve mainly spinal mechanisms in rats at PND 3. However, the involvement of supraspinal regions in the MSG effects in rats at PND 3 cannot be ruled out because only the whole brain was evaluated in this study.

Effect of MSG on Cerebrum

Our brain consists of excitatory principal neurons and inhibitory interneurons which interact in effective way creating a functional balance to avoid any disease.So, changes in neuronal excitability can cause neural networks modifications and possible pathological consequences. Additionally, Glutamate receptorshyperactivation could lead to neuronal death in several brain regions, such as cerebral cortex, cerebellum, and hippocampus**(29).**

Oxidative stress has been described has an important feature of neuronal injury and is characteristic of a number of neurodegenerative diseases. Because of high levels of oxygen consumption by the central nervous system, it is susceptible to free radical damage. MSG consumption has been reported to be related to alterations in the antioxidant status in different brain areas, the superoxide dismutase and catalase activity are strong indications of oxidative stress in the brain that decreased with increasing doses of MSG.this leading to decreasing cell with progressive loss of neurons, cellular inflammation, and cellular swelling. Also, increase in microglia cell density (astrocytes) suggesting a response of toxicity, as astrocytes play a important role in glutamate homeostasis and in the reuptake of free glutamate, thus, prevention of glutamate excitotoxicity **(30).**

Effect of MSG on Cerebellum

MSG, one of its main components is glutamate. So, it may have caused death of Purkinje cells due to excessively activation of glutamate receptors. It leads to motor function disruption and functional impairment.The most common signs of cerebellar diseases involve ataxia, impaired body balance, anxiety disorders, vertigo, and dizziness. Ocular instability and nystagmus may occur as the cerebellum plays a major role in the eye movement control (control of calibration and maintenance of ocular alignment) **(31)**.

Cerebellar dysfunction occurs on the ipsilateral side of the body as the following:

1. Ataxia means loss of muscle coordination and control following cerebellar damage. There are two major forms of cerebellar ataxia:

a) **Disturbances of posture or gait** that result from the vestibulo-cerebellum lesions. Patients have difficulty maintaining posture because of the loss of the fine-control mechanisms

programmed by cerebellar circuits that translate vestibular signals into precise, well-timed muscle contractions. As a result, patients often develop abnormal gait (staggering gait) and a wide base stand to compensate **(32)**.

b) **Decomposition of movement.** Most of our movements involve the coordination of many muscle groups and different joints to produce a smooth path of the body. Patients with cerebellar dysfunction are unable to produce this coordination. Instead, they often break the movements down into their parts to do the desired path. For example, in the cerebellar patients, touching one's finger to one's nose will be performed in sequence, rather than as a single uniform motion, **(33)**.

2. Intention tremor. When moving to a target, cerebellar patients often produce an involuntary tremor that increases as they approach closer to the target **(34)**.

3. Dysdiadochokinesia. Patients have difficulty performing rapidly alternating movements, such as hitting a surface rapidly and repeatedly with the palm and back of the hand **(35)**.

4. Nystagmus is an oscillatory movement of the eyes, resulting from damage to the vestibulo-cerebellum. In addition to movement disorders, cerebellar patients also demonstrate subtle cognitive deficits, such as an impaired ability to estimate time intervals **(36)**.

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