Circadian Variations in Plasma and Erythrocyte Concentrations of Glutamate, Glutamine, and Alanine in Men on a Diet Without and With Added Monosodium Glutamate

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Variations in plasma and erythrocyte concentrations of glutamate, glutamine, and alanine during the day were studied in 10 healthy men fed ordinary Taiwanese meals, first without and, 1 week later, with monosodium glutamate (MSG) added. MSG at a level of 15, 40, and 45 mg/kg (total, 100 mg/kg/d) was added, respectively, to the breakfast, lunch, and dinner meals. Heparinized blood samples were collected over 24 hours with 1- to 3-hour intervals. In both trials, plasma glutamate concentrations increased significantly after lunch and dinner. Although the circadian variations of plasma glutamate were small (between 32 and 53 μmol/L), the levels nevertheless varied significantly as a function of the time of day in both trials. Considering that the dietary intake of glutamate was high when MSG was added, the low plasma glutamate concentration over 24 hours indicates that glutamate is actively metabolized. On the other hand, the concentrations of erythrocyte glutamate (507 to 631 μmol/L) and glutamine (427 to 613 μmol/L) did not show a significant postprandial increase or circadian variation. Nevertheless, the concentration of plasma glutamine (539 to 657 μmol/L) varied significantly as a function of time in both trials. The plasma concentration of alanine (274 to 494 μmol/L) increased significantly after each meal and decreased significantly from 2:00 to 5:00 AM in both trials. Both plasma and erythrocyte alanine concentrations varied significantly as a function of time. These results show that the substantial amount of MSG intake had no apparent effect on the circadian variation profiles of blood glutamate, glutamine, and alanine.

PLASMA FREE AMINO ACID concentrations have been measured for various purposes, such as to evaluate the protein nutritional status, to determine amino acid requirements, and to gain an understanding of the various metabolic aspects of amino acids. Feigin et al[1] and Wurtman et al[2] were the first to show that the concentration of certain individual amino acids in human adults varies with a rhythmicity or periodicity within a day. Higher or lower dietary protein intake reportedly did not affect the plasma amino acid rhythmicity, although the concentration generally increased following ingestion of a larger amount of protein.[3] Human plasma concentrations of all of the large neutral amino acids correlated directly with the protein content of the diet, and increased in the afternoon and mostly attained a significant peak around 11:00 in the evening.[4] In these studies, the circadian variation in plasma amino acid concentrations was based on samples taken at intervals as long as 4 to 6 hours. More recently, plasma large neutral amino acids were shown to have significant circadian rhythms and peak concentrations at 7:00 to 10:00 PM in healthy adults who received hospital meals and had blood samples collected every hour for 24 hours.[5] However, there is no information as to how plasma concentrations of glutamate and glutamine vary over 24 hours in humans consuming a normal diet, and whether the plasma concentration of these amino acids would increase significantly late in the evening as reported for large neutral amino acids.[3-5]

The amount of monosodium glutamate (MSG) consumed by Asians is quite large. MSG may provoke the so-called MSG symptom complex in susceptible persons when a large amount is consumed without a meal.[6] Several factors affecting plasma glutamate concentrations after MSG loading include biological variations in absorption and metabolism, the dosage and form of administration such as in water or with a meal,[7,8] and the composition of the meals.[9] In these previous studies,[7-9] plasma glutamate was evaluated for only 2 to 8 hours after the subjects received a single food or a MSG load. Little is known concerning the effect of MSG administration with meals on human erythrocyte glutamate concentrations over 24 hours.

The goal of this study was to determine the profile and significance of circadian variations in plasma and erythrocyte glutamate concentrations with blood samples collected over a 24-hour period with 1- to 3-hour intervals in 10 healthy men who received ordinary Taiwanese meals with and without added MSG. Erythrocyte and plasma concentrations of glutamine and alanine, which are metabolically closely related to glutamate, were also measured simultaneously.

SUBJECTS AND METHODS

Subjects

Ten healthy young men were recruited from the medical and graduate students of the College of Medicine of National Taiwan University. They showed no abnormalities during screening by routine clinical laboratory analyses. None used any medications during the experiment. The mean age of the subjects was 24 years, 11 months, the mean body weight was 63.8 kg, and the mean height was 170 cm. The purpose of the study was fully explained to each subject, and informed written consent was obtained.

Diets

The menu for the test diet was planned according to the ordinary Taiwanese dietary pattern based on a recent national dietary survey in 1991.[10] The meals were individually prepared for each subject to provide 40 kcal energy/kg/d, with 15% of the energy as protein (1.5 g/kg/d), 55% as carbohydrate, and 30% as fat (polyunsaturated/saturated fatty acid ratio = 1). Pork, milk, fish, and squid provided 49.8% (by weight) of total protein, and the remainder was provided by vegetable proteins from rice, steamed bread, soybean products, fruits,

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and vegetables. Daily cholesterol intake was about 300 mg. Vitamins and minerals were supplemented daily to meet or exceed the recommended dietary nutrient allowances of Taiwan.[11] The protein, carbohydrate, and energy contents of each meal are shown in Table 1.

Experimental Design

Each subject was studied twice with a 1-week interval. The subjects were first adapted to the test diet without added MSG for 2 days, eating the meals at the nutrition unit of the Department of Biochemistry. They were then admitted to a ward of the National Taiwan University Hospital at 9:00 PM on the second day, where they remained for 36 hours. On the third day, meals were eaten at 7:45 AM, 12:15 PM, and 6:00 PM and snacks were eaten at 3:00 and 9:30 PM. Meals and snacks were eaten within 15 to 30 minutes. Blood samples (5 mL) were taken from the forearm vein at 7:30, 9:00, and 10:00 AM, 12:00 noon, 1:45, 2:45, 5:30, 7:30, 9:00, and 11:00 PM, and 2:00, 5:00, and 7:30 AM. Between meal ingestion and blood sampling, the subjects engaged in reading, writing, and light activities and went to bed after blood sampling at 11:00 PM. The lights were turned off between 11:00 PM and 7:00 AM. A dim light was on for 5 minutes when blood was drawn during sleeping hours. A similar trial was performed again the next week. Each subject ate the same meals but with MSG 100 mg/kg body weight/d added (15, 40, and 45 mg/kg in breakfast, lunch, and dinner meals, respectively).

Analytical Methods

For the whole-blood samples, 1 mL heparinized blood was diluted with 1 mL distilled water, frozen in liquid nitrogen, and then quickly thawed. The last two steps were repeated twice to achieve complete hemolysis before deproteinization. The plasma was separated from the blood cells by centrifugation at 2,500 × *g* for 15 minutes at 4°C.

The samples were deproteinized by adding 100 μL 50% (by weight) sulfosalicylic acid solution to either the 1 mL hemolyzed blood or plasma. After vortexing, the mixture was centrifuged at 18,000 × *g* at 4°C for 20 minutes, and the supernatant was stored at −70°C until analysis in order to prevent the loss of glutamine and cystine. Two hundred microliters of the supernatant was diluted with 200 μL LiS buffer containing an internal standard of *S*-2-aminoethyl-l-cysteine to pH 2.2 and then filtered through a 0.2-μm filter (Millipore, Milford, MA). The amino acid concentration of the samples was determined by ion-exchange chromatography using a Beckman 6300 Amino Acid Analyzer (Beckman Instruments, Palo Alto, CA). The System Gold software was used for peak identification using the retention time and for peak integration.[13]

The free amino acid concentrations in erythrocytes (E) were calculated from the whole-blood (WB) and plasma (P) concentrations using the following formula (with the hematocrit [Hct] expressed as a fraction): E = [WB − (1 − Hct) × P]/Hct.

Table 1. Estimated Intake of Protein, Total Glutamate, Carbohydrate, and Energy From the Meals for a 60-kg Man

Meal	Energy % of Total Daily Intake	Carbohydrate (g)	Protein (g)*	Glutamine + Glutamate (g)	
				No MSG	MSG
Breakfast	19.9	61.7	16.2	4.1	5.0
Lunch	34.5	109.8	30.1	5.1	7.5
Snack	5.7	22.4	0.8	0.2	0.2
Dinner	35.2	110.9	41.4	7.0	9.7
Evening snack	4.6	25.9	1.5	0.2	0.2

NOTE. A database for Taiwanese food composition[12] was used to calculate the nutrient composition.

*Calculated amino acid composition of dietary protein (in weight % of total protein): Glu, 18.4; Asp, 9.5; Leu, 8.2; Arg, 7.3; Lys, 6.5; Pro, 5.5; Ala, 5.1; Val, 5.0; Ser, 4.7; Phe, 4.7; Ile, 4.4; Gly, 4.4; Thr, 4.0; Tyr, 3.9; His, 2.7; Cys, 2.6; Met, 2.1; and Trp, 1.1. These values were obtained after acid hydrolysis; glutamate values include both glutamate and glutamine.

Statistical Analysis

The data are presented as the mean ± SD. ANOVA with repeated measures was performed to assess the effect of the time of day and of MSG addition on amino acid concentrations. Comparisons of data within each subject at each sampling time were tested using a nonparametric Wilcoxon test. SAS Version 6.1 (SAS Institute, Cary, NC) was used for the analyses. For all analytic procedures, a P level less than .05 was considered statistically significant.

RESULTS

The amino acid concentrations were calculated in terms of micromolars. Since the individual variation of plasma glutamate, the main object of this study, was large, for the purpose of statistical analysis, plasma glutamate was also expressed as a percentage of the basal concentration, which was measured using the first blood sample obtained before breakfast (7:30 AM). Then, the significance of circadian variations in the concentration (or as a percentage of the basal level) of the amino acids as a function of the time of day was analyzed. Amino acid concentrations before and 1 to 3 hours after meal ingestion were also compared to test whether the differences were significant.

Glutamate

The highest and lowest concentrations (mean ± SD) of glutamate in plasma during the day were 47.6 ± 14.2 and 33.3 ± 15.4 μmol/L when the meals were without MSG, and the corresponding values with MSG added to the meals were 52.6 ± 21.2 and 32.3 ± 13.1 μmol/L, respectively. Figure 1 shows the circadian variations in plasma and erythrocyte glutamate levels plotted as a percentage of the basal concentration in both trials. Circadian variations in plasma glutamate as a function of the time of day were statistically significant in both trials ($P < .01$). In the trial without MSG, postprandial plasma glutamate increased significantly ($P < .05$) after lunch and dinner with a 1.5- to 3-hour interval. Plasma glutamate also increased significantly ($P < .01$) after each meal in the trial with MSG. Although the addition of MSG resulted in the more significant postprandial increase of plasma glutamate, there was no apparent effect of MSG addition on the circadian variation profile of plasma glutamate levels (Fig 1A).

The concentration of glutamate was much higher in erythrocytes than in plasma. The highest and lowest concentrations were 610.3 ± 196.2 and 511.6 ± 145.0 μmol/L when meals were without MSG, and the corresponding values with added MSG were 631.1 ± 222.7 and 520.0 ± 138.1 μmol/L, respectively. Nevertheless, erythrocyte glutamate levels did not vary significantly as a function of the time of day ($P > .05$). Similarly, MSG addition did not significantly affect the circadian variation profile of erythrocyte glutamate levels (Fig 1B).

The absorption and metabolism of both free and peptide-bound glutamate were previously reported to vary considerably in normal adults.[14] Among the 10 subjects of this study, four (H subgroup) showed a higher plasma glutamate concentration than the other six subjects (L subgroup). The difference in the

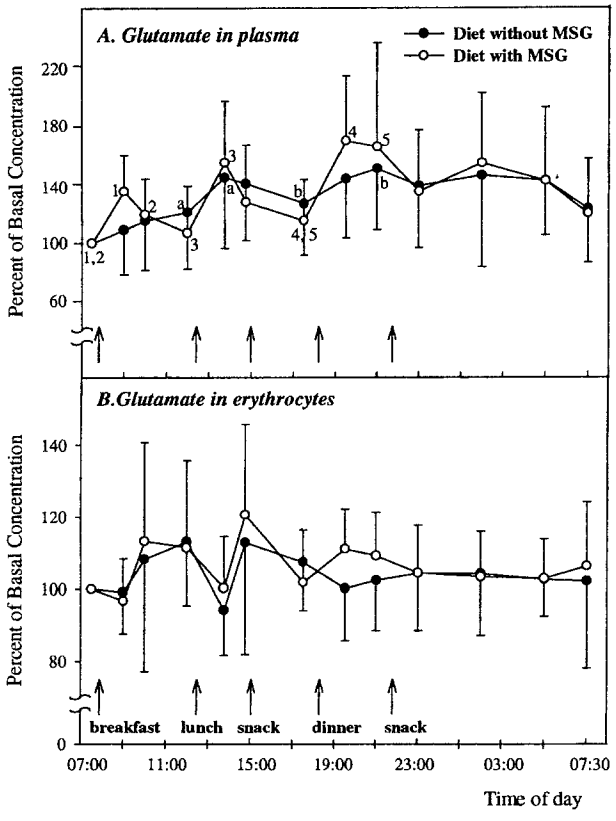

Fig 1. Circadian variation of glutamate levels in plasma (A) and erythrocytes (B) in 10 men who ingested test diets without and with added MSG (100 mg · kg^{-1} · d^{-1}). Data are the mean percent of the basal concentration before breakfast; vertical bars represent the SD. Arrows indicate the time meals were ingested. Basal concentrations (mean ± SD) of glutamate in plasma and erythrocytes in trials without added MSG were 33.3 ± 15.4 and 545.4 ± 149.2 μmol/L, and the corresponding values with added MSG were 32.3 ± 13.1 and 528.6 ± 154.8 μmol/L, respectively. Statistical comparisons between postprandial and preprandial levels were made. Symbols with the same letters or numbers are significantly different ($P < .05$). For all figures, the times are as follows: 07:00, 7:00 AM; 11:00, 11:00 AM; 15:00, 3:00 PM; 19:00, 7:00 PM; 23:00, 11:00 PM; 03:00, 3:00 AM; and 07:30, 7:30 AM.

mean plasma glutamate concentration between the H and L subgroups was approximately 20 μmol/L and was significant ($P < .05$) in both trials (Fig 2). Subjects in the H subgroup had no significant change in the plasma glutamate concentration in both trials. The plasma glutamate concentration did not change significantly in subgroup L after ingestion of meals without MSG, whereas significant ($P < .05$) increases were observed after meals with added MSG.

Glutamine

The highest and lowest concentrations of plasma glutamine during the day were 623.8 ± 63.1 and 538.7 ± 52.7 μmol/L when meals were without MSG, and the corresponding values with MSG added to the meals were 656.8 ± 56.8 and 585.0 ± 69.6 μmol/L, respectively. Plasma glutamine increased significantly ($P < .01$) 1.5 to 3 hours after the dinner meal in both trials, but a significant ($P < .01$) decrease in plasma glutamine after ingestion of lunch was only observed in the trial without MSG. In both trials, plasma glutamine concentrations varied significantly ($P < .05$) as a function of the time of day. MSG addition had no significant effect on the circadian variation profile of the plasma glutamine concentration (Fig 3A). The highest and lowest concentrations of glutamine in erythrocytes were 582.3 ± 192.5 and 417.2 ± 159.6 μmol/L when meals were without MSG, and the corresponding values with MSG added were 627.7 ± 169.6 and 496.0 ± 206.2 μmol/L, respectively. Neither the time of day nor MSG addition had a significant effect on erythrocyte glutamine concentrations (Fig 3B).

Alanine

Since alanine is closely associated with glutamate in metabolism, the data obtained for alanine are also reported here (Fig 4). The highest concentration of plasma alanine was 462.9 ± 47.9 μmol/L when meals were without MSG and 494.1 ± 60.5 μmol/L when MSG was added. The lowest concentration of plasma alanine occurred during sleep between 2:00 and 5:00 AM; it was 296.9 ± 47.1 μmol/L without MSG and 273.6 ± 58.6 μmol/L with MSG. In both trials, plasma alanine increased

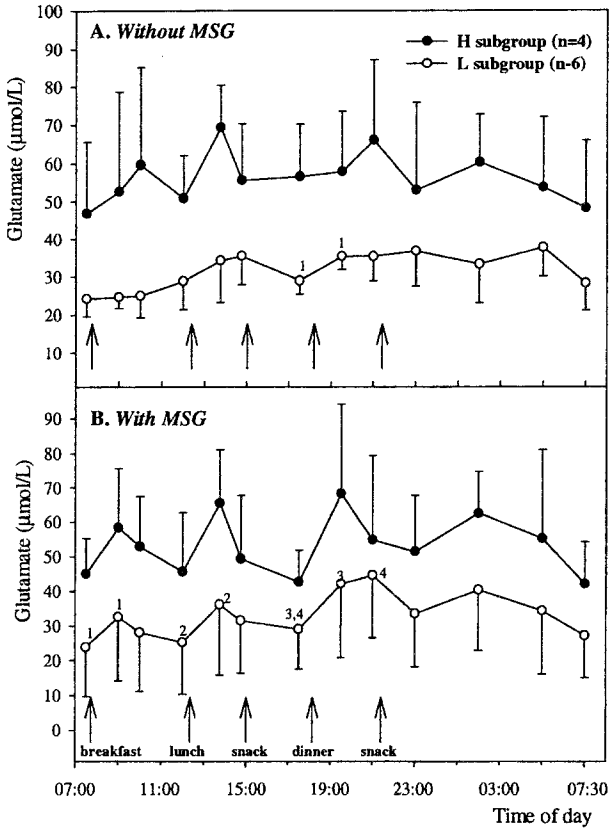

Fig 2. Circadian variation of plasma glutamate concentrations in subgroups H and L of 10 men who ingested test diets without (A) and with (B) added MSG (100 mg · kg^{-1} · d^{-1}). Data are the mean concentration; vertical bars represent the SD. Arrows indicate the time meals were ingested. Statistical comparisons between postprandial and preprandial concentrations were made. Symbols with the same numbers are significantly different ($P < .05$). Plasma glutamate concentrations of each subgroup as a whole were also compared over 24 hours.

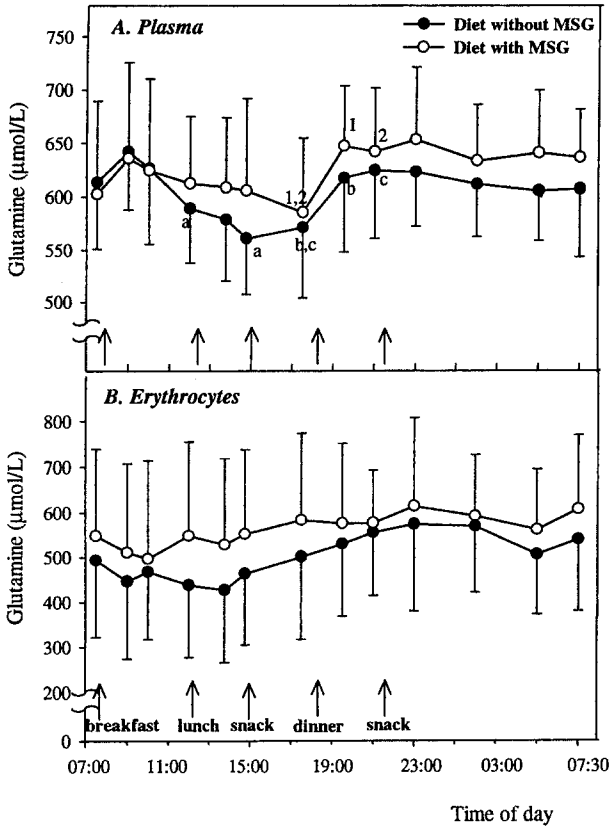

Fig 3. Circadian variation of glutamine concentrations in plasma (A) and erythrocytes (B) in 10 men who ingested test diets without and with added MSG (100 mg · kg^{-1} · d^{-1}). Data are the mean concentration; vertical bars represent the SD. Arrows indicate the time meals were ingested. Statistical comparisons between postprandial and preprandial concentrations were made. Symbols with the same letters or numbers are significantly different ($P < .05$).

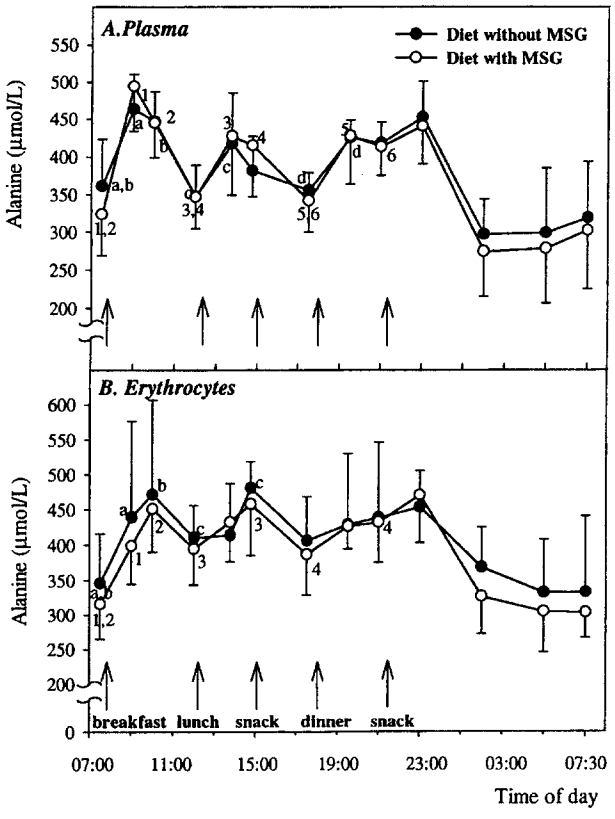

Fig 4. Circadian variation of alanine concentrations in plasma (A) and erythrocytes (B) in 10 men who ingested test diets without and with added MSG (100 mg · kg^{-1} · d^{-1}). Data are the mean concentration; vertical bars represent the SD. Arrows indicate the time meals were ingested. Comparisons between postprandial and preprandial concentrations were made. Symbols with the same letters or numbers are significantly different ($P < .05$).

significantly ($P < .01$) after meal ingestion and returned to near-basal values before the next meal (Fig 4A). Erythrocyte alanine concentrations increased significantly after ingestion of breakfast; they were 471.6 ± 135.3 μmol/L without MSG and 450.9 ± 80.7 μmol/L with MSG. The lowest concentrations of erythrocyte alanine also occurred between 2:00 and 5:00 AM, and were 331.6 ±76.2 μmol/L without MSG and 282.8 ± 36.1 μmol/L with MSG (Fig 4B). Both plasma and erythrocyte alanine concentrations exhibited significant ($P < .001$) circadian variations as a function of the time of day in both trials. However, no significant effect of MSG addition on the circadian profile of either plasma or erythrocyte alanine was observed.

A summary of the effects of MSG addition and time of day using repeated-measures ANOVA is provided in Table 2.

DISCUSSION

To the best of our knowledge, the circadian variations in plasma and erythrocyte concentrations of glutamate and glutamine in humans have not been described previously. The results of the present study show that the concentrations of plasma glutamate, glutamine, and alanine vary as a function of the time of day. Although we studied the concentration variations of these amino acids only twice in two trials, it is possible that there was a circadian rhythmicity as shown previously for the large neutral amino acids.[4,5] However, the plasma concentrations of large neutral amino acids, which were also measured in our study, showed high peaks at about 9:00 to 11:00 PM (data not shown). Such peaks were not found for plasma glutamate, glutamine, or alanine. It is well known that the plasma concentrations of free amino acids exhibit considerable variation generated by the cyclic ingestion of food and variations in meal composition. However, the mechanism of physiological regulation of circadian variations in plasma free amino acids may be complicated.

MSG was classified again recently as "generally recognized as safe" by the US Food and Drug Administration.[15] However,

Table 2. Summary of the Main Effects for MSG Addition and Time of Day Determined by Repeated-Measures ANOVA

Source of Variation	Plasma			Erythrocyte		
	Glutamate	Glutamine	Alanine	Glutamate	Glutamine	Alanine
MSG addition	.73	.82	.75	.39	.22	.66
Time of day	.001	.015	.0001	.06	.10	.0001

NOTE. *P* values are shown.

it was reported to provoke an unpleasant but minor syndrome called the MSG symptom complex.[6] Temporary adverse effects may occur in susceptible persons presumably if a grossly elevated plasma glutamate concentration is present. Therefore, the plasma glutamate concentration is a matter of concern. The present study showed that the highest postprandial plasma glutamate concentration with MSG added to meals was about twofold the basal level, but the actual concentration rarely exceeded 90 μmol/L. Stegink et al[9] reported that the mean peak plasma glutamate concentration in adults who were administered MSG 50 mg/kg body weight in consommé was 170 μmol/L, which produced a plasma glutamate response similar to that expected for an equivalent dose of MSG ingested in water. In contrast, MSG ingested with meals produces a relatively small increase in the plasma glutamate concentration. Baker et al[16] showed that the addition of MSG to a meal (1 g protein/kg) at 34 mg/kg body weight had no significant effect on plasma glutamate concentrations, similar to our results. Stegink et al[17] reported that a single administration of MSG 100 mg/kg body weight in a formula (Sustagen; Mead Johnson, Evansville, IN) to adult humans produced only a small increase in plasma glutamate compared with the values found after ingestion of Sustagen alone, reaching the mean peak of approximately 112 μmol/L. Therefore, it seems unlikely that MSG would cause the MSG symptom complex when added to meals. In the present study, a significant increase in postprandial plasma glutamate after ingestion of meals with MSG was only observed in the L subgroup (Fig 2). This result indicates individual variations in the metabolism of glutamate by normal adults.

Although the proportion between dietary glutamine and glutamate was unknown, the daily intake of glutamate plus glutamine was large (Table 1). The low plasma glutamate concentration and the nonsignificant increase in plasma glutamate after MSG ingestion indicates that the metabolism of glutamate by intestinal mucosa during the absorption process, as well as by other tissues after entering the systemic circulation, was fast. Glutamate originating from protein or in free form was metabolized similarly after digestion and absorption.[6] Previous studies[18,19] showed that the absorption of both glutamate and aspartate by rat small intestine is associated with extensive production of alanine via the process of transamination with pyruvate, which is derived from carbohydrate. Stegink[20] suggested that carbohydrate ingestion might accelerate glutamate and aspartate metabolism in the intestinal mucosa by serving as a source of pyruvate, facilitating glutamate transamination and increasing its rate of catabolism. It is possible that carbohydrate in test meals could permit a greater catabolism of glutamate by intestinal mucosa and result in a decreased release of glutamate to portal blood. Matthews et al[21] reported that most of an enteral dose of labeled free glutamate was metabolized in the first pass by tissues of the splanchnic bed in fasted adult humans. Indeed, it was reported more recently that virtually all glutamate (95%) was completely metabolized in the intestinal wall during the absorption process in piglets.[22]

In humans, it is a common view that splanchnic tissues, including the liver and gut, are the principal site of glutamine disposal.[23] Glutamine and alanine play important roles in the transport of nitrogen and amino acid carbon between organs, resulting in high plasma concentrations. In the present study, postprandial plasma alanine concentrations were significantly elevated and a greater elevation was observed at 9:00 AM. Tovar et al[24] reported that plasma alanine concentrations in subjects consuming an urban Mexican diet (55% of energy from carbohydrate) were highest at 9:30 AM and lowest at 11:00 PM to 3:00 AM. These results are mostly similar to those of the present study. A possible explanation for this may be that overnight fasting tends to transiently increase the absorption rate of amino acids[25] and de novo synthesis. The increase in alanine uptake by the liver and brain could be a means of reducing the plasma alanine concentration between 2:00 and 7:30 AM. Alanine is considered a major gluconeogenic amino acid; thus, a decline in its plasma concentration may occur due to increased utilization of alanine for gluconeogenesis by the liver during sleep. Additionally, the brain might participate in the postabsorptive interorgan amino acid exchange by removing small amounts of most amino acids, especially alanine, glycine, and proline, that are released by the liver.[26] Maher et al[27] and Fernstrom et al[4] reported that the plasma concentration of alanine in the fed state (3:00 to 7:00 PM) was higher than in the fasted state (3:00 to 7:00 AM) in men consuming diets containing 75 or 150 g egg protein per day. The study by Fernstrom et al[4] (blood sampling interval, 4 hours) showed that the highest concentration of plasma alanine occurred at 3:00 to 7:00 PM, which is inconsistent with our results.

In the present study, plasma concentrations of aspartate, another dicarboxylic amino acid, showed significant circadian variation, with a transient increase after each meal. The effect of MSG addition on the circadian variation profile of plasma aspartate was not significant ($P = .051$, data not shown).

Erythrocytes contain a much higher concentration of glutamate than plasma. But unlike glutamine and some other amino acids, glutamate is not transported by human erythrocytes.[28,29] Within human erythrocytes, glutamate is formed from glutamine by glutaminase and serves as one of the substrates for glutathione synthesis. The present results showing that both erythrocyte glutamate and glutamine concentrations did not vary significantly as a function of the time of day may indicate a homeostatic ability of glutamine in human erythrocytes. The human erythrocyte membrane contains an alanine/serine/cysteine neutral amino acid transporter (simply called the ASC transporter) that recognizes alanine, serine, and cysteine. This transporter might be responsible for the fact that the circadian profile of the erythrocyte alanine concentration is similar to that of the plasma concentration.

The present data suggest that, probably due to its rapid metabolism during absorption, MSG intake with typical meals does not significantly affect glutamate, glutamine, and alanine concentrations in plasma or erythrocytes.

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