MONOSODIUM GLUTAMATE SAFETY, NEUROTOXICITY AND SOME RECENT STUDIES

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ABSTRACT

Monosodium glutamate (MSG) is a worldwide flavor enhancer. Despite controversy surrounding the safety of MSG, it is still consumed in large amounts. This review provides a better understanding of the molecular mechanism of MSG induced neurotoxicity including the different ways of glutamate regulation in brain and umami taste signaling pathway. In addition, this review summarizes the history of MSG discovery and synthesis, products and natural food containing MSG, details of MSG safety and toxicity with limited allowed amounts that can be used according to different organizations opinion. Finally, this review enumerates the different MSG studies in both animals and humans in the last 20 years.

Keywords: monosodium glutamate, neurotoxicity, safety, calcium, ROS,

Introduction

1. Chemical and physical properties of monosodium glutamate:

Monosodium glutamate is a sodium salt of glutamic acid with the chemical formula C5H8NO4Na and IUPAC name sodium 2- aminopentanedioate, Melting Point: 232 $^{\circ}$C and Molar Mass: 187.12 grams/mole. Monosodium glutamate is a white crystallized powder, which is readily soluble in water. It is also soluble in ether but insoluble in alcohol, acetone, benzene, methanol and acetic acid (Henry-Unaeze, 2017) **(figure 1)**.

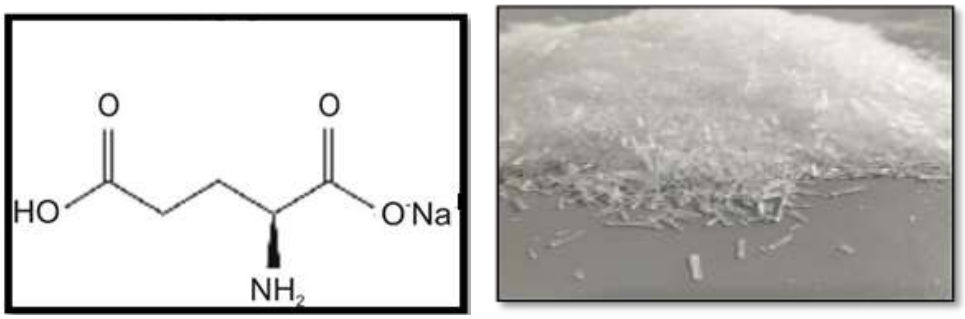


Figure (1): Monosodium glutamate chemical structure and crystals (Henry-Unaeze, 2017)

2. Monosodium glutamate history:

Ritthausen, a german chemist, was the first one to obtain glutamic acid in 1866 as a pure substance through the acidic hydrolysis of wheat gluten component gliadin. Then japanese chemist Kikunae Ikeda found that the good taste of the kelplike seaweed used for the preparation of soup stocks was due to glutamic acid in 1908. The first commercial monosodium glutamate was produced under the trade name Ajinomoto in 1909. After that, MSG came into use as a food additive to enhance the flavor of foods around the world (Ault, 2004). Since 1957, in the United States, Monosodium glutamate was produced from sugar beet molasses and carbohydrate sources (e.g., corn, sugar beet) by bacterial fermentation involving genetically modified bacteria that secrete glutamic acid through their cell walls. Then glutamic acid is then filtrated, concentrated, acidified, and crystallized and converted to its monosodium salt (Henry-Unaeze, 2017; Kazmi et al., 2017).

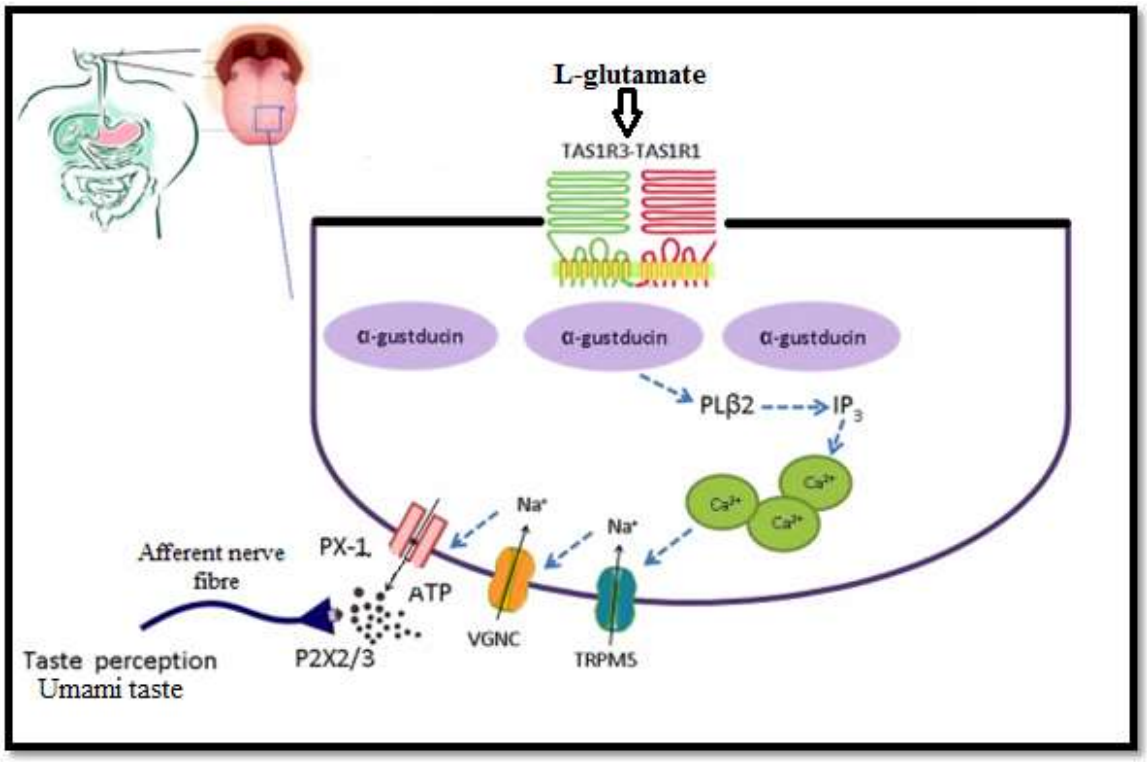
3. Monosodium glutamate uses and sources

Monosodium glutamate is a common food enhancer. It gives a taste described in Japanese as umami. The flavor sensation of MSG is described as "meaty" unlike that of salt (sodium chloride), sweet (sucrose), pungent (chili peppers), bitter (quinine) or sour (lemon juice) basic flavor sensations. In addition, MSG enhances natural taste in vegetables, meat, mushrooms and fish. It has a synergistic effect with disodium inosinate and disodium guanylate, which are found in these foods producing six or eight fold greater umami taste than it produced by MSG alone. In the absence of MSG these

substances are almost tasteless (Ault, 2004). This occurs due to the presence of multiple binding sites in the taste receptor of umami (Depoortere, 2014). It can be used as table salt substitute due to its sodium content. It helps in reducing fats and salts amount in foods without taste alteration. In addition, it is used to develop favorable taste in patients who have lost their appetite (Kazmi et al., 2017).

Umami taste is detected by taste receptors heterodimer (taste receptor type 1 member 1- taste receptor type 1 member 3 "TAS1R1-TAS1R3") in taste cells of the tongue (Nelson et al., 2002). L- Glutamate binds to TAS1R1-TAS1R3 leading to activation of the gustatory G-proteins (α-gustducin) resulting in activation of phospholipase Cβ2 leading to activation of inositol triphosphate which increases the intracellular calcium (Ca^{2+}) release. Calcium activates transient receptor potential cation channel M5 followed by depolarization and generation of action potential with adenosine triphosphate (ATP) release. Adenosine triphosphate acts on purinergic receptors then gustatory afferents activated and finally brain centers of taste perception activation occur (Depoortere, 2014) **(figure 2)**.

Monosodium glutamate is naturally found in many types of food such as, human milk, cow milk, apple, almond, eggs, onion, carrot, potato, walnut and garlic. Now it is added to canned tuna, processed meats, crackers, frozen entrees, soups, salad dressings, cosmetics, infant formula, and dietary supplements, canned foods, fast foods, frozen meals and potato chips. Monosodium glutamate still consumed despite controversy surrounding its safety (Henry-Unaeze, 2017; Kazmi et al., 2017)**.**



Figure(2): Model of the umami taste signaling pathway, with some modification (Depoortere, 2014).

TAS1R1-TAS1R3: taste receptor type 1 member 1- taste receptor type 1 member 3, PLCβ2: phospholipase Cβ2, IP_3: inositol triphosphate, Ca^{2+}: calcium, TRPM5: transient receptor potential cation channel M5, VGNC: voltage gated sodium channel, PX-1: pannexin 1-hemichannel, ATP: adenosine triphosphate, P2X2/3: purinergic receptors.

4. Monosodium glutamate safety:

Globally, increasing the use of prepackaged food and Chinese food containing MSG triggered a new interest in academic community in MSG safety. Because excess of anything is bad, utilization of MSG up to certain level does not have any adverse effects since glutamate is a nutritionally indispensable amino acid (Kazmi et al., 2017).

In 1968, first incidence of side-effects in human after eating MSG was reported and it was called Chinese restaurant syndrome (CRS) which include, weakness, palpitations and numbness at the back of neck and arms after chinese meal ingestion (Geha et al., 2000). Monosodium glutamate was replaced with autolysed yeast and hydrolyzed vegetable protein in baby food in the early 1970s by manufacturing companies. Then in the late 1970s all ingredients containing MSG were eradicated from baby food but remained in infant formula. The United State Food and Drug Administration's reported a mean daily intake of MSG per capita of 550 mg/day in the United States in 1979 (He et al., 2011)**.** World Health Organization stated that the daily consumption of MSG per person should not exceed the safe limit of 120 mg/kg/day (Rachma et al., 2021)**.**

The European Food Safety Authority Committee provided that there are no harmful effects in the short-term studies of the glutamate absorption in the intestine, reproductive and developmental studies. In addition, the only MSG effect observed was spleen and kidneys weight increase without harmful results (Al-Agili, 2020).

In 2017 the European Food Safety Authority set that the permissible amount of glutamic acid per day is (30 mg/kg) of body weight. European Food Safety Authority also clarified the quantities that, when used daily, can cause symptoms are headache (85.8 mg/kg), insulin increase (> 143 mg/kg) and blood pressure increase (150 mg/kg) (Mortensen et al., 2017).

The Food and Drug Administrations declared that limited usage of MSG is safe and increased MSG consumption is linked to several potential side effects such as, circulatory, cardiac, muscular, neurological and gastrointestinal disorders. Clinical trials of human and animal subjects also suggested various potential health hazards. The extrapolation of animal model results to humans is more demanding and strenuous (Kazmi et al., 2017). Monosodium glutamate use is still considered a controversial source (Al-Agili, 2020).

5. Homeostasis of glutamate in brain extracellular fluids:

At a quiescent state, the glutamate concentration in the cytoplasm of glutamatergic neurons is approximately 5−10 mM (Danbolt, 2001), while extracellular

glutamate concentration around neurons is 1−5 uM (Nedergaard et al., 2002: Featherstone, 2010). Plasma glutamate level is 30−50 μM (Danbolt, 2001).

Any small increase in the brain extracellular glutamate level produces damaging effects through increasing the excitability and activating the proteolytic enzymes. So the extracellular glutamate level is adjusted by many ways such as, glutamate transporters found in neuronal cells, astrocytes, endothelial cells of the brain capillaries, astrocytic end foot as well as cystine/glutamate antiporters (xCT) (Albrecht et al., 2010).

5.1. Glutamate transporters:

Glutamate excitatory signal is terminated by active removal of glutamate from the synaptic cleft by several types of sodium dependent high affinity glutamate membrane reuptake transporter proteins, which are located on both presynaptic terminals and perisynaptic astroglia. Glutamate aspartate transporter (human equivalent excitatory amino acid transporter 1 "EAAT") found preferentially in astroglial. Glutamate transporter 1 (human equivalent EAAT2) is commonly expressed in glial cells and excitatory amino acid carrier 1 (human equivalent EAAT3) and EAAT5 in neurons. Excitatory amino acid transporter 4 is expressed predominantly in the cerebellum. Extracellular glutamate concentration is regulated mainly by EAAT2 (Danbolt, 2001).

Cystine/glutamate antiporter is another important molecule modulating both extra and intra-cellular glutamate concentrations. It takes up L-cystine and transports out glutamate. Inside cells, L-cystine is used for glutathione (GSH) synthesis which protects against oxidative insults (Albrecht et al., 2010).

5.2. Glial cells glutamate–glutamine cycle:

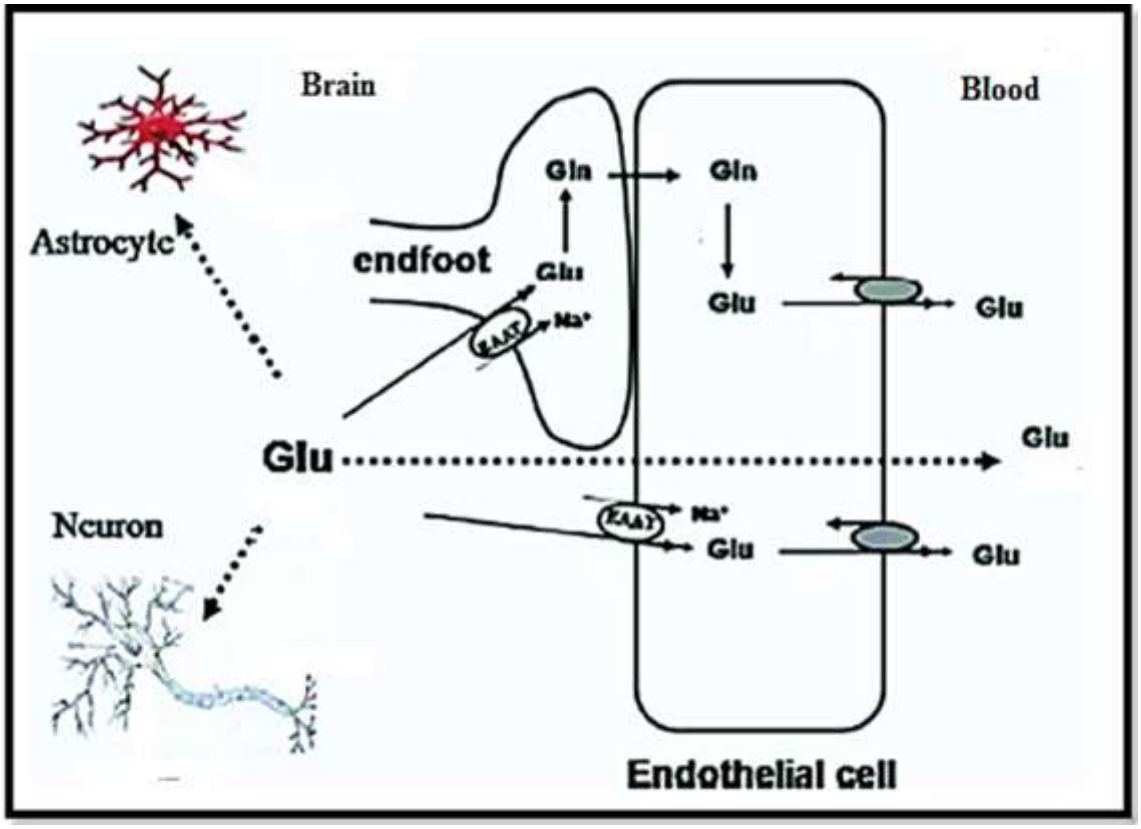
Another important mechanism for replenishing the extracellular glutamate concentration levels is glutamate-glutamine cycle. Glial cells reuptake glutamate which is converted by glutamine synthetase to glutamine thus ending neurotransmission. Then, presynaptic neurons take up glutamine via sodium dependent glutamine uptake systems. In neurons glutamine is converted by glutaminase to glutamate thus completing the glutamate–glutamine cycle offering neuroprotection and preventing excitotoxicity that occurs due to excess extracellular glutamate concentration (Attwell, 2000).

5.3. Glutamate and blood brain barrier:

Under normal conditions, most free L-glutamic acid in brain is derived from local synthesis from Kreb's cycle intermediates and L-glutamine. The glutamate efflux from brain to blood is higher than its influx from blood to brain. So the glutamate concentration in the cerebrospinal fluid is kept low by the blood brain barrier (BBB), which restricts entry of the glutamate in blood and efflux of the excess glutamate to blood**.** When the glutamate extracellular level is increased, glutamate is transported to the endothelial cells of the BBB through EAAT1-3, then it is transported to the blood by facilitated diffusion (Teichberg et al., 2009). Also, glutamate is transported to the astrocytic end foot where it is converted into glutamine. Glutamine transport to the

endothelial cell of the BBB in which it is converted into glutamate and transported to the blood (Lee et al., 1998: Jakovcevic and Harder, 2007). In addition, hydrolysis of glutamine into glutamate and ammonia in endothelial cells provides a way for elimination of brain ammonia (O'Kane et al., 1999) (**figure 3)**. This regulatory role of BBB in cerebrospinal fluid glutamate level is lost in immature or damaged BBB.

Also administration of large systemic doses of MSG in animals increases the plasma osmolarity which damage the BBB followed by entrance of large amounts of glutamate to the extracellular spaces of brain producing damage to different brain areas (McCall et al., 1979; Torii et al., 1981).



Figure(3): Homeostasis of glutamate in brain extracellular fluids, with some modifications (Teichberg et al., 2009).

Glu: glutamate, EAAT: excitatory amino acid transporter, Gln: glutamine, Na^+: sodium.

6. Monosodium glutamate neurotoxicity:

Monosodium glutamate induced neurotoxicity was first reported by Olney, (1969) who observed that administration of MSG in neonatal mice induced acute neuronal necrosis (Mortensen et al., 2017). Burde et al., (1971) found that oral and subcutaneous MSG administration in rats resulted in acute necrotic lesions in hypothalamic neurons. After that, many studies conducted using different doses and duration resulted in diverse neurological phenotypes (Ali et al., 2000; Beas-Zárate et al.,

2002; Kiss et al., 2005; López-Pérez et al., 2010). Also, monosodium glutamate administration led to acute increases in intracerebroventricular and hippocampal glutamate concentrations (López-Pérez et al., 2010).

6.1. Monosodium glutamate excitotoxicity cellular mechanisms:

Monosodium glutamate excitotoxicity is believed to result from increased Ca^{2+}influx through excessive stimulation of glutamate receptors (Rivera-Cervantes et al., 2004; Torres et al., 2006). Glutamate excitotoxicity is a complex process. It starts with excess extracellular glutamate leading to over stimulation of the glutamate receptors followed by intracellular Ca^{2+} overload (Ezza and Khadrawyb, 2014). This initiates several events such as, activation of Ca^{2+} dependent catabolic enzymes including phospholipases, proteases, protein phosphatases and endonucleases, free radical generation and mitochondrial dysfunction resulting in neurons death (Ezza and Khadrawyb, 2014) **(figure 4).**

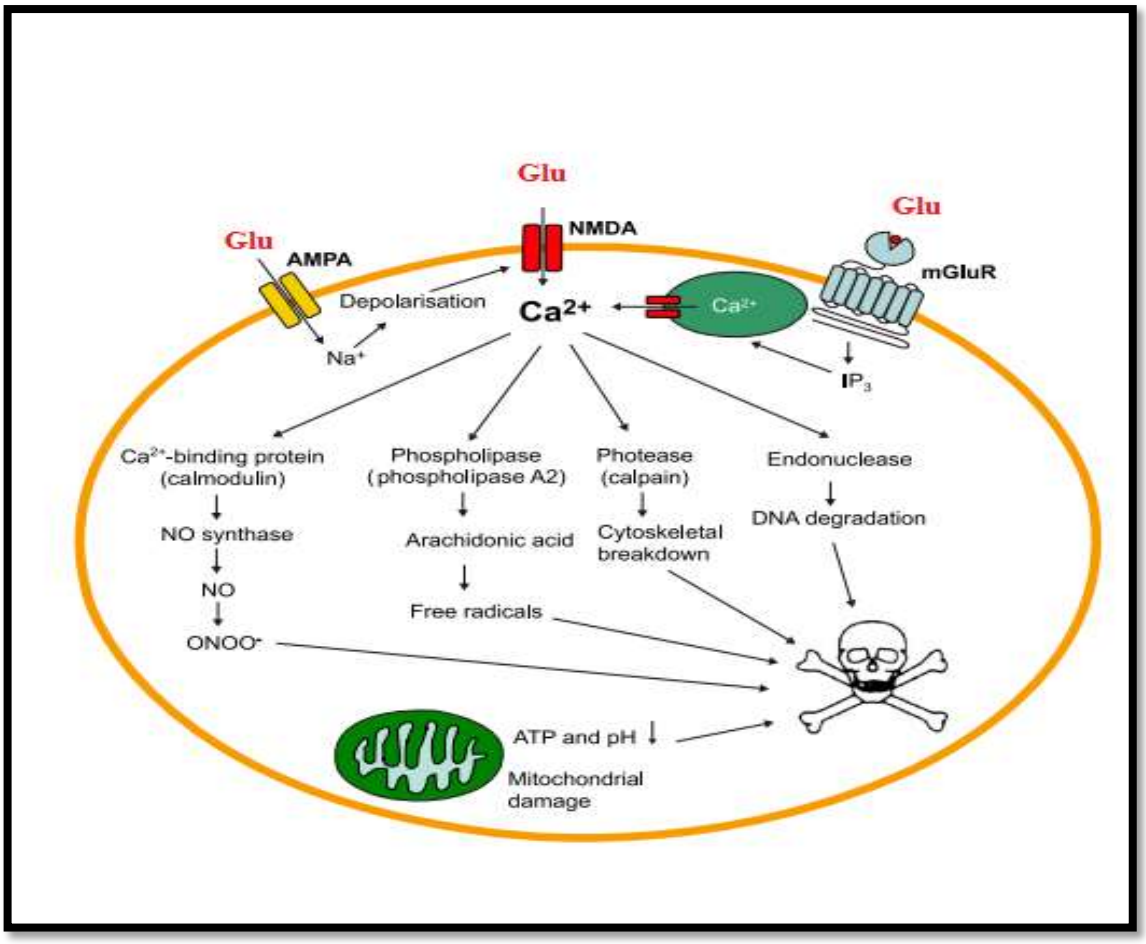


Figure (4): Schematic drawing of the glutamate excitotoxicity process, with some modification (Baskys and Blaabjerg, 2005).

Glu: glutamate, AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, NMDA: N-methyl-D-aspartate receptor, mGluR: metabotropic glutamate receptors,

IP3: inositol-1, 4, 5-bisphosphate, NO: nitric oxide, $ONOO^-$: peroxynitrite, ATP: adenosine triphosphate

6.1.1. Calcium activates calpains:

Calpains are Ca^{2+} dependent proteases that degrade the neurons neurofilaments responsible for maintaining the integrity of the neuronal cytoskeleton (Rothman, 1994). During excitotoxicity excess glutamate over activates glutamate receptors leading to increase in the intracellular Ca^{2+} concentration. Calcium then activates calpains and activated calpains convert BH3-interacting domain death agonist (Bid) to truncated Bid. Then in the mitochondrial membrane truncated Bid combines with Bcl-2-associated x protein and forms mitochondrial transition pores (MTP) resulting in cytochrome c and apoptosis-inducing factor (AIF) release to cytoplasm through the MTP. Cytochrome c initiates a cysteine-aspartic proteases dependent apoptosis and AIF initiates a cysteine-aspartic proteases independent apoptosis of neurons (Culmsee and Krieglstein, 2007). In excitotoxic insults inhibitors of different calpains have protected neurons (Caner et al., 1993) **(figure 5).**

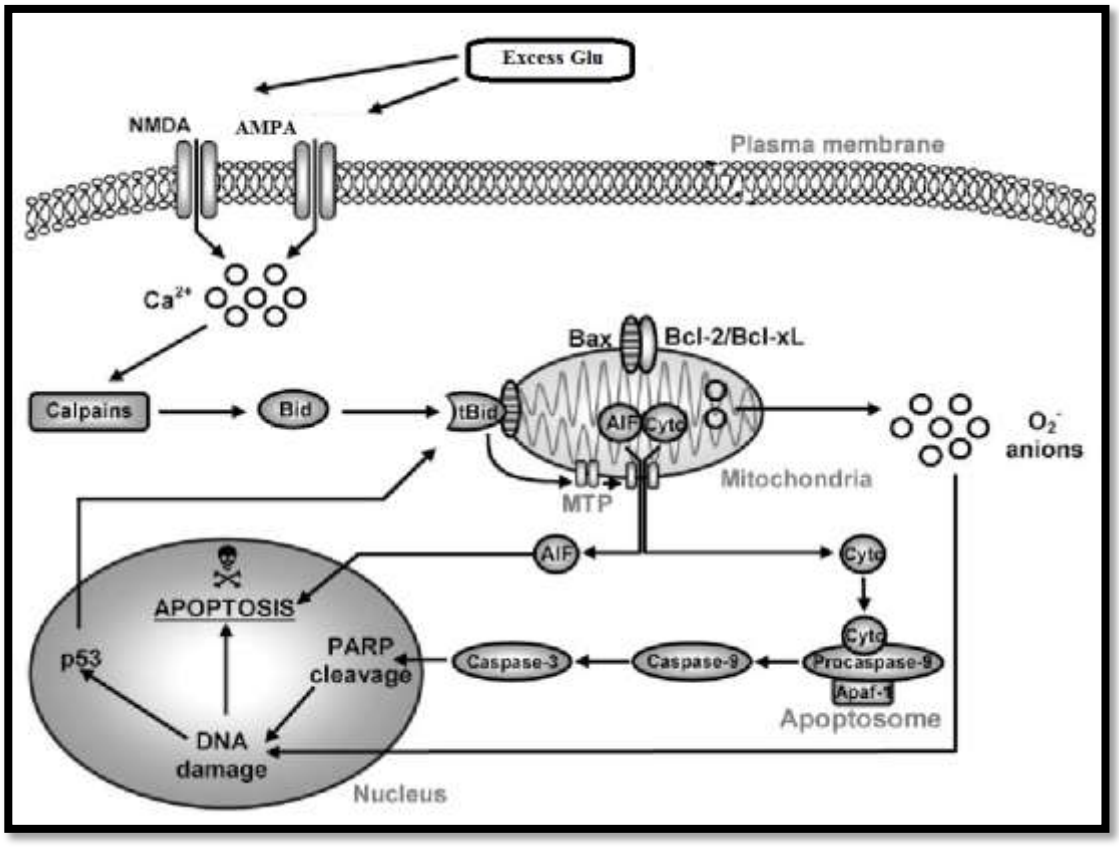


Figure (5): Intrinsic signaling cascade of apoptosis induced by glutamate excitotoxicity, with some modification (Broughton et al., 2009).

BID: BH3-interacting domain death agonist, Bax: Bcl-2-associated x protein, Bcl-2: B-cell lymphoma 2, Cyt c: cytochrome c, AIF: apoptosis-inducing factor, caspase: cysteine-aspartic proteases, PARP: poly (ADP-ribose) polymerase.

6.1.2. Calcium activates neuronal nitric oxide synthase:

Neuronal nitric oxide synthase (nNOS) regulates the nitric oxide (NO) levels in neuron cells. Contribution of nNOS in glutamate induced neurotoxicity was demonstrated in several studies (Huang et al., 1994; Dawson et al., 1996). Also, some studies showed that inhibition of this enzyme can protect neurons from glutamate neurotoxicity (Dawson et al., 1991; Izumi et al., 1992). During excitotoxicity glutamate activates N-methyl-D-aspartate receptors (NMDA) which lead to opening of cation permeable channels and entrance of Ca^{2+} through NMDA to neurons. Post synaptic density protein 95 links nNOS to NMDA receptors allowing Ca^{2+} to activate nNOS (Aarts et al., 2002; Cao et al., 2005).

Nitric oxide is produced by the action of nNOS and acts as inter/intracellular signaling molecule in neurons and glia (Garthwaite, 2008; Garthwaite, 2016). Under physiological conditions in the central nervous system, NO may be involved in the regulation of cerebral blood flow and the maintenance of cellular memory processes, such as, long term potentiation in the hippocampus and long-term depression (Dawson et al., 1994). Nitric oxide production increases in excitotoxicity and causes neuronal death through interaction with superoxides and formation of peroxynitrite. Peroxynotrite initiating protein nitration, DNA injury (Brown and Bal-Price, 2003) and lipid peroxidation (Radi et al., 1991) evidenced by malondialdehyde level elevation.

6.1.3. Glutamate excitotoxicity and arachidonic acid pathway:

Cyclooxygenase-2 (Cox-2) catalyzes conversion of arachidonic acid into prostaglandins and is a key target of non-steroidal anti-inflammatory drugs. It is found in both neurons and microglia which is a resident macrophage-like cell in the brain. Neuronal Cox-2 is found at the postsynaptic dendrites and excitatory terminals of hippocampus, neocortex, the dorsal horn of the spinal cord and amygdala (Yamagata et al., 1993; Kaufmann et al., 1997). Cyclooxygenase-2 is constitutive in discrete populations of excitatory neurons of hippocampus and cerebral cortex (Breder et al., 1995; Kaufmann et al., 1997). Also, Cox-2 is up-regulated during several pathological events, including seizures and ischemia. It has many roles under physiological conditions such as, plasticity and synaptic regulation during brain development (Yamagata et al., 1993).

During glutamate excitotoxicity, excessive Ca^{2+} influx to neuron activates both phospholipase A2 which degrades membrane phospholipids of neurons and Cox-2 enzymes that are involved in arachidonic acid pathways **(figure 6)**. This leads to arachidonic acid production. Arachidonic acid converts into prostaglandins such as, prostaglandin E_2 (Pazdernik et al., 1992; Murphy et al., 1994). Inhibitors of phospholipase A_2 can attenuate NMDA neurotoxicity (Rothman et al., 1993).

In addition, over activation of glutamatergic NMDA overexpresses Cox-2 protein and mRNA during pathological events such as, ischemia and seizures **(figure 6)** suggesting a role of Cox-2 in excitotoxicity (Yamagata et al., 1993; Adams et al., 1996; Marcheselli and Bazan, 1996).

Produced prostaglandin E_2 travels in a retrograde way to bind the prostaglandin E_2 receptor 2 (EP2-R) at the axon terminal of the presynaptic neuron **(figure 6)**. Activated EP2-R triggers exocytosis of glutamate through a cascade of intracellular events (López and Ballaz, 2020). N-methyl-D-aspartate receptors increase in glutamate release through Cox-2 in rat hippocampus (Anneken et al., 2013).

Neuroinflammation occurs mainly due to the glial expression of Cox-2 (Choi et al., 2010). Neuronal Cox-2 can contribute in neuroinflammation (Stark and Bazan, 2011)**.** Due to the oxygenase activity of the Cox-2, it produces superoxide free radicals which increase the oxidative stress of neurons (Pepicelli et al., 2002).

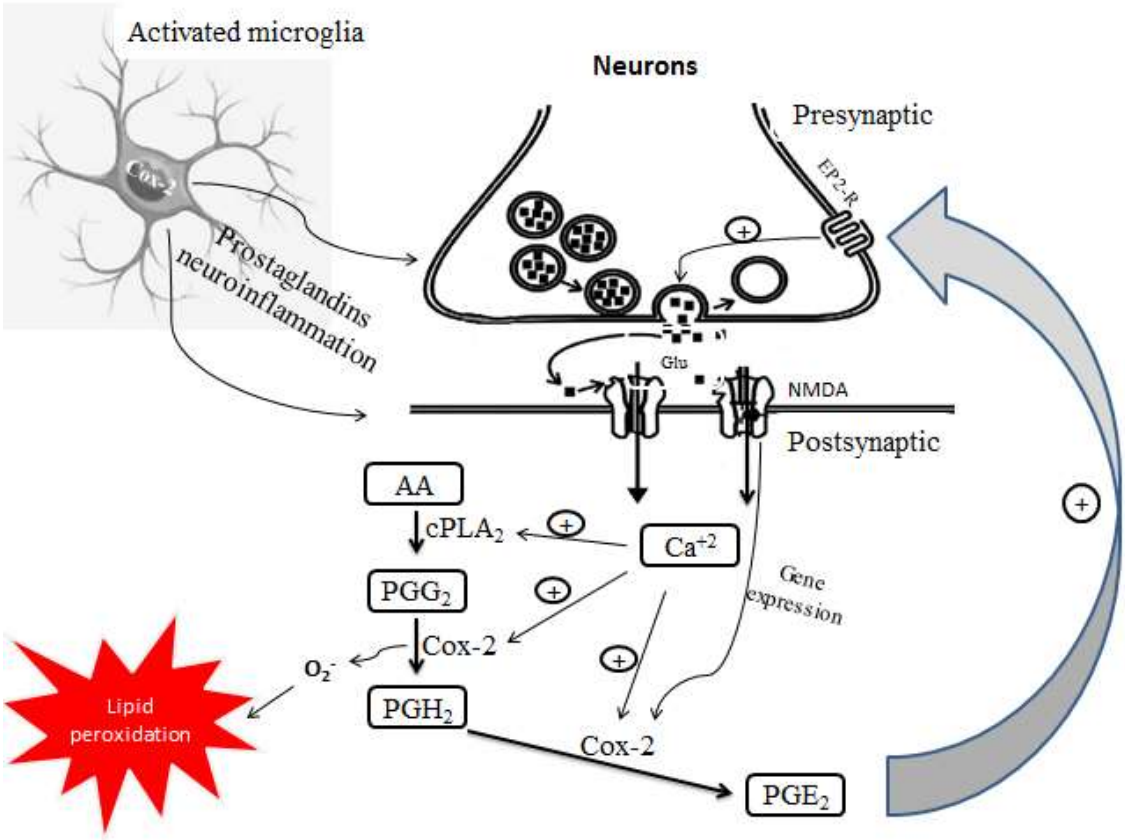


Figure (6): Proposed link between glutamate excitotoxicity and arachidonic acid pathway.

Glu: glutamate, NMDA: N-methyl-D-aspartate receptor, AA: arachidonic acid, Cox-2: cyclooxygenase-2, EP2-R: Prostaglandin E_2 receptor 2, PG G_2, E_2, H_2: prostaglandin G_2, E_2, H_2.

6.1.4. Monosodium glutamate excitotoxicity and oxidative stress:

Free radicals are considered oxidizing agents. They are constantly created in human by internal cellular metabolic process (Albers et al., 2001)**.** Hydroxyl radicals, peroxynitrites and super oxides are the most common cellular free radicals. Normally cells have many antioxidant mechanisms by which they defend against free radical damage. When reactive oxygen species (ROS) production exceeds their elimination or when the antioxidant mechanisms are damaged, this imbalance is called oxidative stress (Dong et al., 2009)**.** Oxidative stress damage proteins, lipids and nucleic acids and open the mitochondrial transition pores which in turn can further stimulate ROS production and release of the proapoptotic cytochrome c that induce apoptosis (Nicholls, 2004)**.**

Oxidative stress is a major player in neurodegenerative diseases pathology (Porta et al., 2007)**.** Oxidative stress occurs in glutamate excitotoxicity due to increase ROS production and decrease in the antioxidant defense mechanisms such as GSH reduction.

6.1.5. 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 Ca^{2+} homeostasis(Ezza and Khadrawyb, 2014). After intracellular Ca^{2+}overload induced by glutamate excitotoxicity, mitochondria attempt to buffer the Ca^{2+} concentration in the cytosol by uptake Ca^{2+} through the mitochondrial Ca^{2+} uniporter (Qiu et al., 2013). This process maintains the cytosolic Ca^{2+} concentrations temporarily. Entry of high amount of Ca^{2+} 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 Ca^{2+} overload increases ROS production (Nicholls, 2004; Mehta et al., 2013) and impairs the mitochondrial antioxidant roles with reduction in ATP synthesis which makes the cell more vulnerable to death insults (Nicholls and Budd, 2000; Fiskum et al., 2003; Kushnareva et al., 2005).

6.1.6. Mono sodium glutamate excitotoxicity and cysteine/ glutamate antiporters:

L-cystine taken up and glutamate transport out of the cells through xCT in a 1:1 ratio. This transport is driven by the transmembrane glutamate gradient. After uptake by xCT system cystine is rapidly reduced to cysteine, which is the rate-limiting amino acid in the GSH synthesis. Glutathione in turn is the most important antioxidant in the brain. System xCT therefore has two roles: the first in the control of extracellular glutamate and the second in the defense against oxidative stress (Albrecht et al., 2010).

During glutamate excitotoxicity high extracellular concentration of glutamate reverse the action of xCT and cystine goes out of the cells. This leads to depletion of the GSH content and decreases the capacity of the cell to scavenge free radicals producing oxidative stress. This initiates several secondary events such as, Bid, AIF production

and ROS accumulation result in cell death. In the absence of glutamate receptors, glutamate oxidative toxicity occur through xCT in a non-receptors mediated Ca^{2+} independent manner (Kritis et al., 2015).

7. Some of Monosodium glutamate studies published in the last 20 years:

Table1. Summary of monosodium glutamate studies published in the last 20 years

Monosodium glutamate-induced neurotoxicity				
Dose and route of administration	Duration of administration	Subject	Findings	Authors
4 mg/g/S.C	at post-natal days 1, 3, 5 and 7	rats	MSG induced cell death and cytoarchitectural changes in hippocampus.	(Beas-Zárate et al., 2002)
4 mg/g/S.C	at post-natal days 1, 3, 5 and 7	rats	MSG induced hyperexcitability and motor behavior alterations.	(López-Pérez et al., 2010)
3 g /kg/oral	14 days	rats	MSG showed toxic effect on nerve cells and astrocytes's GFAP	(Hashem et al., 2012)
2 g/kg/oral or S.C	10 days	rats	MSG decreased AMPK and increased β-amyloid in the hippocampus.	(Dief et al., 2014)
2 g/kg/i.p	7 days	rats	MSG induced excitotoxic neural damage and elevated levels of ROS.	(Swaminathan et al., 2021)
Monosodium glutamate-induced oxidative stress and hepatotoxicity				
0.6 mg/g	10 days	rats	MSG increased lipid peroxidation, AST, ALT and GGT activities in serum.	(Onyema et al., 2006)

0.6 and 1.6 mg/g	14 days	rats	MSG increased liver and kidney weights and Liver ALT and GGT activities	(Tawfik and Al-badr ., 2012)
Monosodium glutamate-induced obesity and diabetes				
4 mg/kg/i.p	5 days	rats	MSG induced obesity and elevation in triglyceride.	(Železná et al., 2001)
2 mg/g/S.C	4 consecutive days starting from birth day.	mice	MSG induced glycosuria, blood glucose level elevation and increased triglycerides levels.	(Nagata et al., 2006)
4 mg/g/S.C	at days 2, 4, 6, 8 and 10 of rat life	rats	MSG induced glucose intolerance, obesity and insulin resistance.	(de Campos et al., 2007)
3 to 4 mg/g/S.C	at days 2, 4, 6, 8 and 10 of rat life	rats	MSG increased body weight, body mass index, cholesterol, triglycerides, VLDL and LDL.	(Savcheniuk et al., 2014)
3 mg/g/via the rear side of the brain	5 days	rats	MSG induced obesity.	(Wang et al., 2015)
3.0 g/kg /S.C	from the first to the fifth day after birth	mice	MSG increased body weight, Lee's index, food intake, fat weight, cholesterol, TG, LDL, HDL and blood glucose levels.	(Jin et al., 2015)
5 g/kg/oral	15 days	rats	MSG increased body weight and food, and water intake.	(Nandan et al., 2018)

3.33 and 6.6 mg/ml of drinking water	14 days	rabbits	MSG induced diabetes with semen morphological defects.	(Yahaya et al., 2021)
Monosodium glutamate clinical studies				
Soup containing MSG	2 days	32 volunteers	MSG increased food intake and hunger.	(Yeomans et al., 2008)
Oral/Topical	14 days	men with prostate cancer	MSG reduced Ga-PSMA-11 uptakes in salivary glands.	(Armstrong et al., 2021)

GFAP: glial fibrillary acidic protein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GST: glutathiones-transferase, PSMA-11: prostate-specific membrane antigen, VLDL: very low density lipoproteins, LDL: low density lipoprotein, AMPK: AMP-activated protein kinase, ROS: reactive oxygen species, TNF-α, tumor necrosis factor alpha, SOD, superoxide dismutase, NO: nitric oxide, S.C: subcutaneous, i.p: intraperitoneal.

Conclusion

Monosodium glutamate produces a specific taste called umami through activation of the TAS1R1-TAS1R3 in the tongue. Due to its unique taste the use of MSG is increased worldwide. Monosodium glutamate safety is controversial so it should be used with limitation according to the permissible amounts stated by different organizations to avoid its adverse effects. Monosodium glutamate induces neurotoxicity through excessive activation of glutamate receptors in brain resulting in cascades of several events that lead to neurons death in different brain areas. Further studies are needed to confirm and investigate the harmful effects of MSG in human.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this review.

Abbreviations

AIF: apoptosis-inducing factor. ; ATP: adenosine triphosphate. ;BBB: blood brain barrier. ;Bid: BH3-interacting domain death agonist. ; Ca^{2+}: calcium. ;Cox: cyclooxygenase. ; EAAT: excitatory amino acid transporter. ; GSH: glutathione. ; EP2-R: Prostaglandin E_2 receptor 2. ; MTP: mitochondrial transition pores. ; MSG: monosodium glutamate. ; nNOS: neuronal nitric oxide synthase. ; NO: nitric oxide. ;NMDA: N-methyl-D-aspartate receptors. ; ROS: reactive oxygen species. ; TAS1R1-

TAS1R3: taste receptor type 1 member 1- taste receptor type 1 member 3. ; xCT: cystine/glutamate antiporters.

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سلامة استخدام الغلوتامات أحادية الصوديوم والسمية العصبية المحدثة عنها وبعض الدراسات الحديثة الخاصه بها

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الملخص

تستخدم الغلوتامات أحادية الصوديوم كمُحسِّن للنكهة في جميع أنحاء العالم. على الرغم من الجدل الدائر حول سلامة مادة الغلوتامات أحادية الصوديوم , إلا أنها لا تزال تستهلك بكميات كبيرة. توفر هذه المراجعة فهماً أفضل للآلية الجزيئية للسمية العصبية التي يسببها الغلوتامات أحادية الصوديوم بما في ذلك الطرق المختلفة لتنظيم مستوي الغلوتامات في الدماغ وفهم مسار إشارات تذوق الأومامي. بالإضافة إلى ذلك تلخص هذه المراجعة تاريخ اكتشاف الغلوتامات أحادية الصوديوم وتصنيعه والمنتجات والأغذية الطبيعية التي تحتوي على الغلوتامات أحادية الصوديوم وتفاصيل سلامة الغلوتامات أحادية الصوديوم وسميتها والكميات المسموح باستخدامها من هذه المادة وفقًا لأراء المنظمات المختلفة. أخيرًا هذه المراجعة تلقي الضوء علي الدراسات المختلفة الخاصه بالغلوتامات أحادية الصوديوم في كل من الحيوان والإنسان في العشرين عامًا الماضية.

الكلمات المفتحية : جلوتامات أحادية الصوديوم , السمية العصبية , الأمان , الكالسيوم , الشوارد الحره.