

## The Administration to Indonesians of Monosodium L-Glutamate in Indonesian Foods: An Assessment of Adverse Reactions in a Randomized Double-Blind, Crossover, Placebo-Controlled Study<sup>1</sup>

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**ABSTRACT** Monosodium L-glutamate (MSG) has been suggested to cause postprandial symptoms after the ingestion of Chinese or oriental meals. Therefore, we examined whether such symptoms could be elicited in Indonesians ingesting levels of MSG typically found in Indonesian cuisine. Healthy volunteers ( $n = 52$ ) were treated with capsules of placebo or MSG (1.5 and 3.0 g/person) as part of a standardized Indonesian breakfast. The study used a rigorous, randomized, double-blind, crossover design. The occurrence of symptoms after MSG ingestion did not differ from that after consumption of the placebo. *J. Nutr.* 130: 1074S–1076S, 2000.

**KEY WORDS:** • *monosodium glutamate* • *randomized double-blind challenge* • *adverse reactions* • *humans*

Monosodium glutamate (MSG), manufactured by fermentation, is a common food ingredient in South East Asia. In Indonesia, the per capita intake is  $\sim 0.6$  g/d (Muhilal and Tarwotjo 1986). Since the first reports of adverse effects of MSG (Kwok 1968), numerous studies have been conducted and have yielded no consistent results. In South East Asia, only one Thai group (Tanphaichitr et al. 1983) has studied symptomology after MSG ingestion in local foods (despite the common use of MSG in this region).

The occurrence of psychosomatic symptoms is well known (Shorter 1993). For example, it is known that many more people believe they are "allergic" to foods and food additives than are actually identified on objective examination (Altman and Chiaramonte 1996). For example, the importance of familiarity and beliefs in the generation of psychosomatic symptoms has been described previously for odors; perceived intensity (Dalton 1996) and adverse symptoms (Lees-Haley and Brown 1992) have been found to be influenced by a subject's familiarity with an odor stimulus and beliefs regarding its effect on health.

Because MSG is an effective flavor enhancer, it is questionable that its taste can really be masked by food. In the earlier Thai study (Tanphaichitr et al. 1983), although the ability of subjects to identify the MSG taste in food was controlled, and no adverse symptoms were reported after the ingestion of MSG-containing meals, it could be argued that the subjects tasted the MSG, and because it was an accepted flavor, elaborated or reported no symptomology. In the one study that used a combination of a food and encapsulated MSG [to prevent tasting the MSG (Tarasoff and Kelly 1993)], the subjects were mainly Caucasian, and the food was a Western style light snack, not a full breakfast as is consumed frequently by Asians.

Hence, because it prevented the taste of MSG in the mouth, we decided to use the design employed by Tarasoff and Kelly (1993) in a group of healthy Indonesian subjects to evaluate the prevalence of adverse symptomology in response to the ingestion of MSG in combination with a typical Indonesian meal.

### SUBJECTS AND METHODS

**Recruitment of subjects.** Subjects were recruited through advertisements in three subdistricts of Yogyakarta municipality. To avoid demand bias, suggestive wordings such as "MSG," "Chinese Restaurant Syndrome" and "adverse effect" were not used in advertisements (Kerr et al. 1979). The incentive for healthy volunteers, who were not self-identified MSG responders, to participate in a 3-d study was the provision of a small fee. They were registered by a representative of each subdistrict and were then referred to the Department of Pharmacology, Faculty of Medicine, Gadjah Mada University for further examination.

Candidate subjects were excluded from the study if they were

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TABLE 1

*Standardized meals for the study<sup>1</sup>*

Day	Breakfast	Lunch	Dinner
1	Plain rice Jack-fruit soup Boiled egg and fried chicken	Plain rice Mixed vegetables Fried egg and fried sweet tofu	Plain rice Fried chicken Vegetables and hot chili
2	Plain rice Stirred mixed-vegetables  Chicken fried with hot chili and fried soybean	Plain rice Jack-fruit soup  Fried meat and soybean	Plain rice Chicken boiled with crushed coconut Chicken liver fried with hot chili
3	Plain rice Stirred green beans Fried meat and soybean	Plain rice Mixed vegetables Fried chicken stirred with hot chili	Plain rice Chili fried with jack fruit Chicken boiled with coconut water and tofu

<sup>1</sup> All standardized meals were prepared without added monosodium glutamate (MSG) at the Department of Pharmacology. Subjects ate breakfast at the Department of Pharmacology, immediately after ingesting capsules containing placebo or MSG. Lunch and dinner were delivered to the subjects.

pregnant or had a history of any of the following conditions: bronchial asthma, general allergy syndromes, epilepsy, diabetes mellitus, moderate or severe hypertension, gastric or duodenal ulcer, alcoholism, drug dependence or psychiatric disease. They were also excluded if they had been taking prescription drugs  $\leq 1$  wk before the study began. Otherwise healthy subjects of either sex, between the ages of 18 and 65 y, were recruited into the study.

The aim and design of the study were explained, and informed consent forms were signed by the subjects before their participation. Medical histories and physical examinations were completed before study commencement. Healthy volunteers ( $n = 52$ ) were selected (mean age  $29.6 \pm 6.5$  y; mean mass  $53.4 \pm 7.4$  kg; mean height  $159.9 \pm 7.7$  cm).

**Experimental protocol.** Opaque capsules were filled with food-grade MSG (P. T. Ajinomoto Indonesia, Jakarta, Indonesia) or pharmaceutical grade lactose (supplied by Faculty of Pharmacy, Yogyakarta, Indonesia). Each capsule contained one of the following: 1) 1.0 g lactose, 2) 0.5 g of MSG and 0.5g of lactose powder, or 3) 1.0 g MSG. Treatment packages containing either placebo or MSG capsules were prepared by the Faculty of Pharmacy of the University. A random table was used to code the packages. The master code was stored with confidentiality in a sealed envelope and was opened only after completion of the study.

A double-blind, randomized, controlled protocol was used. Participants were allocated randomly to each of three treatments suc-

cively on each day; i.e., capsules with 1.5 g MSG, 3 g MSG or placebo (lactose). The list for assigning subjects to treatment was generated using simple randomization with crossover, to ensure an equal number of subjects in each treatment.

Subjects arrived in the morning at the Department of Pharmacology after fasting for 10 h. Blood pressure, and pulse and respiratory rates were measured (in triplicate), and the subjects then ingested three capsules containing MSG or placebo. A standardized breakfast was provided and consumed immediately after capsule ingestion. Thereafter, blood pressure, and pulse and respiratory rates were again measured, and the subjects were asked to go about their normal activities (but to refrain from eating, except for bread and snacks that did not contain added MSG). Standardized lunches and dinners were also provided during test days. All standardized meals were prepared without added MSG at the Department of Pharmacology. Lunch and dinner were delivered to the subjects by research assistants (Table 1).

On each test day, after ingestion of the capsules and breakfast, the subjects were provided with open-ended questionnaires, which asked them to list any sensations or discomforts experienced (other than taste). On each study day, they completed questionnaires four times (at 0.5, 1, 2 and 3 h) after breakfast. If sensations were identified, the subjects were asked to rank the intensity on a scale of 1 (low) to 5 (high). These questionnaires were collected each day by the research assistants.

TABLE 2

*Number of symptoms after capsule administration of 1.5 g monosodium glutamate (MSG), 3 g MSG or placebo*

Symptom	1.5 g MSG					3.0 g MSG					Placebo				
	0–0.5 h	0.5–1 h	1–2 h	2–3 h	0–3 h	0–0.5 h	0.5–1 h	1–2 h	2–3 h	0–3 h	0–0.5 h	0.5–1 h	1–2 h	2–3 h	0–3 h
	(number of symptoms/interval)					(number of symptoms/interval)					(number of symptoms/interval)				
Dizziness	2	4	3	3	12	5	4	2	2	13	3	3	4	4	14
Headache	0	2	1	1	4	1	1	0	0	2	1	0	1	1	3
Neck-stiffness	1	1	0	0	2	2	0	2	2	6	5	2	0	0	7
Palpitation	0	1	1	1	3	0	1	0	0	1	1	2	0	0	3
Weakness	1	3	4	4	12	2	5	6	6	19	2	6	5	5	18
Chest pain/Burning	0	0	0	0	0	0	1	2	2	5	2	1	1	1	5
Gastric	0	1	1	1	3	0	0	1	1	2	4	2	0	0	6
Nausea	2	5	3	3	13	2	0	1	1	4	0	1	0	0	1
Thirst	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
All others	3	7	8	8	26	5	10	11	11	37	2	7	10	10	29

TABLE 3

Symptom scores following capsule administration [placebo, 1.5 or 3.0 g monosodium glutamate (MSG)]<sup>1</sup>

Interval after treatment	Sum of symptom scores			Friedman <i>t</i> test ( <i>P</i> -value)	Significance
	MSG (1.5 g)	MSG (3.0 g)	Placebo		
0–0.5 h	12	24	25	0.099	NS
0.5–1 h	33	24	29	0.769	NS
1–2 h	34	29	30	0.876	NS
2–3 h	34	29	30	0.740	NS
0–3 h	113	106	114	0.878	NS

<sup>1</sup> Sum of symptom scores = summed intensities of all symptoms reported [1 (low) to 5 (high) for each symptom]. NS = not significant. Friedman test for symptom totals was factored by three MSG levels and blocked by 52 levels of patient values.

**Treatment and statistical analysis of results.** Reported symptoms were grouped by the investigators into 10 standard symptom headings, as listed in Table 2. The Friedman test, which is the nonparametric equivalent of the two-way ANOVA procedure, was conducted using MINITAB (Version 8.1, Minitab, State College, PA). Differences in period effect were tested separately for the three challenge days. If the probability level was  $< 0.05$  ( $P < 0.05$ ), the statistical tests were considered significant.

## RESULTS

There were no significant differences in blood pressure, pulse and respiratory rates among the MSG (1.5 or 3.0 g) or placebo treatment days, at any of the time intervals measured. No subject reported an "aftertaste." There was no difference in period effects among the three challenge days. The incidence of each reported symptom is shown in Table 2; although the number is too small for convincing statistical analysis, there was generally no difference among the groups. The incidence of nausea at 1.5 g MSG was higher than placebo, but was also higher than that at 3.0 g MSG.

Because the incidence of each symptom was low, the intensities of the symptoms (symptom score) were summed for further statistical analysis to maximize the chance of detecting possible responses. The Friedman test for the sum of symptom values, factored by three MSG levels, revealed no significant difference among the three treatment groups (Table 3). The Friedman test of the results shows that the *P*-value was always  $> 0.05$  and that consequently, the symptoms after MSG ingestion were not different from symptoms after placebo ingestion.

## DISCUSSION

This study, in addition to being the first to examine the issue of adverse responses to MSG in Indonesians, employed a complex food system together with capsules to minimize MSG taste and thus subject bias.

In this study, there were no differences in the symptoms reported between MSG and placebo. A higher incidence of nausea was seen at 1.5g MSG (vs. placebo), but because there was no dose response, this effect was probably not MSG-related. Headache has been reported by some to be a typical adverse effect of MSG ingestion (Kenney and Tidball 1972, Schaumburg 1968). However, it should be noted that when

MSG taste is successfully masked, as in our study, no difference in the incidence of headache is observed between MSG and placebo test days. For subjective symptoms such as headache, the importance of successfully masking the sensory (taste) properties of the presumed active substance in a double-blind trial cannot be overemphasized.

MSG has been subjected to repeated regulatory review over the past decade (Commission of the European Communities 1991, Joint FAO/WHO Expert Committee on Food Additives 1988, Life Sciences Research Office 1995) and has been deemed safe for the general population. Our results in healthy Indonesian subjects, suggesting that adverse effects are not elicited by MSG (at doses up to 3 g), support this conclusion.

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