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INVITED REVIEW

Is there a relationship between dietary MSG obesity in animals or humans?

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Abstract The sodium salt of glutamate (monosodium glutamate; MSG) imparts a savory/meaty taste to foods, and has been used as a flavoring agent for millennia. Past research on MSG/glutamate has evaluated its physiologic, metabolic and behavioral actions, and its safety. Ingested MSG has been found to be safe, and to produce no remarkable effects, except on taste. However, some recent epidemiologic and animal studies have associated MSG use with obesity and aberrations in fat metabolism. Reported effects are usually attributed to direct actions of ingested MSG in brain. As these observations conflict with past MSG research findings, a symposium was convened at the 13th International Congress on Amino Acids, Peptides and Proteins to discuss them. The principal conclusions were: (1) the proposed link between MSG intake and weight gain is likely explained by co-varying environmental factors (e.g., diet, physical activity) linked to the "nutrition transition" in developing Asian countries. (2) Controlled intervention studies adding MSG to the diet of animals and humans show no effect on body weight. (3) Hypotheses positing dietary MSG effects on body weight involve results from rodent MSG injection studies that link MSG to actions in brain not applicable to MSG ingestion studies. The fundamental reason is that glutamate is metabolically compartmentalized in the body, and generally does not passively cross biologic membranes. Hence, almost no ingested glutamate/MSG passes from gut into blood, and essentially none transits placenta from maternal to fetal circulation, or crosses the blood–brain barrier. Dietary MSG, therefore, does not gain access to brain. Overall, it appears that normal dietary MSG use is unlikely to influence energy intake, body weight or fat metabolism.

Keywords Monosodium glutamate · Glutamic acid · Epidemiology · Amino acid metabolism · Obesity · Fat metabolism

Abbreviations

BAT	Brown adipose tissue
BMI	Body mass index
FDA	Food and Drug Administration
GLP1	Glucagon-like peptide 1
GRAS	Generally recognized as safe
GLU	Glutamate
HDL	High-density lipoprotein
MetS	Metabolic syndrome
MSG	Monosodium glutamate
OP	Obesity prone
SES	Socioeconomic status
TFA	Trans-fatty acid

Introduction

Monosodium glutamate (MSG) has been employed as a flavor additive in Asian (and other) cuisines for over a century, and for millennia before as a component of solutions derived from natural foods, such as the Japanese

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seaweed and fish stock *dashi* (although the flavor was not known to be due to the presence of MSG) (Yamaguchi and Ninomiya 2000; Curtis 2009; Sano 2009). As an additive, it imparts a savory flavor to foods, a taste known as "umami" in Japanese, which is also identified in flavorful foods that naturally contain MSG, such as ripe tomatoes, cheeses, and cooked and aged meats (Yamaguchi and Ninomiya 2000). Recently, a specific umami taste receptor has been identified on tongue taste bud cells (Li et al. 2002). Umami taste is now considered a basic taste, along with sweet, sour, salty and bitter (Kurihara 2009).

Several decades ago, the U.S. Food and Drug Administration (FDA) undertook a review of all food additives approved as GRAS ("generally recognized as safe"), including MSG (Raiten et al. 1995). At the time, glutamate was being studied for many of its metabolic functions, including its possible role as an excitatory neurotransmitter in the brain. One line of investigation involved injecting very large doses of glutamate (as the sodium salt, MSG) into animals in high concentrations, and studying the effects on brain. In particular, its subcutaneous injection into newborn mice, repeatedly over a period of days, was observed to destroy some neurons in the mediobasal hypothalamus, an area that governs anterior pituitary function and participates in the control of body energy balance (Olney 1969). This damaging effect was attributed to excessive stimulation of neurons by glutamate, leading to their death. The animals survived, but as they grew, took on a body morphology not unanticipated from the observed hypothalamic effects: as adults, they were short and obese. At the time of the FDA review of GRAS food additives, MSG use in the diet was speculated to cause these effects as well (Olney 1969). Such speculation led to a substantial research effort over the next two decades, which greatly expanded the fund of knowledge regarding the metabolic handling of dietary glutamate in the gastrointestinal tract, liver, placenta and brain [e.g., see (Filer et al. 1979; Brosnan and Brosnan 2013)]. The conclusion from such metabolic studies was that dietary glutamate, which includes the glutamate present in food proteins, the free glutamate naturally present in many foods, and the glutamate added to foods as MSG to enhance flavor, does not cause the constellation of effects associated with the injection of very large doses of the amino acid. Hence, eating glutamate (including MSG) does not lead to short stature and obesity.

Despite this fund of knowledge, several population-based studies have appeared over the past five years that attempt to link the use of MSG to the growing problem of obesity in rapidly developing Asian countries. In cases where a positive association is reported, reference has been made to the earlier studies in animals injected with glutamate (above) as a likely mechanism for such associations [e.g., (He et al. 2011; Insawang et al. 2012)]. The flavor-enhancing property of MSG has also been invoked as a possible explanation, inasmuch as it should increase food palatability and thus energy intake (He et al. 2011), despite the fact that a body of evidence already exists that indicates this is not the case (discussed below). Recently, MSG has also been examined in animals fed diets containing macronutrients now thought to be metabolically unhealthy, such as high-fructose corn syrup and trans-fatty acids (TFA). MSG has been argued to be involved in some of the observed changes in body fat distribution and metabolism, and as a potential mechanism of action, the same animal studies involving subcutaneous MSG injection (above) have been invoked (Collison et al. 2010a).

It therefore seems appropriate to reexamine these recent studies in the context of the earlier MSG (and glutamate) metabolic database, as this body of literature appears largely to have been ignored or misunderstood. The information that follows first considers briefly the amounts of glutamate present in the diet in its various forms. It then examines the recent population-based studies that have explored the relationship of MSG ingestion to overweight and obesity, followed by a review of the body of human and animal intervention studies in which MSG has been administered under controlled conditions, and body weight parameters examined. Finally, it reviews the metabolic findings for glutamate and MSG, particularly in relation to the diet, to evaluate whether there is any scientific basis that can support renewed speculation that dietary glutamate might be responsible for observed changes in body weight, fat mass, and related metabolic sequelae.

Glutamate in food

Glutamate occurs naturally in foods in both free and protein-bound forms. It constitutes about 8–10 % of the amino acid content of the average dietary protein (not counting glutamine) (Munro 1979; Raiten et al. 1995). For American adults, who consume about 100 g protein/day (Austin et al. 2011), the glutamate intake is 8–10 g, or 110–140 mg/kg (for a 70 kg body mass). The free glutamate content of foods varies widely, but is low in most. However, it is relatively high in some common foods, such as tomatoes (250–750 mg in a tomato) and some cheeses (e.g., parmesan cheese, 500–900 mg/ounce) (Maga and Yamaguchi 1983; Yamaguchi and Ninomiya 2000; US Department of Agriculture and Agricultural Research Service 2011). Consuming a tomato and a few ounces of cheese during a meal might thus add 20–40 mg/kg MSG. Hence, total daily glutamate ingestion from natural sources in the American diet (i.e., naturally present in foods) is probably in the range of 130–180 mg/kg/day. The daily intake from added

MSG averages 350–500 mg/day/person in the United States (Giacometti 1979; Raiten et al. 1995). For a 70 kg person in the U.S., daily glutamate intake as MSG might thus vary between 5 and 10 mg/kg/day, a very small fraction of total glutamate intake from natural sources (less than 5–10 %). Estimates of the amounts of MSG ingested by extreme consumers are also relatively small (e.g., 99th percentile of intake, 12 mg/kg/day) (Stegink et al. 1979).

Past estimates of MSG intake in Asian diets vary from 1,120 to 1,600 mg/day in the Japanese population, 1,570 to 2,300 mg/day in the South Korean population, and 3,000 mg/day in the Taiwanese population (Giacometti 1979; Lee and Lee 1986; Raiten et al. 1995). As an example of the proportion of total daily glutamate intake represented by MSG intake in Asian societies, data for Taiwan show energy intake to be around 40 kcal/kg/day and protein intake 15 % of energy intake [see (Tsai and Huang 1999)]. For a 60 kg Taiwanese individual ingesting 2,400 kcal/day, protein intake would be about 90 g/day. Ninety grams of protein would contain about 9 g of glutamate; hence, the glutamate intake from dietary protein would be about 150 mg/kg/day, and the MSG intake would be around 50 mg/kg/day, or about 25 % of total daily glutamate intake. Recent estimates of MSG intake in relation to total daily glutamate intake in the diet are discussed below for additional Asian countries (Vietnam, Thailand, People's Republic of China).

Population-based studies

Five recent epidemiologic studies have examined the association of added MSG, body weight and health in three Asian countries. The studies, based on both urban and rural populations, were carried out in China, Thailand, and Vietnam (He et al. 2008, 2011; Insawang et al. 2012; Vu et al. 2013). The findings have been inconsistent. Associations between added MSG consumption, obesity and the metabolic syndrome (MetS) were found in two cross-sectional studies conducted in rural China (He et al. 2008) and in rural Thailand (Insawang et al. 2012), respectively. No link between added MSG consumption and obesity prevalence was reported in a cross-sectional study in Vietnam (Vu et al. 2013). One longitudinal study from China did report a link between added MSG consumption and incident obesity (He et al. 2011), whereas another study did not (Shi et al. 2010).

There are standard principles for attributing causation in observational studies. The first requirement is appropriate study design. While randomized, controlled trials remain the clinical gold standard, they are not practical in large population-based studies. Cross-sectional studies collect data at a single point in time, and search for associations between dietary exposure variables and outcome variables. In the studies reported below, exposure variables were the estimates of added MSG consumed in foods prepared at home, restaurants, condiments and processed foods. The outcome variables were body weight and body mass index (BMI), and (in one study) the range of symptoms that make up MetS (Insawang et al. 2012). Socio-demographic (age, gender) and other dietary variables were covariates. In cross-sectional studies, associations between dietary exposure and the health outcomes of interest are typically adjusted for likely confounders by age, gender, energy intakes or socioeconomic status. However, it is generally accepted that cross-sectional studies do not meet the necessary standards for causality.

Longitudinal studies assess dietary exposure at baseline and test the same study participants some time later. The lag period can vary from several months to many years. The goal is to link degrees of dietary exposure at baseline with incident (i.e., not previously seen) health outcomes at a later time, such as new cases of obesity, diabetes, or MetS. In general, the outcome variables in longitudinal studies are dichotomized (yes/no) and the goal is to examine the impact of dietary factors on disease risk. In several well-known studies, data from longitudinal cohorts were used to demonstrate the impact of different diets on the risk of cardiovascular disease, obesity, diabetes, or different forms of cancer (Willett 2012).

The second requirement is for accurate assessment of nutrient exposure, body weights/BMI and health. In studies discussed below, the focus was on added MSG. The assumption was that most of the MSG consumed in Asian countries was added during cooking at home. Some studies also examined added MSG consumed in restaurant foods, processed foods, and condiments (e.g., soy sauce). The amount of free glutamate naturally present in foods, especially fermented foods (apart from soy sauce), was not part of the dietary intake assessment. However, significant amounts of free glutamate are present naturally in many foods (Maga and Yamaguchi 1983; Yamaguchi and Ninomiya 2000). Hence, the method of dietary intake assessment, based on MSG added in cooking may not reflect total free glutamate intake.

The third requirement is that the relation between dietary exposure and the primary health outcomes is consistent, graded, and strong. Convincing dose–response curves should demonstrate the relation between degrees of dietary exposure and body weight or other health outcomes. In some studies discussed below, the relations were inconsistent. For example, whereas the link between MSG consumption and the overall diagnosis of MetS was significant, the links to individual MetS criteria were not (Insawang et al. 2012).

Fourth, a plausible biological mechanism needs to link degrees of nutrient exposure with the observed health outcome. The postulated mechanisms for added MSG action have ranged from taste-driven increases in energy intakes to a direct biochemical action of MSG on brain centers that regulate body energy balance and thus body mass (He et al. 2011; Insawang et al. 2012). However, in some studies, higher intakes of MSG were also associated with the key elements of "nutrition transition" (Drewnowski and Popkin 1997), notably the switch from (a) a plant-based diet to a diet higher in animal protein, fat and cholesterol and (b) active to more sedentary lifestyles. Whether nutritional epidemiology can unambiguously assign a causal role to a specific food, nutrient, or dietary ingredient is an important question. In general, longitudinal studies provide better answers than do cross-sectional studies. These principles should be borne in mind when evaluating the recent observational studies linking added MSG intake to BMI and health.

The INTERMAP study was a cross-sectional study of 752 healthy Chinese adults, age 40–59 years, randomly sampled from three rural villages in north and south China (He et al. 2008). Degrees of dietary exposure were estimated by asking participants to demonstrate MSG addition during cooking using a shaker. Amounts shaken were weighed by trained interviewers. If soy sauce was used, the content was determined from labels or the manufacturer. Dietary intake data were collected using a multi-pass 24-h recall method. Though most subjects consumed only food prepared at home, for those who ate in restaurants or consumed prepared foods at home, the MSG content was estimated through interviews with the restaurant staff and with food manufacturers. The procedure for assessing subject exposure to added MSG thus seemed thorough and most (82 %) study participants reported using added MSG. Participants were then divided by tertiles of MSG consumption. The average intake was estimated to be 0.33 g/day, with the median intake in the highest tertile listed as 0.70 g/day. These values are surprisingly low; all other studies in Asian countries have consistently estimated average daily MSG intake to be in the range of 1.5–3 g/day [see below; (Giacometti 1979; Maga and Yamaguchi 1983; Lee and Lee 1986)]. The daily intake of glutamate as a component of dietary protein was reported to be around 15 g/day. Hence, the glutamate reported to be ingested as added MSG was a tiny fraction of the total daily intake. Since free glutamate and the glutamate in dietary protein are handled metabolically in the same manner by the intestines (i.e., they are almost completely metabolized; see below), the method of assigning dietary glutamate exposure by tertile of MSG use was most likely incorrect. When it comes to daily glutamate consumption from all sources, the non-users (the reference group) and the users may not have been that different. Rather, the use of added MSG may have been a marker for other dietary behaviors.

The investigators reported that for MSG users in the highest tertile of intake, compared to non-users of MSG (the reference group), the adjusted odds ratio of being overweight (BMI $\geq$23) was 2.10. The study concluded that added MSG intake was associated with higher overweight risk, independent of total energy intakes. Since total dietary glutamate intake must have been very similar between the subjects who reported ingesting no MSG and those in the highest tertile, some other feature must explain the difference noted in BMI across MSG user (and non-user) groups.

One possibility is the significant difference in diet quality. Proceeding from non-user progressively through the three tertiles of MSG use (low to high), subjects consumed more calories, more animal protein, fat and cholesterol, and less vegetable protein, total carbohydrates, starch and fiber. These findings indicate that the groups may simply differ in socioeconomic status (SES). Recent studies of countries undergoing rapid economic advancement show that as citizens rise in SES, the old diet, consisting of low amounts of fat and animal protein, and high amounts of complex carbohydrates, with little variety, is gradually replaced by a diet of greater variety, containing more fat, animal protein and sugars, less complex carbohydrates, and more calories (a process termed "nutrition transition") (Drewnowski and Popkin 1997). Moreover, in developing nations, higher SES is associated with higher BMIs, especially among women (Monteiro et al. 2004), much as reported by He et al. (He et al. 2008). Disentangling the impact of socio-demographic factors on health from the impact of single foods, nutrients or dietary ingredients is notoriously difficult.

Indeed, a more recent cross-sectional study by Vu and associates (Vu et al. 2013) examined this same issue in 1,528 adults (20 years or older) from both rural and urban areas of Vietnam. Dietary intake data were collected in subjects' homes, using a 24-h recall method for three consecutive days. During these days, subjects were asked to eat meals prepared at home. A researcher visited the home before and after each meal, to weigh bottles of MSG and other seasonings containing MSG. Following each meal, subjects were also queried regarding the composition of the meal and how much was consumed. MSG ingestion was determined from how much MSG and seasoning were used in meal preparation, and the amount of food consumed by each subject. In this study, 81 % of subjects were MSG users. Mean MSG intake was estimated to be 2.2 g/day (1.9 g/day glutamate) among users. Subjects ingested around 70 g/day of plant and animal protein, which was reported to yield 14–15 g/day of glutamate ingested in protein. This estimate of daily MSG intake is more typical for Asian countries (Giacometti 1979; Maga and

Yamaguchi 1983). Hence, glutamate intake as MSG was about 12 % of reported total daily glutamate ingestion in food.

The authors noted no significant difference between urban and rural samples in MSG intake, but rural subjects had a significantly lower incidence of overweight/obesity. Rural subjects also consumed significantly less animal protein and energy than urban subjects. From the data, factors predicting overweight were less physical activity (occupational heavy work) and more food ingestion (dietary energy, animal protein, saturated fat and carbohydrate intakes). The dietary and physical activity findings, together with the observation that rural living was associated with a lower incidence of obesity, suggest that lifestyle changes associated with rapid economic development and the attendant "nutrition transition" in Vietnam, as in China, may be important determinants of the increase in overweight and obesity. In this study, MSG consumption was apparently without any significant effect.

Another recent cross-sectional study in rural Thai subjects ($n = 349$, 35–55 years, 62 % women) examined the incidence of the MetS in relation to MSG use (Insawang et al. 2012). The MetS consists of a set of risk factors for the development of heart disease and diabetes, and includes abdominal obesity, atherogenic dyslipidemia (elevated plasma triglycerides and reduced high-density lipoprotein (HDL)-cholesterol), elevated plasma glucose, and elevated blood pressure (Grundy et al. 2005). Dietary intake data were collected using 24-h recall diaries for three consecutive days. Dietary exposure to added MSG was assessed by measuring the use of MSG in cooking at home over a 10-day period. Participants were provided with a container of MSG by the investigators and were asked to use only this supply of MSG in preparing food at home. A physical examination was administered, and a fasting blood sample taken for measurements of metabolic variables.

MSG users were divided into tertiles, with median MSG intakes of 1.9, 3.6 and 6.0 g/day. The investigators reported a significant trend towards an increased prevalence of overweight (% of tertile having a BMI >25) and metabolic syndrome (% of tertile having MetS) with increasing MSG intake across the three tertiles. It is noteworthy in this study that no differences in total energy, fat, carbohydrate or protein intakes were found, nor was there any difference in the level of physical activity, across the tertiles. That is, no changes in energy input or output were noted; hence, appropriately, no change in body mass across groupings was observed.

The diagnosis of MetS was then made on the basis of accepted criteria (listed above). There were no significant differences by MSG consumption tertile on any of the individual diagnostic criteria for MetS (Grundy et al. 2005). However, the composite diagnosis of MetS (defined as the presence of any three risk factors) did rise across the MSG consumption tertiles, even though BMI did not. This is curious, since it is generally accepted that high BMI is one predictor of the MetS (Janssen et al. 2004). In this study, MetS seemingly increased with added MSG consumption, but BMI and the individual MetS components did not.

The longitudinal Jiangsu Nutrition Study examined the potential impact of MSG ingestion on weight gain over a 5-year period in Chinese adults (509 men, 718 women, average age about 50 years) living in rural and urban communities (Shi et al. 2010). Dietary and baseline BMI measurements were made at the outset of the study, and follow-up BMI determinations were then obtained 5 years later. Food intake interviews at baseline used a household food frequency questionnaire to estimate monthly intakes, and individual 3-day weighed food diaries to corroborate food frequency questionnaire data. At baseline, mean MSG consumption was estimated to be 3.8 g/day for the entire sample, with 72 subjects reporting no MSG use. Median MSG intake across quartiles was estimated to be 0.8, 2.0, 3.7 and 6.9 g/day. At baseline, across quartiles, total glutamate intake (from protein and MSG) was about 14 g/day, except in the highest MSG quartile, where total glutamate intake was about 19 g/day. Daily energy and protein intakes were not significantly different across MSG quartiles, although intake of fat and animal-derived foods increased with increasing MSG intake, while carbohydrate intake declined. Central obesity, body weight and BMI declined across quartiles with higher MSG use.

At the end of the 5-year period, there was no clear trend in the association of baseline MSG intake with weight change, BMI change, or changes in waist circumference or central obesity. For example, comparing the fourth (highest) and first (lowest) quartiles of MSG intake, the fourth quartile had lower BMI and weight gains than the first quartile, but a greater increase in waist circumference, and yet a lower percentage of central obesity. Linear regression of MSG intake and the development of a 5 % or greater weight gain revealed an inverse association. The investigators concluded that MSG intake was associated neither with obesity nor with clinically significant weight gain over 5 years.

One other longitudinal study, based on data from the China Health and Nutrition Survey, examined the consumption of added MSG in relation to incident overweight in 10,095 healthy Chinese adults (18–65 years; approximately 55 % women) (He et al. 2011). The mean follow-up was 5.5 years. MSG intake assessment was based on a weighted food inventory (primarily MSG and soy sauce) and three 24-h recalls. At baseline, mean added MSG consumption was estimated to be 2.2 g/day. Energy intake was approximately 2,300 kcal/day, and total protein intake about 30 g/1,000 kcal, indicating that daily protein intake

was about 70 g/day. Since this level of protein intake is close to that in similar Chinese studies, where glutamate intake data were also provided (He et al. 2008; Shi et al. 2010), the total dietary glutamate intake should also have been quite similar, around 14 g/day. Hence, the total glutamate intake each day (from protein and MSG) most likely ranged between 14.4 and 19.9 g/day (lowest to highest quintiles of MSG intake; see Table 1 in (He et al. 2011).

Participants in the highest quintile of added MSG intakes were reported to have a 1.33 hazard ratio for overweight, adjusting for age, dietary energy, physical activity and other lifestyle factors. However, study respondents with higher MSG intakes also had higher incomes and higher intakes of dietary energy, fat and sodium, and lower physical activity levels. As shown in Table 1 of He et al. (2008), differences in fat intake per 1,000 kcal were especially noteworthy. Rising consumption of dietary fat certainly offers a portion of the explanation for rising obesity rates in China, and is generally explicable in terms of the broad dietary changes occurring with the "nutrition transition" in Asian countries undergoing rapid economic development (Drewnowski and Popkin 1997; Gordon-Larsen et al. 2014).

Viewing all of these studies together, the evidence thus far is not compelling that MSG intake in Asia is associated with increased BMI or risk of developing the MetS. MSG, and prior to its isolation and purification, food preparations containing MSG (konbu in Japan, soy sauce, fish sauces) have been components of Asian diets for millennia (Yamaguchi and Ninomiya 2000; Curtis 2009). A more productive search for the dietary source of the rapid increase in BMI and co-morbidities in Asian populations seems to be the "nutrition transition" occurring with the rapid economic development of many Asian countries, including China (Drewnowski and Popkin 1997; Gordon-Larsen et al. 2014). More generally, given the major and multiple shifts in socio-demographic and dietary factors linked to the "nutrition transition", it may be premature to claim that obesity in this context is caused by a single food, nutrient or dietary ingredient. Indeed, nutritional epidemiology is gradually making the transition from a focus on single nutrients to the analysis of composite meal patterns and their impact on health. With regard to MSG, an indispensable component of future research will be the development of a dietary glutamate database, allowing researchers to make clear distinctions between added MSG, and the considerable amounts of glutamate present in proteins and occasionally as free glutamate (sometimes as MSG) present naturally in foods.

Intervention studies: MSG and body weight

While findings from population-based studies do not prove causation, associations identified from such investigations are often useful in hypothesizing causal links, which can then be examined through controlled intervention studies. In the case of MSG, a large number of such studies, in both animals and humans, exist and indeed preceded the above epidemiologic studies. As discussed below, they demonstrated (and continue to demonstrate) that MSG ingestion in the diet does not stimulate food intake or promote weight gain.

First, in humans, single-meal selection studies, in which subjects (elderly and diabetic individuals were studied separately) ingested a meal with or without MSG added to food, the inclusion of MSG increased the intake of foods to which MSG had been added, but reduced the intake of other food items. As a consequence, the total energy intake from the meal was unaffected by the inclusion of MSG [see (Bellisle 1999)]. In another study, chicken broth pre-meals that either contained or lacked MSG were found to have no effect on energy intake during a cafeteria style lunch made available following the pre-meals (Carter et al. 2011). Similar effects were reported by others (i.e., a pre-meal containing MSG had no effect on subsequent energy intake during a test meal) (Rogers and Blundell 1990; Finlayson et al. 2012), except in one study which employed a high-protein pre-meal (Luscombe-Marsh et al. 2009). In addition, female subjects susceptible to overeating (scoring high in "disinhibition"), while consuming more energy in a test meal following a sweet preload, compared to subjects having low "disinhibition", did not consume more in the test meal when the pre-meal contained MSG. In other words, in subjects susceptible to overeating, MSG appeared not to be a stimulus for overeating (although sweet taste was) (Finlayson et al. 2012). Hence, almost all of these studies show that while MSG can improve the palatability of foods (Yamaguchi and Kimizuka 1979; Yamaguchi and Takahashi 1984), its inclusion in the diet does not appear to promote increased caloric intake, even in individuals susceptible to overeating.

The few longer-term studies in humans also indicate that MSG inclusion in the diet does not promote increased food intake or weight gain. For example, one series of studies examined the effects of MSG ingestion by young-middle-aged males on serum cholesterol concentrations (Bazzano et al. 1970; Olson et al. 1970). MSG was given in doses of up to about 150 g/day for as long as 6 weeks (these are very large daily glutamate doses—the average intake from all dietary sources, including protein, might reach 15 g/day (Panel on Macronutrients 2005), and had no effect on body weight. MSG has also been studied for its ability to increase food intake and body weight in diabetic and elderly subjects. In one series of studies in institutionalized subjects, MSG was added to typical food items (e.g., a meat dish) in amounts appropriate to improve flavor (savoriness; 300 mg/dish), and the effect on food intake

and body weight was followed over 16 weeks. No effect on food intake or body weight was noted (Essed et al. 2007).

Second, animal studies show that MSG does not increase food intake or body weight, even when administered in extremely large doses for extended periods of time. Early studies were conducted to evaluate food intake and body weight in relation to safety, not satiety. Nonetheless, they offer useful information on this issue. Later studies focused specifically on appetite and body weight effects of MSG. In the studies of the simplest design, MSG was included in standard lab diets in amounts up to 4 % (i.e., 4 grams MSG/100 g diet, which tripled the total dietary glutamate content) and fed to weanling or young adult rats for two years (approximately their natural life span). No differences in body weight were noted among the groups (which included animals fed a diet lacking MSG) (Owen et al. 1978; Ebert 1979), and no differences in food intake were observed in the study in which it was measured (Ebert 1979). Multi-generation studies have been conducted in mice. In a two generation study, MSG was included in a standard rodent diet (0, 2 or 4 % by weight), beginning 2 weeks prior to mating. Both the parent and offspring generations consumed about 4,000 and 8,000 mg/kg/day MSG on the 2 and 4 % MSG diets, respectively (Yonetani et al. 1979). No differences in food intake or body weight were noted in either generation. Anantharaman conducted a three-generation study in mice, adding 0, 1, or 4 % MSG to the diet. These doses produced daily MSG doses in males and non-lactating females of 1,000–2,000 mg/kg/day (1 % MSG diet) and 6,000–7,000 mg/kg/day (4 % MSG diet). In lactating females, because food intake rose to meet the metabolic demands of nursing, the daily MSG dose rose as high as 25,000 mg/kg/day (4 % MSG diet). MSG ingestion had no effect on food intake or body weight in parental or offspring generations (Anantharaman 1979). It is noteworthy that these daily doses of MSG are often much greater than those shown to produce growth and reproductive abnormalities when injected repeatedly into newborn mice by the subcutaneous route (e.g., 3,000 mg/kg/day for 6 days (Olney 1969; Bunyan et al. 1976)), an outcome difference that is explained by the fact that the gastrointestinal tract metabolizes essentially all ingested glutamate (Reeds et al. 1996, 2000) (discussed below). Indeed, Bunyan and associates demonstrated the route-of-administration dichotomy in one series of studies in mice (Bunyan et al. 1976). They administered MSG by the dietary route (10 % MSG diet) from conception through weaning. Other animals received repeated, subcutaneous injections of MSG during the early post-natal period. When examined as adults, mice exposed to MSG via the diet were of normal weight and fat content, while those injected post-natally with MSG were overweight and obese (Bunyan et al. 1976).

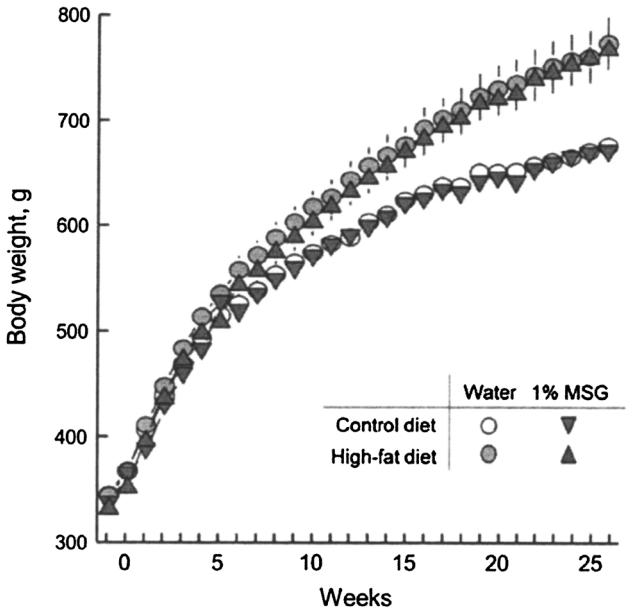

Fig. 1 Body weights of male obesity-prone (OP) rats fed AIN-76A control diet or a high-energy diet. Half the rats fed each diet had access to 1 % MSG solution in addition to water to drink. The experiment began when the rats were 9 weeks of age and ended 25 weeks later. Data are means ± standard errors (*vertical lines*); standard error bars obscuring symbols are not shown. Source: (Tordoff et al. 2012)

More recently, Kondoh and Torii administered MSG chronically via drinking water (1 % MSG); rats prefer 1 % MSG to water, and voluntarily consumed around 650 mg/kg/day (Kondoh and Torii 2008). This dose of MSG, which is quite large, did not elevate plasma glutamate concentrations over those observed in animals consuming only water, even when measured during the time of day when rats were most actively drinking (dark period). In one study, pregnant rats were provided with 1 % MSG from birth through weaning, and their male offspring continued on 1 % MSG for an additional 18 weeks (controls were given water). In another study, young adult male rats were provided with water or 1 % MSG for 15 weeks. Subgroups were maintained on one of several diets, varying in fat or sugar content. The key finding of these experiments was that, if anything, animals ingesting MSG had slightly reduced body weights, and significantly lower intra-abdominal and subcutaneous fat masses, independent of diet (measured by magnetic resonance imaging of the animals' torsos). Tordoff and associates recently expanded on this observation by studying the effects of MSG ingestion on body weight, fat mass and food intake in several rat and mouse models. No effect of MSG ingestion on any of these parameters was observed (Tordoff et al. 2012). For example, in one study, rats were examined that have a natural tendency to become obese on high-fat diets ["obesity-prone rats" (Levin et al. 1997)]. Young adults

were fed either a normal diet or one with a high-fat content for 26 weeks. Half of the animals in each group had access to 1 % MSG, and consumed around 750 mg/kg MSG each day. The animals ingesting the high-fat diet gained more weight (and weighed more) than those ingesting the normal diet, but there was no difference in each diet group between those rats ingesting MSG and those ingesting water alone (Fig. 1). Similar observations have also been made by Collison and associates in mice, albeit at markedly smaller daily doses, with the high-fat diet consisting of trans-fatty acids and another diet containing high-fructose corn syrup. MSG was supplied via the drinking water to mating couples prior to conception, continued through weaning, and then provided to the offspring for as long as 32 weeks of age. In what appears to have been a single, large dietary study, MSG ingestion was reported to be associated with either unchanged or reduced body weight, compared to control values on all diets in both male and female offspring (standard lab diet, trans-fatty acid-containing diet, high-fructose corn syrup-containing diet) (Collison et al. 2009, 2010a, b).

MSG has also been reputed to produce abnormalities in fat metabolism without changing body weight (i.e., the overall size of body fat stores). For example, it was reported to produce abnormalities in hepatic fat metabolism, leading to fatty liver (e.g., non-alcoholic fatty liver disease) (Malik and Ahluwalia 1994; Yoshida et al. 1995; Diniz et al. 2004; Nakanishi et al. 2008). Such studies have almost always administered MSG by subcutaneous injection, not ingestion, to animals at the same very high doses (2,000–8,000 mg/kg) and repeated administration schedules used decades ago to produce lesions in retina and hypothalamus [e.g., (Olney 1969)]. The findings are thus not relevant to the use of MSG in the diet, particularly since the reported changes in liver histology and size have never been observed in studies in which MSG has been provided in the diet, even in enormous doses for long periods of time (Owen et al. 1978; Yonetani et al. 1979; Nakamura et al. 2013). In one study, however, MSG was reported to produce some abnormalities in hepatic (and visceral) fat stores in animals chronically ingesting very low levels of MSG along with diets containing trans-fatty acids or fructose (Collison et al. 2009, 2010a, b, 2011). Trans-fatty acids and fructose are macronutrients known to produce abnormalities in fat metabolism in liver and adipose tissue, as well as to increase body mass (Song et al. 2007; Tetri et al. 2008; Obara et al. 2010; Mells et al. 2012). However, in this study, the ingestion of MSG along with the control or TFA-containing diet did not influence body weight, liver triglyceride content or visceral adipocyte volume, although TFA by itself produced clear effects (Collison et al. 2009). Some differences in fasting concentrations of serum triglycerides and free fatty acids were reported, but the usefulness of the data is unclear, given the extremely low serum glucose levels (around 50 mg/dl, or 2.5 mM, or less than half normal), indicating that the animals were likely fasted 12–16 h (a very long time metabolically for mice, which have a metabolic rate ~7-times that of humans (Kleiber 1947). The HFCS diet did not alter body weight, and ingestion of MSG did not affect final body weight. But, MSG was reported to stimulate the increase in abdominal girth (circumference) as the animal grew, although absolute values at the termination of the study were not provided (Collison et al. 2010a). The addition of MSG to the diet, however, did not affect visceral adipocyte area. It should be noted that such effects of MSG on liver and abdominal fat have not been found by other investigators using the same, or higher MSG doses, administered in the same manner (in the drinking water) (Kondoh and Torii 2008; Nakamura et al. 2013).

Generally speaking, the paucity of data linking dietary MSG to changes in fat distribution and metabolism is not surprising. No doubt, one reason is the difficulty in identifying a mechanism by which ingested MSG could selectively influence hepatic and adipose tissue fat synthesis and/or turnover. First, if the proposed mechanism is that MSG (glutamate) would enter the circulation and the target organs (liver, adipose tissue) to produce its effect (discussed in further detail below), the ingestion of the amounts of MSG in these studies [e.g., (Collison et al. 2009; Nakamura et al. 2013)] would be dwarfed by the glutamate provided in dietary proteins, and thus have no impact on plasma glutamate concentrations (Fernstrom 2007). Second, even if plasma glutamate did rise following MSG ingestion, and managed to enter hepatocytes, the only enzyme in fatty acid biosynthesis that has been directly linked to glutamate, Acetyl-CoA carboxylase (a key enzyme in the control of fatty acid biosynthesis) (Boone et al. 2000), has a Km of 25 mM for activation by the amino acid, and thus would not be affected by glutamate concentrations normally present in hepatocytes ($\leq$2.5 mM) (Williamson et al. 1967; Wijekoon et al. 2004). This enzyme is thus not responsive to glutamate in the physiologic range of hepatic glutamate concentrations. Third, marked increases in plasma glutamate (11-fold above normal excursions over the course of the day) can cause a modest increase in plasma insulin concentrations in humans (Fernstrom et al. 1996), but such an effect does not occur in the range of MSG intakes considered normal (Hosaka et al. 2012). Hence, MSG ingestion cannot induce fatty acid synthesis through a direct mechanism involving insulin. Fourth, could MSG have an action within the gut lumen that indirectly influences fat metabolism elsewhere in the body? MSG ingestion has been reported to produce a small increase in circulating concentrations of the gut hormone glucagon-like peptide-1 (GLP1) (Hosaka et al.

2012). As an incretin, GLP1 enhances the secretion of insulin (Vilsboll et al. 2009), which promotes lipid storage via several actions within the adipocyte (Lafontan 2008). However, GLP1 agonists given to animals fed a high TFA/high HFCS diet reduce fat depots and liver weight (a direct GLP1 action on liver), and improve glucose tolerance (Mells et al. 2012). The GLP1 agonist Exendin-4 also reverses hepatic steatosis in genetically obese mice (ob/ob) (Ding et al. 2006). Human hepatocytes express GLP1 receptors, and respond to GLP1 in vitro by reducing their fat content (Gupta et al. 2010). Hence, stimulation of GLP1 secretion from enteroendocrine cells by luminal glutamate (MSG) would not be expected to promote increased fat deposition. Fifth, MSG has been reported to enhance brown adipose tissue (BAT) thermogenesis in rats during the first several minutes after meal initiation, suggesting an indirect action mediated via the sympathetic innervation of BAT (Smriga et al. 2001). Such an effect, if real, would indicate an action of dietary MSG to reduce, not increase fat depots. However, the effect is small, transient, confined to young animals, and at present appears not to have been pursued further. This issue therefore awaits further clarification.

Dietary and metabolic issues relevant to MSG (glutamate) absorption and distribution within the body

Recent studies proposing that dietary MSG might promote obesity in humans and animals base their hypotheses on one of two notions: (a) MSG enhances food palatability and causes overeating and weight gain (Shi et al. 2010; He et al. 2011), or (b) MSG ingestion damages a portion of the brain (the hypothalamus) involved in regulating energy balance in the body, resulting in a net increase in energy accretion (i.e., body fat) (He et al. 2008, 2011; Collison et al. 2010a, b; Insawang et al. 2012). The human and animal studies discussed in "Intervention studies: MSG and body weight" indicate that the ingestion of MSG does not cause overeating (or obesity), and thus this issue will not be discussed further. However, the issue of dietary MSG causing damage to the brain requires discussion, as MSG injection studies are offered in support of this connection, not MSG ingestion studies. The vast bulk of this literature clearly indicates that MSG ingestion does not cause hypothalamic damage, and thus provides no basis for thinking that such a mechanism links dietary MSG to obesity.

The originally hypothesized mechanism by which dietary MSG would cause direct disruption of brain circuits that regulate energy balance (notably the mediobasal hypothalamus) requires that ingested MSG be absorbed from the intestines into the circulation in amounts that cause increases in plasma glutamate concentrations large enough to overwhelm the blood-barrier mechanism that prevents glutamate penetration into brain, allowing the influx of large amounts of glutamate (Olney 1994). Since glutamate is an excitatory neurotransmitter (indeed, the dominant excitatory transmitter in brain), its flooding into brain would cause some neurons (notably those in hypothalamus) to be so over-stimulated metabolically that they die. Some of these neurons are components of neuronal circuits that control energy balance, the argument goes, and as a consequence of their demise, energy-balance circuits malfunction, leading ultimately to aberrant energy balance and weight gain.

It is certainly true that when animals are injected subcutaneously with extremely large doses of MSG, such effects occur [e.g., (Olney 1969)]. But it should be recalled that the doses required to produce such effects are typically in the range of 1,000–8,000 mg/kg per injection, and such injections are usually administered to newborn rodents repeatedly over several days. Moreover, the plasma concentrations of glutamate required to induce such direct effects in brain are a minimum of 20-fold above normal [e.g., (Hu et al. 1998)]. When MSG is instead ingested (not injected) by rodents, even at very high doses, plasma glutamate concentrations do not rise appreciably [e.g., (Kondoh and Torii 2008)], and it is thus not surprising that the consequences expected from injection studies do not occur [e.g., see (Bunyan et al. 1976)]. Such is also the case in humans. For example, in one study, subjects were studied on a hospital ward on two separate days, during which they received all meals and snacks at normal times of day (Tsai and Huang 1999). The base diet provided was the same on the two occasions, and by itself contained no MSG. On one day, the diet alone was provided; on the second day, this same diet also contained 100 mg/kg MSG, divided between breakfast, lunch and dinner. This study was conducted in Taiwanese subjects; the dose of MSG employed was twice the estimated average amount consumed in the Taiwanese diet each day (Giacometti 1979). Blood samples were drawn repeatedly throughout the day, and plasma analyzed for glutamate. The results showed that the addition of MSG to the diet had no effect on plasma glutamate concentrations throughout the day (Fig. 2). The neurotoxic hypothesis requires that the plasma glutamate concentration rises (and rises substantially). Since it does not, an effect on brain cannot be expected. Indeed, the hypothesis does not work in humans even when plasma glutamate concentrations are artificially increased. When humans are given a single, very high dose of MSG (150 mg/kg) in a non-caloric liquid immediately following an overnight fast, plasma glutamate concentrations can be increased tenfold over about an hour (Fernstrom et al. 1996). Even such increases, which are never observed following MSG ingestion in the diet, produce no brain effects, as reflected

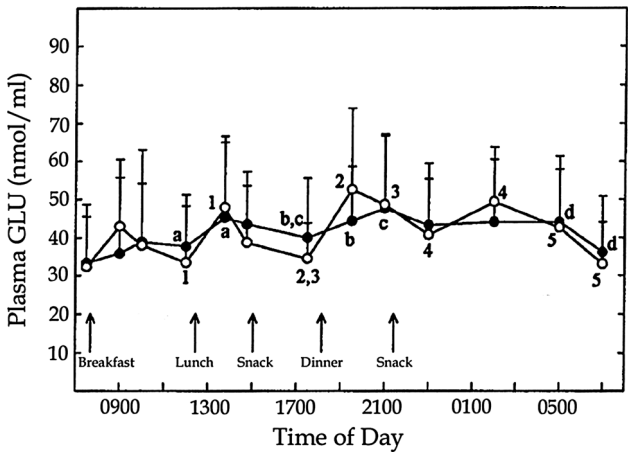

Fig. 2 Circadian variations in the concentration of glutamate (GLU) in plasma in ten adult men ingesting test a diet without (*filled circle*) or with (*open circle*) added monosodium glutamate (MSG) [100 mg/(kg day)]. Concentrations are expressed in nmol/mL; *vertical bars* represent SD. The *arrows* indicate the time of ingesting meals and snacks. The concentrations at different time points with the *same letters* (for *filled circle*) or numbers (for *open circle*) are significantly different ($P < 0.05$). Source: (Tsai and Huang 1999)

by the absence of changes in the plasma concentrations of pituitary hormones (e.g., prolactin, growth hormone) that are under the control of hypothalamic glutamate synapses (Terry et al. 1981; Fernstrom et al. 1996). As noted above, plasma glutamate would have to rise 20-fold or more to gain access to hypothalamus in rodents (Hu et al. 1998), which may explain why no effects are seen in humans. The findings underscore the notion that brain (hypothalamic) effects of exogenous glutamate are produced when MSG is injected, but not when ingested.

The gastrointestinal tract is, therefore, a barrier to the penetration of ingested MSG (glutamate) into the body. The basis for this effect is metabolic. When glutamate, whether free or protein derived, is absorbed from the intestinal lumen, almost all is immediately metabolized by intestinal cells (enterocytes) (Windmueller and Spaeth 1975). It is oxidized to generate ATP, converted to other non-essential amino acids (e.g., alanine, aspartate) and other small molecules (e.g., glutathione), and incorporated into intestinal proteins. Less than 5 % of the ingested glutamate ultimately finds its way into the portal circulation (Reeds et al. 1996, 2000; Hays et al. 2007). For this reason, when MSG is ingested with food, even in large amounts, plasma glutamate concentrations do not rise (Tsai and Huang 1999; Kondoh and Torii 2008). To add a fine point, MSG added to food would be treated in the same manner metabolically as the free glutamic acid naturally present in foods, inasmuch as they are simply ionic forms of the same molecule, and also likely to be in the same (sodium) form at intestinal pH (Fagerson 1954).

The metabolic argument can be carried further. Some investigators have reported biologic effects in animals whose mothers consumed MSG in the diet during gestation and weaning, and attribute these effects to direct exposure to MSG during prenatal and post-natal development [e.g., (Collison et al. 2009, 2010a)]. Such is unlikely to be the case. First, the dietary MSG dose employed was too small to produce increases in maternal plasma glutamate concentrations (while plasma glutamate was not measured in these studies, it was in another study using the same method of MSG administration but at much higher doses, and no rise in plasma glutamate was observed (Kondoh and Torii 2008). Second, metabolic studies show that the placenta is a natural barrier to the penetration of glutamate from the maternal into the fetal circulation. Indeed, even when maternal plasma glutamate concentrations are raised 20-fold by intravenous infusion into non-human primates,

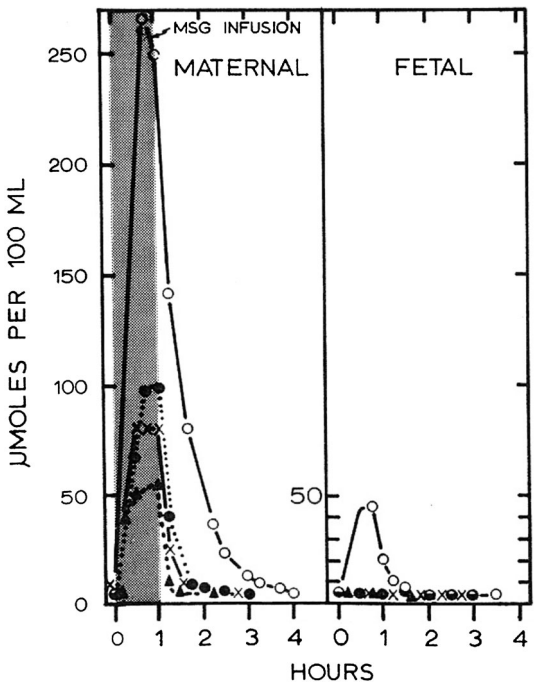

Fig. 3 Fetal plasma glutamate response to the intravenous infusion of glutamate into the maternal circulation. Catheters were placed into the maternal inferior vena cava and a vein in the arm, and into an interplacental vein (fetal circulation) of anesthetized female rhesus monkeys during the last trimester of pregnancy ($n = 5$). Monosodium glutamate was infused into the maternal vena cava over 1 h, and blood was repeatedly sampled from the maternal arm vein and the interplacental vein. The glutamate doses were: *filled triangle* 150 mg/kg; *times symbol* 170–190 mg/kg (mean of two animals); *filled circle* 220 mg/kg; *open circle* 400 mg/kg. The baseline level of plasma glutamate in the mothers was 4–5 μmol/100 mL (40–50 nmol/ml). No rise in fetal plasma glutamate occurred up to a maternal plasma concentration of 100 μmol/100 mL (1,000 nmol/ml; 20-times normal); an increase in fetal plasma glutamate (to about 50 μmol/100 mL, or 500 nmol/ml) occurred when the maternal plasma glutamate concentration reached 280 μmol/100 mL (2,800 nmol/ml; 70-times baseline). Source: (Stegink et al. 1975)

no increase in fetal plasma glutamate occurs (Stegink et al. 1975) (Fig. 3). This effect occurs because the placenta uses glutamate extensively as an energy substrate, and extracts it from the maternal circulation for this purpose (Battaglia 2000). The placenta also extracts glutamate from the fetal circulation to generate energy (Battaglia 2000). The fetal liver actually synthesizes glutamate (from glutamine) and exports it into the fetal circulation for use by the placenta (and fetal tissues). The extraction of glutamate from the fetal circulation is reportedly as high as 90 % (Battaglia 2000). Thus, the placenta normally extracts glutamate from both maternal and fetal circulations, which no doubt accounts for the observed difficulty in raising fetal plasma glutamate concentrations by elevating maternal plasma concentrations. Third, at birth, the newborn human gastrointestinal tract, like that of adults, is capable of metabolizing large amounts of ingested glutamate (Hays et al. 2007). In addition, human breast milk-free glutamate concentrations do not increase when fasting mothers ingest a single dose of 150 mg/kg MSG (a very large dose), despite a sevenfold rise in plasma glutamate concentrations (Baker et al. 1979). Supplying MSG in the maternal diet, therefore, would not be expected to increase the nursing infant's exposure to free glutamate via breast milk. Finally, on weaning, since infants metabolize ingested glutamate as rapidly as adults (Stegink et al. 1986), no increase in plasma glutamate should result from ingesting the maternal diet containing MSG, and thus no increase in plasma glutamate should be observed. Together, this assembly of facts regarding glutamate metabolism indicates that ingestion of MSG in the maternal diet would not expose the fetus or newborn animal (or human) to any increase in glutamate concentrations in biological fluids (blood, breast milk), as has recently been suggested (Collison et al. 2010a, b), and thus would not present any neurotoxic hazard. Consequently, any attribution of effects reported in offspring from adding MSG to the maternal diet during gestation and post-natal life requires a new hypothesis.

Conclusions

The body of recent population-based studies from economically developing Asian countries that examines whether associations exist between the ingestion of MSG in the diet and the incidence or risk of developing obesity or metabolic syndrome at best paints an inconsistent relationship between these variables. The association reported in some studies is more likely explained by co-varying factors in the environment (including diet and physical activity) linked to the "nutrition transition" phenomenon in rapidly developing Asian countries. Moreover, controlled studies involving the addition of MSG to the diet of animals and humans, often in extremely large doses over extended periods of time, show no effect on body weight. Finally, mechanisms put forth to argue for an effect of dietary MSG on body weight depend on data from very large dose injection studies in rodents that link MSG administration to an action within the brain. Such studies have been shown to have no relevance to animals or humans under normal or even extreme conditions of MSG ingestion. The fundamental reason is that glutamate is metabolically compartmentalized in the body, and generally does not passively cross biologic membranes. Hence, almost none of the ingested glutamate (including MSG) passes from the gut lumen into the circulation, and essentially none transits the placenta in either direction between maternal and fetal circulations, or crosses the blood–brain barrier. Ingesting MSG (glutamate) in food, therefore, does not cause elevations in glutamate concentrations in brain.

Conflict of interest Presented in the symposium "monosodium glutamate: effects on appetite, food intake/selection and body weight" at the 13th International Congress on amino acids, peptides and proteins (ICAPP) held October 5–7, 2013, in Galveston TX. The symposium was sponsored by the International Glutamate Technical Committee. The authors received a modest honorarium for their participation in the symposium and the development of this manuscript, as well as travel funding to attend the symposium.

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