REVIEW OF STUDIES WITH EFFECTS OF MSG IN LIVER, KIDNEY AND OTHER TISSUES IN ANIMAL MODEL

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ABSTRACT

A naturally found excitatory neurotransmitter, known for its UMAMI taste, is Monosodium Glutamate (MSG). It was known to be safe prior to 1950. People were enchanted with the delicious recipes of some of the restaurants in Far East. Regular restaurant visitors started getting trouble with particular food items. These food items had MSG as one of the chief ingredients. In 1968, an author described the Chinese restaurant syndrome (Kwok's Disease) with symptoms of headache, chest discomfort and facial flushing. Since then several researchers launched extensive research projects in search of toxic role of MSG in human beings. It was documented in late 60s that MSG produces oxygen derived free radicals as evidenced by increased lipid peroxidation products and disturbance of central endocrine axis affecting wide spread areas in body along with causing learning difficulty and obesity in children, irreversible hepatic damage and gonadal dysfunction. An attempt is made to review the studies with effects of MSG in liver, kidney and other tissues in Animal model.

Keywords: Monosodium Glutamate, Kwok's Disease, Neurotransmitter.

INTRODUCTION

Although most of the body tissues are affected by MSG but liver, as chief metabolic centre and kidney as chief organ of excretion, have been main targets of researchers after central nervous system.

Hamaoka & Kusunoki studied the growth pattern of visceral organs in monosodium L-glutamate treated obese mice having hypothalamic lesion. After subcutaneous injections of MSG (2mg/g b.w. for 5 days) to neonatal mice they found reduction of the weights of kidney, heart and testes while they observed weight of liver to be low up to 12 weeks and identical with control mice thereafter which they attributed to occurrence of fatty change in a hypoplastic liver [1].

Malik et al. (1994) observed significant increase in content of total lipids, phospholipids, triglycerides and free fatty acids in liver of adult male mice 31 days after the last injection of MSG (2 mg, 4 mg and 8 mg/g of b.w., for 6 days). They also observed shifting of carbohydrate metabolism towards lipogenesis leading to hyperlipidemia [2].

Yoshida et al found that MSG treated (2mg/g b.w., s.c.) mice became obese 9 weeks after birth and were found with higher blood levels of glucose, total cholesterol, HDL - cholesterol, GPT and cholinesterase along with greater triglyceride content of liver relative to control mice. They noted marked fatty change in liver of 'MSG obese' mice. In another set of 'MSG obese mice' they observed that high fat diet with probucol for 2 weeks significantly reduced the development of fatty liver [3].

Choudhary et al observed increased level of calcium, ascorbic acid and lipid peroxidation products in hepatic microsomes after subcutaneous injection of MSG (4 mg and 8 mg/g b.w. for 6 days) to adult mice. They also found decreased glutathione content and increased activities of enzymes like superoxide dismutase, indicating oxidative stress in hepatic microsomes in treated mice [4].

Diniz et al did a study on adult male Wister rats that were fed with MSG along with standard diet. They observed a rise in voluntary food intake and food conversion ratio. They concluded that MSG caused overfeeding that induced metabolic disorders associated with oxidative stress in absence of obesity that could be reduced by supplementation of dietary fibres [5].

Al-Agha carried out a study to demonstrate toxic effects of oral administration of MSG (2 mg/g b.w. and 3 mg/g b.w.) in adult albino rats. He found dose depended damage to kidney that included loss of brush border of proximal tubules, necrotic changes in tubular lining, infiltration of inflammatory cells in interstitium,

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shrinkage and diffuse hyaline thickening of capillary endothelium [6].

Kaledin et al observed reduction in incidence of liver tumor nodule formation by diethyl nitrosamine (known carcinogen) after a prior exposure of neonatal mice to MSG (2 and 4 mg/g of body weight on alternate days from 1st to 9th day after birth) substantiating anti tumorogenetic role of MSG. They also found reduction of body size, weight of testes and seminal vesicles and increase in fat content of body which they attributed to disturbance of functional activity of sex steroids and other hormones taking part in the regulation of metabolism of body fat and energy [7].

Ortiz et al administered MSG by high intraperitoneal dose that caused appearance of epileptic seizures in Wister rats. On sacrificing the animal 15, 30 and 45 minutes after the seizure they found increase in serum concentration of Alanine aminotransferase, aspartate aminotransferase and lipid peroxidation products (as evidence of oxidative stress) along with degenerative changes in liver and kidney [8].

Farombi et al examined the modulatory role of dietary antioxidants vitamin C, vitamin E and quercetin on MSG (injected at a dose of 4 mg/g b.w. intraperitoneally) induced oxidative damage in liver, kidney and brain of rats. They also documented preventive role of simultaneously administered dietary vitamin C and quercetin on genotoxicity of MSG in bone marrow of rats [9].

Onyema et al found hepatotoxicity in young rats induced by gavage of MSG for ten days (0.6 mg/g b.w.). They found that on simultaneous administration of vitamin E at a dose of 0.2mg/g b.w. there was amelioration of the MSG induced lipid peroxidation evidenced by a several biochemical parameters indicating reduction in reactive oxygen species (ROS) in liver [10].

Eweka and Om'Iniabohs studied the effect of oral administration of MSG on the kidney of adult rat. MSG at a dose of 3 g and 6g in two batches of rats respectively (each weighing 185 g), was fed with growers' mesh for fourteen days. They found dose dependant distortion of cytoarchitecture of renal cortex in the form of reduction in Bowman's space and number of renal corpuscles with stromal vacuolation and distortion of renal corpuscles [11].

Eweka and Om'Iniabohs also studied the effect of oral administration of MSG in a dose of 3 g and 6 g in adult Wistar rats. MSG was given with growers mesh for fourteen days. Exposed rats after sacrifice on fifteenth day of experiment showed dose dependent cyto-architectural distortions, atrophic and degenerative changes in hepatocytes along with dilatation of central veins [12].

Review of studies showing effect of MSG in other tissues

Lechan et al studied the synthesis of luteinising hormone releasing factor and thyrotropin releasing factor in the hypothalamus of MSG treated neonatal albino mice. They found marked reduction in the number of neuronal cell bodies within arcuate nucleus of hypothalamus [13].

Pizzi et al found that neonatal administration of MSG in male and female mice manifested in reduced reproductive ability in adulthood. They experimented with both sexes of mice by injecting MSG in a gradually increasing dose ranging from 2.2 - 4.2 mg/g of b.w. starting from 2nd day to 11th day of neonatal life. They observed that there was impairment of hypothalamo-hypophysial regulation of reproductive function [14].

Kuznetsova et al observed that neonatal administration of sodium glutamate (2 mg/g of b.w. alternate day for 5 days) decreased the motor and investigative activity, anxiety and sexual motivation and increased basal corticosterone in adult mice [15].

Dhindsa et al with doses of 2 mg/g, 4mg/g and 6mg/g of MSG studied the histogenesis of bone and bone marrow after subcutaneous, intraperitoneal and oral administration of MSG in mice. They found repression of ossification of developing endochondral bone and massive accumulation of adipose tissue with receded haemopoietic tissue within bone marrow [16].

Rigdon et al observed that administration of high doses of MSG to rats during first postnatal week resulted in severe loss of retinal ganglion cells and interneurons [17].

Bouvier et al observed that uptake of glutamate into retinal glial cells helped to terminate its neurotransmitter action by keeping its extra cellular concentration below neurotoxic level [18].

Kubera et al found that treatment with MSG in neonatal mice and rats significantly reduced cell mediated immunity in the form of decreased host versus graft reactions. Babu et al claimed that generation of free radicals was the cause of damage to circumventricular organs of the brain of mice [19].

Fajrman et al. (1995) reported an excitatory amino acid transporter protein for L-aspartate and L-glutamate in cerebellum of frogs that maintained extra cellular glutamate concentration below excitotoxic levels and claimed that it might limit the activation of adverse reproductive outcome of MSG [20].

McCall et al claimed that hyperosmolarity was a prerequisite for MSG induced neurotoxic changes in brain of rat, based on their observation that brain lesion was not induced in animals fed with excessive doses of MSG with free access to water [21].

Tsukahara et al found that 'MSG induced obese mice' were unable to maintain body temperature on cold exposure. They explained it to be due to blockage of deiodinase activity for thyroxin in brown adipose tissue under the effect of MSG [22].

Dingledine and Conn reported that central ionotropic receptors served as primary taste transducer of MSG and peripheral metabotropic glutamate receptor modulated the flavour enhancing effect of MSG in mammalian brain [23].

Singh K et al observed that subcutaneous injection of MSG (4 & 8 mg/g b.w.) to adult male mice induced oxidative stress in arterial tissue by lowering the activity of anti-oxidant enzymes. Lucinei et al found that oversecretion of insulin in low glucose in 'MSG obese mice' was due to enhancement of general parasympathetic tonus [24].

Atlasz et al. (2007) observed the neuro protective effect of Diazoxide in rat whose retina was destroyed by perinatal injection of MSG [25].

Matyskova et al carried out a comparative study of neonatally induced MSG obesity and diet induced obesity in mice. They found significantly increased leptin and glucose levels and increased 'fat to body weight ratio' in MSG induced obesity which they attributed to lesion in arcuate nucleus of hypothalamus [26].

SUMMARY AND CONCLUSION

The dietary intake of Monosodium glutamate (MSG) in human at present is not that great to cause such changes but looking at gross individual variations in pattern of injury and susceptibility in animals, MSG should always be used with caution.

Finally it is recommended that monosodium glutamate be considered as a potentially toxic substance on liver and kidney of mammalian tissue and chronic use should be avoided.

REFERENCES

1. Hamaoka K and Kusunoki T. Morphological and cell proliferative study on the effects of visceral organs in monosdium L-glutamate –treated obese mice. *J of Nutritional Science & Vitaminology*, 32, 1986, 395-411.
2. Malik VP and Ahluwalia. Studies on effect of monosodium glutamate (MSG) on various fractions of lipids and certain carbohydrate metabolic enzymes in liver and blood of adult mice. *Toxicol Lett*, 74 (1), 1994, 69-77.
3. Yoshida T, Yoshioka K, Sakane N, Umekawa T. and Kondo. Probucol prevents the progression of fatty liver in MSG obese mice. *Experiments in Clinical Endocrinology and Diabetes*, 103(2), 1995, 119-122
4. Choudhary P, Malik V B, Puri S and Ahluwalia P. Studies on the effects of monosodium glutamate on hepatic microsomal lipid peroxidation, calcium, ascorbic acid and glutathione and its dependent enzymes in adult male mice. *Toxicol Lett*, 89(1), 1996, 71-76.
5. Diniz Y.S., Fernandes A.A., Campos K.E., Mani F, Ribas BO and Novelli E. Toxicity of hypercaloric diet and monosodium glutamate, oxidative stress and metabolic shifting in hepatic tissue, *Food Chem Toxicologyl*, 42(2), 2004, 313-19.
6. Al- Agha S. Histological, histochemical and ultra-structural studies on the kidney of rats after administration of monosodium glutamate. 2006. http,//www.alagsa.edu.ps/ara/aqsamagazine/sience/alive/3.pdf.
7. Kaledin VI, Il'nitskaia SI, Kuznetsova EG and Amstislavskaia TG. Sodium glutamate on some physiological features and chemically induced hepato carcinogenesis in neonatal period in male mice. *Ross Fiziol Zn Im I M Sechenova*, 91(5), 2005, 574-580.
8. Ortiz GG, Bitzer-Quintero O K, Zarate CB, Rodriguez-Reynoso S, Larios-Arceo F, Velazquez-Brizuela IE, Pacheco-Moises F and Rosales–Corral SA. Monosodium glutamate-induced damage in liver and kidney, a morphological and biochemical approach. *Biomedicine and Pharmacotherapy*, 50(2), 2006, 86-91.
9. Farombi EQ and Onyems OQ. Monosodium glutamate- induced oxidative damage and genotoxicity in the rat, modulatory role of vitamin C, vitamin E and quercetin. *Hum Exp Toxicology*, 25(50), 2006, 251-259.
10. Onyema OO, Farombi EO, Emerole GO, Ukoha AI and Onyeze GO. Effect of vitamin E on monosodium glutamate induced hepatotoxicity and oxidative stress in rats. *Indian Journal of Biochemistry & Biophysics*, 43, 2006, 20-24.
11. Eweka AO and Om'lniabohs FAE. Histological studies of the effects of Monosodium glutamate on the kidney of adult wister rats. *The Internet Journal of health*, 6(2), 2007.
12. Eweka AO and Om'Iniabohs. Histological studies of the effects of monosodium glutamate on the liver of wistar rats. *The Internet Journal of Gastroenterology*, 6(2), 2008, 1528-8323.
13. Lechan Ronald M, Alepert LC, Ivor MD. Synthesis of luteinising hormone releasing factor and thyrotrphin–releasing factor in glutamate–lesioned mice. *Nature*, 264(2), 1996, 463-465.
14. Pizzi WJ and Fanslow DJ. Monosodium glutamate administration to the new born reduces reproductive ability in female and male mice. *Science*, 196, 1977, 452-454.
15. Kuznetsova EG, Amstislavskaya TG, Bulygina VV, Il'nitskaya SI, Tibeikina MA and Skrinskaya YA. Effects of administration of sodium glutamate during the neonatal period on behavior and blood corticosterone levels in male mice. *Neuroscience Behav Physiology*, 37(8), 2007, 827-833.
16. Dhindsa KS, Omran Reff G and Bhup Rohan. Effect of monosodium glutamate on the histogenesis of bone and bone marrow in mice. *Acta anat*, 101, 1978, 212-217.
17. Rigdon GC, Boyes WK and Dyer RS. Effect of perinatal monosodium glutamate administration on visual evoked potentials of juvenile and adult rats. Neurotoxicology and Teratology. 11(2), 1989, 121-128.
18. Adamo NJ and Ratner A. Monosodium Glutamate, Lack of effect of brain and reproductive function in rats. *Science*, 169, 1970, 673-674.
19. Bouvier M, Szatkowski M, Amato Alessandra & Attwell D. The Glial cell glutamate uptake carrier counter transports Ph-changing anions. *Nature*, 360, 1992, 471-474.
20. Kubera M, Bubak- Satora M, Skowrol- Cendrzak A, Mazur- Kolecka B, Stedra J, Holan V. Effect of monosodium glutamate on cell- mediated immunity. *Pol J Pharmacol Pharma*, 43, 1991, 39-44.
21. Fajrman WA, Vandenberg RJ, Arriza JL, Kavanaugh MP and Amara SG. An excitatory amino-acid transporter with properties of a ligand-gated chloride channel. *Nature*, 375, 1995, 599- 601.

22. McCall A, Glasser BS, Millington W and Wurtman RJ. Monosodium glutamate neurotoxicity, hyperosmolarity and blood–brain barrier dysfunction. *Neurobehav Toxicol*, 1(4), 1997, 279-283.
23. Tsukahara F, Uchidda Y, Ohba K, Nomoto T and Muraki T. Defective stimulation of thyroxine 5'-deiodinase activity by cold exposure and norepinephrine in brown tissue of monosodium glutamate obese mice. *Horm Metab Res*, 29(10), 1997, 496-500.
24. Dingledine R and Conn PJ. Peripheral glutamate receptors, molecular biology and role in taste sensation. *J Nutrition*, 130 2000, 1039-1042.
25. Singh K and Ahluwalia P. Studies on the effect of Monosodium glutamate (MSG) administration on some antioxidative enzymes in the arterial tissue of adult male mice. *J Nutritional Science and Vitaminology (Tokyo)*, 49(2), 2003, 145-148
26. Atlasz T, Babai N, Reglodi D, Kiss P, Tamas A, Bari F, Domoki F, Gabriel R. Diazoxide is protective in the rat retina against ischemic injury induced by bilateral carotid occlusion and glutamate- induced degeneration. *Neurotox Res*, 12(2), 2007, 105-111.
27. Matyskova R, Maletinska L, Maixnerova J, Pirnik Z, Kiss A and Zelezna B. Comparison of the obesity phenotypes related to monosodium glutamate effect on arcuate nucleus and/or the high fat diet feeding in C57B1/6 and NMRI mice. *Physiological Research*, 2007.