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Does Dietary Monosodium Glutamate Cause Neuro-toxicity on The Central Nervous System? A Review

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Abstract

Objective: Monosodium glutamate (MSG) is an additive which is substantially applied in commercially processed foods in order to increase the flavor and sapidity and make a unique flavor which cannot be provided by any other ingredient. Since the discovery of endogenous amino acid glutamate (as a neurotransmitter) in human body, the possible toxicity of exogenous glutamic acid has attracted the attention of numerous scholars. Accordingly, various animal studies have been documented on toxic impacts of MSG on different parts of the body including central nervous system, liver, adipose tissue, reproductive organs, and other systems. Thus, since that time, the safety of MSG has repeatedly been checked and reaffirmed within the scientific communities due to the contradict results. This literature review article specifically aimed to discuss the probable safety of dietary MSG for central nervous system and also provide an integrated information from several studies documented on possible neurotoxic effects of monosodium glutamate on glutamate receptors of Central Nervous System in order to elevate the public awareness about it.

Material and Methods: Literature search of this review was done by keywords of "sodium glutamate" "monosodium glutamate", "MSG", "central nervous system", "CNS", "neurotoxicity", toxic effects of MSG on "glutamate receptors", "hypothalamus" and "pituitary" in Google Scholar and PubMed databases and almost all of the 70 relevant articles from 1984-2021 were considered and among those with similar contents, newer ones were included and the others were excluded. Finally, 32 articles were used to write this literature review article.

Conclusion: Collecting the results of all studied articles seems to supports the hypothesis of safety. In fact, it seems that MSG as a food additive within the limited amounts as well as natural levels of glutamic acid which is present in food supplies provides no serious hazard to the human CNS.

Introduction

Different food additives have been applied in the industry for many years to improve and enhance the color, taste, texture, properties and safety of foods. Monosodium glutamate (MSG) as one of the most common consumed food additives around the world, is invented in 1908 by Kikuna Ikda in Japan [1]. It is used in foods to not only intensify the taste, but also to create a special Umamy flavor, which in Japanese means a pleasant taste of meat and is known as the

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fifth flavor [2, 3]. MSG ($C_5H_8NNaO_4$) contains some anions which are mainly responsible for creating the taste for Umamy flavoring [4].

MSG consists of 78% glutamic acid ($C_5H_9NO_4$), 21% sodium (Na) and 1% pollutants and water and it was formed earlier by hydrolysis of plant proteins with hydrochloric acid with the aim of breaking the peptide bonds and starch fermentation by *Corynebacterium glutamicum*. However, nowadays it is produced by the microbe *Corynebacterium glutamicum* in fermentation process from the starch and sugar (beet or cane) [5].

Evidence demonstrates that the production and industrial consumption of MSG have considerably increased recently, especially in Asia, due to the changes happened in dietary culture and pattern, improvement in food processing industries and living standards. As this flavor enhancer is applied in meat dishes, canned and tuna, soups, frozen foods and food supplements, thus, the countries with the highest consumption of instant and fast foods are located at the top of MSG consumption list, such as china in 2018 [6].

Generally, sodium salt of amino acid glutamic acid is naturally present in some foods like tomato, mushrooms, meat, fish sauce, potato, broccoli and soya souse and leads to nearly no problem. Totally, it has been maintained that natural amount of glutamic acid found in foods is not harmful, but industrially produced synthetic glutamic acid can act as a toxin [1, 5, 6]. The same as salt, pepper, vinegar and baking soda, at first, MSG was invented and considered as a safe ingredient by the Food and Drug Administration (FDA) in 1958. However, over the time, the safety of MSG has repeatedly been reaffirmed within the scientific communities due to the contradictory reports originated from various animal researches. Therefore, in 1991 the European Communities Scientific Committee has categorized MSG in "acceptable daily intake" group which is the most favorable one for a food ingredient. After that, in 1993, the FDA recommended adding the phrase "contains glutamate" to the products containing specific amount of glutamate. The average lethal dose (LD 50) of MSG has been estimated between 15 and 18 g/kg body weight in mice and rats, five times higher than LD50 salt (3 g/kg in mice) [5].Dietary intake of naturally occurring free glutamate estimate to average about 1 g/day in Europe and the United States, and also 0.3–1 g/day from food additive sources of glutamate [1].

This review mainly aimed to discuss the safety of dietary MSG for central nervous system and also provide an integrated information from several studies documented on possible neurotoxic effects of monosodium glutamate on glutamate receptors of Central Nervous System.

Materials and Method

Literature search of this review was done by keywords of “sodium glutamate” “monosodium glutamate”, “MSG”, “central nervous system”, “CNS”, “neurotoxicity”, toxic effects of MSG on “glutamate receptors”, “hypothalamus” and “pituitary” in Google Scholar and PubMed databases and almost all of the 70 relevant articles from 1984-2021 were considered and among those with similar contents, newer ones were included and the others were excluded. Finally, 32 articles were used to write this literature review article.

Results

Glutamate function in CNS as a main component of MSG:

Since 1950s glutamate has been identified as an excitatory neurotransmitter in central nervous system (CNS) of all mammalians including human beings which is playing a vital role in memory, neuronal development, synaptic plasticity and also death of neuronal cells [7]. The receptors of glutamate are categorized into two main groups of ionotropic [N-methyl-D-aspartate (NMDA), kainite, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)] and metabotropic, G protein-linked glutamate receptors (mGlu1 to mGlu8) [8]. Both ionotropic and metabotropic receptors lie at different parts of CNS including hippocampus, hypothalamus and amygdala regulating essential autonomic and metabolic functions [7] including having critical role in energy (glucose) homeostasis (by NMDA) [9], hippocampal long-term potentiation, learning, and memory (via mGluR) [10], modulation of cardiovascular responses recalled from hypothalamic nucleus [11], anxiety disorders (via mGluR) [12] modulation of pain sensation and transmission [13], regulation of amygdala-dependent emotional- affective behaviors (via mGluR of amygdala) [14].

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Common routs of exposure Subcutaneous transmission

Despite specific doses of MSG delivered to many children and infants via different vaccinations, it has been abandoned in foods of infants and children especially under the age of one by U.S. Environmental Protection Agency reports [5].

Dietary transmission

In spite of extensive use of it in different packaged foods and restaurant and industrial food, food processors and manufacturers do not list the exact amount of MSG in labelling or packaging. Therefore, there is no reliable information/way to recognize that how much MSG is ingested by a person in a day [5].

When the neurotoxic effects of MSG have been discovered?

After glutamate discovery as a neurotransmitter performing important functions in CNS, concerns about its transfer from exogenous sources such as glutamate include foods into the blood has been started [15]. In 1970s, MSG safety as a flavoring agent in meat products attracted much attention after a published report that demonstrated the rapid degenerative changes in brain as a result of high doses of subcutaneous injection [16]. Therefore, neurotoxic effects of MSG on human body has intrigued many researchers to do numerous animal studies in order to examine hypothesis of glutamate transfer from blood to brain and also its implications on CNS.

Totally, it has been reported that excessive use of glutamate may be linked to some neurological problems due to imbalance of glutamate occurring in neurons leading to overexcite of cells to the point of damage or enzymatic cascades and cell death [17]. Some scholars have claimed that overexposure to MSG may contribute to some neurological conditions entailing seizures, hyperactivity, attention deficit disorders, migraines, Alzheimer's disease, autism, Parkinson's disease, multiple sclerosis (MS) and Lou Gehrig's diseases [5].

To date the conducted studies on neurotoxicity of MSG can be divided into 2 main groups:

a. Studies on rodents and non-human primates

b. Studies on and human beings

Accordingly, a literature of toxic effects of MSG on CNS of both laboratory animals and human has been reviewed in the following parts.

Studies on rodents and non-human primates

This group of studies can be categorized into 2 groups based on the goal of surveys:

(I) To find that whether dietary ingestion could produce appreciable increase in plasma concentration of glutamate and the occurrence of hypothalamic lesions as a result of MSG function and dose and also the administration method. (II) To examine pathophysiologic effects in adults arisen from chronic exposure of animals to MSG added to their food or water [15]. As shown in table 1 a small literature review has been done to demonstrate the recent animal studies about the neurotoxic impacts of MSG in rodents.

Table1. *Animal studies documented to examine neurotoxicity of MSG*

Type of animal	Dose (mg/kg of bw)	Possible toxic effects/implications	Year	Ref.
monkey	250-4000	Multiple sequential injection of very high dose MSG or glutamate receptor agonists lead to no adverse effect on pituitary function (No adverse effect was observed)	1979	[18]
rat	4	neuronal necrosis in hypothalamic arcuate nuclei in neonatal rats (in high doses)	1999	[17]
rat	4	Prefrontal cerebral cortex changes (such as fewer neurons, shorter and less ramified dendritic processes)	2001	[19]
rat	0.004	postnatal loss of cortical cell number	2004	[20]
rat	0.004	Degenerative changes as pyknotic Purkinje and areas of granular cells in granular layer	2012	[21]

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mice	100, 250, 500	Did not produce significant memory dysfunction and behavioral modification (anxiety and depression) at lower doses, induces oxidative stress in brain tissue (and liver)	2015	[22]
mice	40-80	Histological and histomorphetic alterations including neuronal damage were observed in the hippocampus, cerebrum and cerebellum structure. Alterations in brain structure and antioxidant status.	2016	[23]
rat	200	Accelerating memory impairments (vascular dysfunction, and induction of type2 diabetes)	2018	[24]
rat	0.004	Developmental neurotoxicity	2018	[25]
mice	2000, 4000, 8000	Produce memory (and hepatic) dysfunction	2020	[26]

Studies on human

Researchers have subscribed to the belief that a complete hypothesis about the food related neurotoxicity of MSG have been took shaped as a result of several studies which have been conducted over time. It claims that high dose oral ingestion of MSG would cause an increase in concentration of plasma glutamate resulting in high levels of glutamate in circumventricular organs (notably median eminence) which lacks blood brain barriers (BBB). Normally, endothelial cells of capillaries are joined by tight junctions (which is are the physical location of BBB) prohibiting the entrance of glutamate from blood to brain [27]. Median eminence is a part of hypothalamus containing neurons that plays an important role in hormone release of pituitary. So, it has been maintained that any notable elevation in plasma glutamate may lead to pituitary dysfunction [28].

The most problematic part in the rodent animal surveys was that the doses and the way of administration were not the same as humans MSG intake. Thus, a much debated question is whether toxic implications of animal studies are applicable to human being as well? Actually, up to now there has been a few real studies on neurotoxic effects of MSG on central nervous system of human. Therefore, much research has been done to explore the neurotoxic effects in non-human primates and human originated from plasma glutamate alterations as a result of MSG consumption alone, in foods and beverages [15].

At first Scientists were concerned about the safety of administration of high dose MSG to human, however they start trying on some experiments in adults as an oral single dose up to 150mg/kg such as references [29, 30]. After recognizing the fact that MSG is safe to study in human, at very high doses, the number of experiments and their methods increased, recently. Since scientists cannot look directly into the human brain changes to determine whether specific neurons are firing at abnormal high rate in the hypothalamus, etc., they decided to provide a reliable and indirect measure via measurement of pituitary hormone secretion. In this way, neuro-endocrinologists have long did experiments on control of pituitary hormone secretion through neurons of hypothalamus [15].

Does dietary consumption of MSG affect the CNS of human?

At first the question of "How much dose plasma glutamate normally increase with the consumption of MSG containing foods?" must be answered. According to the recent published articles, it seems that even if there is a single dose of MSG that will stimulate pituitary hormone secretion, it is above the 150 mg/kg of body weight (bw) and it is related to no effect response. Such kind of increase in glutamate levels of plasma in human body never happens even in large amounts of MSG in daily meals. Because, human foods may contain MSG at high concentrations which are improbably ever to ingest at a dose of 150 mg/kg of bw in food origin. [15, 29, 31]. In

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addition, based on a 2007 issue of 'European Journal of clinical Nutrition', the international team of scientists have considered the MSG "harmless for the whole population" in the society and they have recommended 16 mg/kg of bw per day as the safe limit [32].

Conclusion

This review attempts to describe why experiments of non-human models via massive doses of MSG injections are not useful for generalizing it to human in order to evaluate the MSG safety in human food supply regarding to CNS dysfunction. Gathering all the information of experiments, it seems that MSG as a food additive within the limited amounts set by the global committees as well as natural levels of glutamic acid which is present in food supplies provides no serious hazard to the human CNS.

Data/Material availability

Data is available on request from the authors

Ethical approval

There was no practical experiment on human or animals.

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Conflict of interests

The authors have no conflicts of interest.

References

1. Beyreuther K, Biesalski HK, Fernstrom JD, Grimm P, Hammes WP, Heinemann U, et al. Consensus meeting: monosodium glutamate–an update. European J Clin Nutr 2007;61(3):304-13. doi: 10.1038/sj.ejcn.1602526.
2. Yeomans MR, Gould NJ, Mobini S, Prescott J. Acquired flavor acceptance and intake facilitated by monosodium glutamate in humans. Physiol Behav 2008; 93(4-5):958-66. doi: 10.1016/j.physbeh.2007.12.009.
3. Zhang Y, Venkitasamy C, Pan Z, Liu W, Zhao L. Novel umami ingredients: Umami peptides and their taste. J Food Sci 2017; 82(1):16-23. doi: 10.1111/1750-3841.13576.
4. Yamaguchi S. Basic properties of umami and its effects on food flavor. Food Rev Int 1998; 14(2-3):139-76.
5. Chakraborty SP. Patho-physiological and toxicological aspects of monosodium glutamate. Toxicol Mechan Meth 2019; 29(6): 389-96.
6. Thuy LN, Salanta L, Tofana M, Socaci SA, Fărcaș AC, Pop C. A Mini Review About Monosodium Glutamate. Bulletin UASVM Food Sci Technol 2020; 77(1):1-12. doi: http://dx.doi.org/10.15835/buasvmcn-fst:2019.0029
7. 7. Husarova V, Ostatnikova D. Monosodium glutamate toxic effects and their implications for human intake: a review. Jmed Res 2013(2):1-12. DOI:10.5171/2013.608765
8. 8. Meldrum BS. Glutamate as a neurotransmitter in the brain: review of physiology and pathology. J Nutr 2000; 130(4): 1007S-15S.
9. Collison KS, Makhoul NJ, Zaidi MZ, Al-Rabiah R, Inglis A, Andres BL, et al. Interactive effects of neonatal exposure to monosodium glutamate and aspartame on glucose homeostasis. Nutr Methabol 2012;9(1):1-13. doi: 10.1186/1743-7075-9-58.
10. Mukherjee S, Manahan-Vaughan D. Role of metabotropic glutamate receptors in persistent forms of hippocampal plasticity and learning. Neuropharmacol 2013; 66:65-81. doi: 10.1016/j.neuropharm.2012.06.005.
11. López-González M, Díaz-Casares A, González-García M, Peinado-Aragonés C, Barbancho M, de Albornoz MC, et al. Glutamate receptors of the A5 region modulate cardiovascular responses evoked from the dorsomedial hypothalamic nucleus and perifornical area. J Physiol Biochem 2018; 74(2):325-34.
12. Ferraguti F. Metabotropic glutamate receptors as targets for novel anxiolytics. Current Opin Pharmacol 2018; 38:37-42. doi: 10.1016/j.coph.2018.02.004.
13. Pereira V, Goudet C. Emerging trends in pain modulation by metabotropic glutamate receptors. FrontMolecular Neurosci 2019; 11:464. doi: 10.3389/fnmol.2018.00464.
14. Ferraguti F. Metabotropic Glutamate Receptors in Amygdala Functions. mGLU Receptors: Springer; 2017. p. 241-77.
15. Fernstrom JD. Monosodium glutamate in the diet does not raise brain glutamate concentrations or disrupt brain functions. Annals of Nutrition and Metabolism. 2018; 73(5):43-52. doi: 10.1159/000494782.

[DOR: 20.1001.1.26767414.2022.4.1.10.5]
[DOI: 10.52547/pbp.4.1.8]

16. Olney JW. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. Science. 1969;164(3880):719-21.
17. Amat P, Peláez B, Blazquez J, Pastor F, Sánchez A. Lectinhistochemistry and ultrastructure of microglial response to monosodium glutamate-mediated neurotoxicity in the arcuate nucleus. Histol Histopathol 1999; 14(1):165-74.
18. Reynolds WA, Lemkey-Johnston N, Stegink L. Morphology of the fetal monkey hypothalamus after in utero exposure to monosodium glutamate. Glutamic Acid: Adv Biochem Physiol 1979:217-29.
19. Gonzalez-Burgos I, Perez-Vega M, Beas-Zarate C. Neonatal exposure to monosodium glutamate induces cell death and dendritic hypotrophy in rat prefrontocortical pyramidal neurons. Neurosci letters 2001; 297(2):69-72. doi: 10.1016/s0304-3940(00)01669-4.
20. Rivera-Cervantes M, Torres JS, Feria-Velasco A, Armendariz-Borunda J, Beas-Zárate C. NMDA and AMPA receptor expression and cortical neuronal death are associated with p38 in glutamate-induced excitotoxicity in vivo. J Neurosci 2004; 76(5):678-87. doi: 10.1002/jnr.20103.
21. Hashem HE, Safwat ME-D, Algaidi S. The effect of monosodium glutamate on the cerebellar cortex of male albino rats and the protective role of vitamin C (histological and immunohistochemical study). J Molecular Histol 2012; 43(2):179-86. doi: 10.1007/s10735-011-9380-0.
22. Umukoro S, Oluwole GO, Olamijowon HE, Omogbiya AI, Eduviere AT. Effect of monosodium glutamate on behavioral phenotypes, biomarkers of oxidative stress in brain tissues and liver enzymes in mice. World J Neurosci 2015; 5(05):339. doi: 10.4236/wjns.2015.55033
23. Onaolapo OJ, Onaolapo AY, Akanmu M, Gbola O. Evidence of alterations in brain structure and antioxidant status following 'low-dose'monosodium glutamate ingestion. Pathophysiol 2016; 23(3):147-56. doi: 10.1016/j.pathophys.2016.05.001.
24. Saikrishna K, Kumari R, Chaitanya K, Biswas S, Nayak PG, Mudgal J, et al. Combined administration of monosodium glutamate and high sucrose diet accelerates the induction of type 2 diabetes, vascular dysfunction, and memory impairment in rats. J Environmental Pathol Toxicol Oncol 2018; 37(1). doi: 10.1615/JEnvironPatholToxicolOncol.2018017186.
25. Vorhees CV. A test of dietary monosodium glutamate developmental neurotoxicity in rats: a reappraisal. Annals Nutr Metabol 2018; 73(5):36-42. doi: 10.1159/000494781.
26. Omogbiya AI, Ben-Azu B, Eduviere AT, Eneni A-EO, Nwokoye PO, Ajayi AM, et al. Monosodium glutamate induces memory and hepatic dysfunctions in mice: ameliorative role of Jobelyn® through the augmentation of cellular antioxidant defense machineries. Toxicol Res 2020:1-13. doi: 10.1007/s43188-020-00068-9.
27. Hawkins RA. The blood-brain barrier and glutamate. Am J Clin Nutr 2009; 90(3):867S-74S. doi: 10.3945/ajcn.2009.27462BB
28. Peruzzo B, Pastor FE, Blázquez JL, Schöbitz K, Peláez B, Amat P, et al. A second look at the barriers of the medial basal hypothalamus. Experimental Brain Res 2000; 132(1):10-26. doi: 10.1007/s002219900289.
29. Fernstrom JD, Cameron JL, Fernstrom MH, McConaha C, Weltzin TE, Kaye WH. Short-term neuroendocrine effects of a large oral dose of monosodium glutamate in fasting male subjects. The J Clin Endocrinol Metabol 1996;81(1):184-91.
30. Graham T, Sgro V, Friars D, Gibala M. Glutamate ingestion: the plasma and muscle free amino acid pools of resting humans. Am J Physiol Endocrinol Metabol 2000; 278(1):E83-E9. doi: 10.1152/ajpendo.2000.278.1.E83.
31. Yamaguchi S, Takahashi C. Hedonic functions of monosodium glutamate and four basic taste substances used at various concentration levels in single and complex systems. Agric Biolog Chem 1984; 48(4):1077-81.
32. Husarova V, Ostatnikova D. Monosodium glutamate toxic effects and their implications for human intake: a review. European J Clin Nutr 2007; 34:758-65. doi: 10.5171/2013.608765

[DOR: 20.1001.1.26767414.2022.4.1.10.5]
[DOI: 10.52547/pbp.4.1.8]