

Epidemiological Studies of Monosodium Glutamate and Health

Hien VuThiThu¹, Andrea Wakita², Saiko Shikanai², Tamami Iwamoto², Noriko Wakikawa² and Shigeru Yamamoto^{2*}

¹National Institute of Nutrition, Hanoi, Vietnam

²Asian Nutrition and Food Culture Research Center, Jumonji University, Saitama, Japan

Abstract

Epidemiology studies regarding to monosodium glutamate and health are limited, since three studies surveyed by questionnaires the relation between monosodium glutamate and Chinese restaurant syndrome; five studies analyzed the association of monosodium glutamate and overweight or obesity; one study related the monosodium glutamate and hypertension; one study investigated the improvement of hemoglobin in Chinese; and another study the association of sleep-disordered breathing. The results of this studies showed that in one of the Chinese restaurant syndrome study conducted by a questionnaire on dietary frequency of monosodium glutamate in Hawaiian men, neurological symptom occurred significantly less often among men who used monosodium glutamate than among non-users. What is more, in another survey conducted in the US found that those people who believed they had experienced Chinese restaurant syndrome reported non-specific symptoms. On the other hand, overweight and monosodium glutamate has been also a concern. Results of these studies have been controversial since from five surveys, two found no associations while three found associations. One of the group of investigators to whom it was reported that monosodium glutamate was not associated with prevalence of weight gain in 2010, the following year published that monosodium glutamate could raise blood pressure in people who took hypertension medication. In 2012 they reported that monosodium glutamate improved the hemoglobin, having an inverse relationship between monosodium glutamate intake and the risk of anemia, and in the last publish, they reported that monosodium glutamate was associated with sleep-disordered breathing.

This review covers these epidemiological studies. However, since then they reported controversial results as well as limit number of surveys conducted, it is difficult to make a conclusion. We need further studies to understand and analyze better the relation between monosodium glutamate and health in free-living subjects.

Keywords: Epidemiology; Monosodium glutamate; Chinese restaurant syndrome; Obesity; Hypertension

Introduction

The ancient Romans used garum as a condiment to season their dishes. Garum is similar to the fish sauce used in many Asian countries today, which is rich in umami substances, such as free glutamate.

Monosodium Glutamate (MSG) has been used for more than a century in Japan and worldwide. It was in 1908 that Ikeda [1] discovered the umami taste derived from the glutamate found in seaweed called Kombu (Kelp). Dietary free glutamate improves taste and palatability. The glutamate is one of the amino acids more abundant in food protein. The protein bound glutamate become free only after it goes to small intestine, hence the glutamate as bound of protein has no such effects of enhancing the taste of food at this level. Recent evidence suggests that taste and palatability are mediated through specific glutamate receptors located on the taste buds and in the stomach [2,3] and plays physiologic actions beneficial to gut function by stimulating the gastric vagus nerve [4]. Even that it was found receptors and physiologic function of glutamate, most of the population associate the MSG with so called "Chinese Restaurant Syndrome" (CRS). The CRS was first reported in the letter to the editor of the New England Journal of Medicine by Kwok [5] in 1968 describing symptoms experienced after eating Chinese meal at Chinese restaurants. It did not take long for media attention to be attracted to the comments in his letter, even though they had not been proven scientifically. In 1969, Schaumberg et al. [6] reported that all, except one of 56 subjects, who received soup with MSG felt symptoms such as burning sensation on their skin, a feeling of pressure in the face, and pain in the chest. This study was not double-blind or placebo-controlled, hence it is criticized later [7]. What is more, the Joint FAO/

WHO Expert Committee on Food Additives (JECFA) concluded that controlled double-blind crossover trials have failed to demonstrate the relationship between CRS MSG intakes. Even that US Food and Drug Administration (FDA) and the Federation of American Societies for Experimental Biology (FASEB) did not discount the present of a sensitive subpopulation, they affirmed the safety of MSG at levels normally consumed by the general population, and concluded that there is no evidence regarding to MSG food use and serious, long term medical problems [8]. In 2000, Geha et al. [9] conducted a multicenter, double-blind, placebo-controlled, multiple-challenge evaluation of the reported reactions to MSG. They concluded that large doses of MSG given without food could cause more symptoms than a placebo in individuals who believe that they react adversely to MSG. However, neither persistent nor serious effects from MSG ingestion were observed, and the responses were not consistent on retesting. Despite these reports and conclusions, the effects of MSG on human health have been controversial.

***Corresponding author:** Shigeru Yamamoto, Asian Nutrition and Food Culture Research Center, Jumonji University, Saitama, 2-1-28 Sugawara, Niiza-City, Saitama 352-8510, Japan, Tel: +81-48-260-7613; E-mail: syamamototokushima@hotmail.com

Received January 03, 2013; **Accepted** January 24, 2013; **Published** January 26, 2013

Citation: VuThiThu H, Wakita A, Shikanai S, Iwamoto T, Wakikawa N, et al. (2013) Epidemiological Studies of Monosodium Glutamate and Health. J Nutr Food Sci S10: 009. doi:10.4172/2155-9600.S10-009

Copyright: © 2013 VuThiThu H, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

MSG and Chinese Restaurant Syndrome

The first epidemiological study investigating the relation between MSG and health was carried out in 1973 in Hawaii in 4,938 ethnically Japanese men aged 45 to 69. Data were drawn from the Honolulu heart program. The dietary frequency of MSG was categorized and coded once or more a day. They did not classify Chinese Restaurant Syndrome (CRS) itself, but reported instead several neurological symptoms, such as blurring, hazy or cloudy vision; numbness and tingling in the right arm; and numbness or paralysis of the face. Results showed that neurological symptoms occurred significantly less among men who used MSG at meals than among non-users [10].

In 1976, Reif-Lehrer et al. [11] surveyed 1,500 subjects with a questionnaire to study the prevalence of CRS. They found that 25% reported some adverse reactions possibly caused by MSG in food. The commonest symptoms were: tightness, burning sensation, and headache. Later in 1977, Kerr et al. [12] conducted a survey by two-part questionnaire to determine the association of unpleasant symptoms with specific foods in 530 subjects drawn from students and employees of Harvard University and its Medical Center. In the first part, questions were asked about unpleasant symptoms associated with various foods, food groups and specific ethnic foods, but did not mention the phrase “Chinese restaurant syndrome”. As a result, no one reported CRS, though 6.6% of subjects could be classified as having experienced possible CRS. However, when in the second part of the questionnaire subjects were asked whether they had ever heard of CRS, what its characteristics were and whether they had personally experienced it, 31% of respondents believed that they were personally susceptible to it. Since this two-part questionnaire had been distributed to subjects who could have been health-aware, Kerr et al. [13] conducted another study attempting to define the prevalence of symptoms characteristic of CRS in the general population using the same two-part questionnaire. Data were obtained from the National Consumer Panel of the Market Research Corporation of America. Of 3,222 subjects, only 1-2% reported symptoms characteristic of CRS, and only 0.19% associated CRS with Chinese food consumption. Furthermore, most of the responders who were “aware” of CRS and believed they had experienced it reported non-specific symptoms. The difficulty in drawing an objective conclusion from questionnaires is that these studies are based on “symptoms” which involve a subjective description, as well as we do not know the quantity of MSG used. When we talk about the effects of foods on health, it seems impossible without knowing the quantity ingested.

MSG and Overweight or Obesity

One of the major world-wide public health issues has been the increasing prevalence of obesity because its consequences raise the predisposition to develop chronic diseases such as diabetes, dyslipidemia, and heart disease. Since some early animal experiments have reported that large amount of MSG injection to neonatal rodents could develop brain lesions resulting in obesity [14], whether MSG affect in human health had been raised. Although it was established that MSG ingestion with food does not cause brain lesions and obesity in animal and human [15], epidemiological studies have been carried out.

The first study was published in 2008 by the International Population Study on Macronutrients and Blood Pressure (INTERMAP group) [16], followed by Shi et al. [17], He et al. [18], Insawang et al. [19] and Hien et al. [20]. Table 1 describes the differences among these studies. They were conducted in different regions of Asia, using different methods, especially with regard to the MSG and food records. In the INTERMAP study data collection was conducted in 1997. In total, 752 healthy subjects were asked to come to the local research center four times: two visits on consecutive days and two additional visits on average 3 weeks later. Dietary data were collected at each visit by the in-depth multipass 24 hr recall method. To assess MSG intake, participants were asked to demonstrate the amount shaken out and this was weighed by trained interviewers using a precise scale. MSG from soy sauce was calculated from the labeling, and if participants reported they had eaten commercially processed foods during the survey, the interviewers obtained the product to calculate the amount of MSG. If participants ate restaurant foods, interviewers visited restaurant and chefs were asked to demonstrate the amount of MSG added to dishes [16].

A second epidemiological study was carried out in China. This was the Jiangsu Nutrition Study (JNS) and data were analyzed from the Jiangsu Nutrition Study of Chinese Adults. The food intake was calculated from a food frequency questionnaire (FFQ). To determine the amount of MSG intake, each household was asked about the monthly consumption of MSG and other seasonings. Individual consumption of MSG was calculated according to the total amount of MSG consumed in the household divided by the number of individuals per household, and then adjusted for the proportion of the household energy intake by each individual. These subjects were surveyed in 2002 and followed for 5 years. In 2007, interviewers did not ask the amount of MSG consumed in a month, as 2002; however, authors considered

Effect of MSG on overweight/obesity	Authors (Journal, Year)	Data collection (Year of survey)	Subjects (n)	Country of survey and geographic area	MSG intake (g) (mean $\pm$ SD)
Negative Association	Hien VT et al (Public Health Nutr 2012)	Survey for MSG and obesity study (2008)	1,528	Vietnam (rural and urban areas) Hanoi, Thua Thien-Hue province and Ho Chi Minh City	2.20 $\pm$ 1.80 g/day
	Zumin Shi et al (Br J Nutr, 2010)	Jiangsu Nutrition Study. Second study published. (1 st data: 2002, 2 nd data: 2007)	1,282	China (urban and rural areas) Jiangsu (Southern China)	3.80 $\pm$ 4.30 g/day
Positive Association	Ka He et al (Obesity, 2008)	INTERMAP study. First publication about MSG and obesity in human study (1997).	752	China (urban and rural areas) Northern and Southern China	0.33 $\pm$ 0.40 g/day
	Ka He et al (Am J Clin Nutr, 2011)	China Health and Nutrition Survey. (Open cohort ongoing nation- wide survey) (1991-2006)	10,095	China (urban and rural areas)	2.20 $\pm$ 1.60 g/day
	Insawang T et al (Nutr Metab 2012)	General adult population (2009 – 2010)	349	Thailand (rural area) Khon Kaen Province	4.0 $\pm$ 2.2 g/day

Table 1: Summary of epidemiological studies in monosodium glutamate and overweight or obesity INTERMAP: International Population Study on Macronutrients and Blood Pressure SD: Standard deviation.

valid the MSG calculated from the FFQ, and the relation of MSG and obesity was not analyzed in 2002 [17].

Another report, the China Health and Nutrition Survey (CHNS), was a prospective open-cohort study, conducted from 1991–2006 with 10,095 subjects participating in the study. Although the number of subjects was large, it is not clear whether there were individuals among the participants whose MSG intake was assessed more than once. MSG, soy sauce and all other condiments were weighed before and after the 24 hr recall. MSG intake was estimated based on the proportion of each individual's food consumption [18].

Recently, another study has been published. It was conducted in six villages located in a rural area of Khon Kaen province, Thailand. The survey was carried out between October 2009 and April 2010. In the final analysis, the study screened 349 subjects aged 35–55. Use of MSG during food preparation was one of the inclusion criteria. For this study, participants were provided 250 g of MSG in a plastic box to use as the source of MSG for food preparation for 10 days. The amount used was recorded on day 10, according to the amount remaining in the box. The MSG consumption was calculated by dividing the number of subjects aged over 10 years to estimate grams/person/day. However, MSG intake was not calculated as the ratio of energy or food intake to determine the proportion of MSG intake by subject. Energy intake was calculated from randomized selected 3-days periods using a 24 hr recall diary, which participants had kept as they were trained by the health volunteers [19].

Furthermore, in 2008, we conducted a study to investigate the relation of MSG and obesity in rural and urban areas of Vietnam in three different regions: Hanoi (North), Thua Thien-Hue province (Central) and Ho Chi Minh City (South). The MSG intake was measured by the weighing method in 1,528 subjects aged 20 years and above. The MSG consumed in the household was divided by the number of individuals, adjusted for the proportion of the food intake, and the nutrient intake was calculated from 3 days of 24 h-recall [20].

The INTERMAP [16] and CHNS [18] studies were conducted by primarily the same researchers in different Chinese subjects within a 4 year period and concluded that MSG consumption was positively associated with overweight development. However, the problem with the group was the overly large differences in the mean MSG intakes. The INTERMAP study showed only 0.33 g/day (SD 0.40) [16] but the CHNS study showed 2.2 g/day (SD 1.6) [18]. The mean intake of the INTERMAP was close to the lowest group in the CHNS study. This makes it difficult to assess the accuracy, and hence the reliability of these studies.

The study from Thailand found that the average intake of MSG was 4.0 g (SD 2.2 g) [19]. They concluded that MSG was associated with an increase in prevalence of overweight (over 25 kg/m²).

In our study [20], the average intake was similar to the second study by He et al. (2.20 ± 1.80 g/day) [18]. However, we did not find an effect of MSG on overweight. Indeed, we found that overweight was associated with increasing age, less physical activity, and increase in the intake of energy, carbohydrate, saturated fat, and animal protein. Furthermore, in our study MSG used as seasoning was measured by the weighing method for every meal during 3 consecutive days, which may be a more reliable method than that used by He et al. [16], since they assessed the amount of MSG seasoning intake by 24 h recall and asked users to demonstrate the amount of MSG seasoning added during food preparation, or, for men and for those subjects who had meals outside the home, by asking the persons who prepared the food to demonstrate

the amount of MSG seasoning added. In the Jiangsu Nutrition Study (JNS), the average consumption was higher than in both He studies [16,18] and close to Insawang et al. [19] as much as 3.8 (SD 4.3) g/day and results showed no association between MSG and obesity. The conclusions of Shi et al. [17] and Hien et al. [20] were similar to a previous Hawaiian study [10] which suggests that MSG has no effect on the body weight.

MSG and Hypertension

Hypertension has been also another common concern in public health around the world. In order to prevent heart disease, WHO has recommended a maximum consumption of 5 g of NaCl per day. If we compare MSG with NaCl, MSG has only 12% sodium, while NaCl contains 40% sodium. However, only one epidemiological study has been conducted, investigating the association of MSG with hypertension [21]. Data were analyzed from the Jiangsu Nutrition Study mentioned above. For this analysis, the MSG calculated and analyzed came mainly from seasonings. When blood pressure was evaluated at baseline and again at follow-up, there was no association between MSG intake and incidence of hypertension. However, at follow-up, association between MSG intake and blood pressure appeared. This is puzzling because the Chinese have been using MSG for almost a century, hence, if MSG intake has a blood pressure increasing effect, it must be accumulative and result in association between MSG intake and blood pressure and incidence of hypertension, not only at follow-up but also at the baseline. When data were adjusted for a number of covariates, it was found that there were significant interactions for MSG intake and blood pressure among participants who took hypertension medication. These results are inconsistent with previous short-term placebo-control studies in humans, which did not find effect of MSG on blood pressure [7,22,23].

MSG and Hemoglobin

Iron deficiency is the most prevalent nutritional problem worldwide. An estimated 2.15 billion people are anemic because of iron deficiency. Most affected are children and women in the developing world. The most commonly used screening methods for the presence of iron deficiency in a population are the measurement of hemoglobin or hematocrit concentration for the presence of anemia [24]. Mulhail et al. [25] found a significant increase in hemoglobin level in children when MSG was fortified with vitamin A in a population trial. A recent epidemiological study reported the relation between MSG and hemoglobin from the Jiangsu Nutrition (JIN) Cohort Study. The method used is described briefly above. In this study [26], it was found that MSG had a positive association with change in hemoglobin levels in men, but not in women. Among participants who were anemic at baseline, there was a significant inverse relationship between MSG intake and the risk of anemia at follow-up, independent of dietary pattern and other lifestyle factors. The increase in hemoglobin was generally seen only in those who were anemic at baseline, suggesting that anemic participants either improved overall nutrition or took other measures to control anemia. Since only one study reported a relation between MSG and hemoglobin, it is necessary to carry out further studies before drawing the conclusion that MSG improves the hemoglobin level.

MSG and Sleep-Disordered Breathing

Sleep-Disordered breathing (SDB) a disorder characterized by abnormalities of respiratory pattern (pauses in breathing) or the quantity of ventilation during sleep, is becoming another public health concern, since could increase the mortality and morbidity such as by cardiovascular or pulmonary disease. SDB also include the obstructive

sleep apnea (OSA). Several risk factors are known for SDB and OSA, such as age and body weight [27]. Recently, the SDB was also associated with the consumption of MSG in the Jiangsu Nutrition (JIN) Cohort Study amount Chinese adults in normal weight [28,29]. Furthermore, MSG was associated with snoring in normal weight. They suggested that a part of the cranial morphology among races, such as Asian having more upper airway and retrognathia than white, they found that MSG could increase the gastrointestinal motility that could explain the increase gastro esophageal reflux. This reflux was associated with OSA.

Conclusions

Even though the Joint FAO/WHO Expert Committee on Food Additives JECFA, the US Food and Drug Administration (FDA) and the Federation of American Societies for Experimental Biology (FASEB) have concluded that MSG is safe for the general population, the alleged health impact of MSG has been an issue of concern because studies in neonate rodents have found that injecting massive amounts of MSG presented adverse effects [27]. In humans, undesirable symptoms have also been reported as mentioned above; however, before drawing conclusions, it is necessary to consider the methods used, the period of the intervention, and the reproducibility of the study, issues that we are not going to discuss in this review. On the other hand, epidemiological studies present some limitations such as the impossibility of conducting a study during the course of a whole year to avoid seasonal variations and the fact that some portion of the findings could likely be due to chance because we are dealing with many variables in the statistical models.

It is interesting to note that the epidemiological studies presented in this review did not coincide in their results, even though three of them were conducted in China, a country with a high level of MSG in its cuisine. Furthermore, none of the authors reported cases of CRS or mentioned it as exclusion criterion, even though in the second study by He et al. [16] the number of participants was 10,095. Hence, it is necessary to conduct further studies in different ethnic and cultural groups to understand the relation between MSG and health.

Acknowledgement

We would like to thank Dr. Andrew Durkin for his assistance in editing the English grammar of this paper.

References

- Ikeda K (2002) New Seasonings. *Chem Senses* 27: 847-849.
- Chaudhari N, Landin AM, Roper SD (2000) A metabotropic glutamate receptor variant functions as a taste receptor. *Nat Neurosci* 3: 113-119.
- Nelson G, Chandrashekar J, Hoon MA, Feng L, Zhao G, et al. (2002) An amino-acid taste receptor. *Nature* 416: 199-202.
- Uneyama H, Nijijima A, San Gabriel A, Torii K. (2006) Luminal amino acid sensing in the rat gastric mucosa. *Am J Physiol Gastrointest Liver Physiol* 291: G1163-G1170.
- Kwok RHM (1968) Chinese restaurant syndrome. Letter to the editor. *N Engl J Med* 278: 796.
- Schaumburg HH, Byck R, Gerstl R, Mashman JH (1969) Monosodium L-glutamate: its pharmacology and role in the Chinese restaurant syndrome. *Science* 163: 826-828.
- Tarasoff L, Kelly MF (1993) Monosodium L-glutamate: a double-blind study and review. *Food Chem Toxicol* 31: 1019-1035.
- Walker R, Lupien JR (2000) The safety evaluation of monosodium glutamate. *J Nutr* 130: 1049S-1052S.
- Geha RS, Beiser A, Ren C, Patterson R, Greenberger PA, et al. (2000) Multicenter, double-blind, placebo-controlled, multiple-challenge evaluation of reported reactions to monosodium glutamate. *J Allergy Clin Immunol* 106: 973-980.
- Go G, Nakamura FH, Rhoads GG, Dickinson LE (1973) Long-term health effects of dietary monosodium glutamate. *Hawaii Med J* 32: 13-17.
- Reif-Lehrer L (1977) A questionnaire study of the prevalence of Chinese restaurant syndrome. *Fed Proc* 36: 1617-1623.
- Kerr GR, Wu-Lee M, El-Lozy M, McGandy R, Stare FJ (1977) Objectivity of food-symptomatology surveys. Questionnaire on the "Chinese restaurant syndrome". *J Am Diet Assoc* 71: 263-268.
- Kerr GR, Wu-Lee M, El-Lozy M, McGandy R, Stare FJ (1979) Prevalence of the "Chinese restaurant syndrome". *J Am Diet Assoc* 75: 29-33.
- Olney JW (1969) Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. *Science* 164: 719-721.
- Takasaki Y (1978) Studies on brain lesions after administration of monosodium L-glutamate to mice. II. Absence of brain damage following administration of monosodium L-glutamate in the diet. *Toxicology* 9: 307-318.
- He K, Zhao L, Daviglus ML, Dyer AR, Horn LV, et al. (2008) INTERMAP Cooperative Research Group. Association of monosodium glutamate intake with overweight in Chinese adults: the INTERMAP Study. *Obesity* 16: 1875-1880.
- Shi Z, Luscombe-Marsh ND, Wittert GA, Yuan B, Dai Y, et al. (2010) Monosodium glutamate is not associated with obesity or a greater prevalence of weight gain over 5 years: findings from the Jiangsu Nutrition Study of Chinese adults. *Br J Nutr* 104: 457-463.
- He K, Du S, Xun P, Sharma S, Wang H, et al. (2011) Consumption of monosodium glutamate in relation to incidence of overweight in Chinese adults: China Health and Nutrition Survey (CHNS). *Am J Clin Nutr* 93: 1328-1336.
- Insawang T, Selmi C, Cha'on U, Pethlert S, Yongvanit P, et al. (2012) Monosodium glutamate (MSG) intake is associated with the prevalence of metabolic syndrome in a rural Thai population. *Nutr Metab (Lond)* 9: 50.
- Thu Hien VT, Thi Lam N, Cong Khan N, Wakita A, Yamamoto S (2012) Monosodium Glutamate is not associated with overweight in Vietnamese adults. *Public Health Nutr* 16: 1-6.
- Shi Z, Yuan B, Taylor AW, Dai Y, Pan X, et al. (2011) Monosodium glutamate is related to a higher increase in blood pressure over 5 years: findings from the Jiangsu Nutrition Study of Chinese adults. *J Hypertens* 29: 846-853.
- Yang S, Liu S, Wang Y, Wan H, Zhao D, et al. (2011) High blood pressure in Chinese ethnic minorities: report from rural Yunnan province. *Am J Hypertens* 24: 1209-1214.
- Zanda G, Franciosi P, Tognoni G, Rizzo M, Standen SM, et al. (1973) A double blind study on the effects of monosodium glutamate in man. *Biomedicine* 19: 202-204.
- Khusun H, Yip R, Schultink W, Dillon DH (1999) World Health Organization hemoglobin cut-off points for the detection of anemia are valid for an Indonesian population. *J Nutr* 129: 1669-1674.
- Muhilal, Permeisih D, Idjradinata YR, Muherdiyantiningsih, Karyadi D. (1988) Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial. *Am J Clin Nutr* 48: 1271-1276.
- Shi Z, Yuan B, Taylor AW, Dal Grande E, Wittert GA (2012) Monosodium glutamate intake increases hemoglobin level over 5 years among Chinese adults. *Amino Acids* 43: 1389-1397.
- Ancoli-IS, Kripke DF, Klauber MR, Fell R, Stepnowsky C, et al. (1996) Morbidity, mortality and sleep-disordered breathing in community dwelling elderly. *Sleep* 19: 277-282.
- Shi Z, Wittert GA, Yuan B, Dai Y, Gill TK, et al. (2012) Nutrition. Association between monosodium glutamate intake and sleep-disordered breathing among Chinese adults with normal body weight.
- Beyreuther K, Biesalski HK, Fernstrom JD, Grimm P, Hammes WP, et al. (2007) Consensus meeting: monosodium glutamate - an update. *Monosodium-glutamate. Eur J Clin Nutr* 61: 304-313.

This article was originally published in a special issue, **Nutrition and Human Health: Health Benefits of Umami Taste in Asian Cuisine** handled by Editor(s). Dr. Hisayuki Uneyama, Ajinomoto Co., Inc., Japan.