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Monosodium glutamate raises antral distension and plasma amino acid after a standard meal in humans

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¹INRA, Research Center for Human Nutrition-IdF, UMR914 and ²AgroParisTech, Research Center for Human Nutrition-IdF, UMR914 Nutrition Physiology and Ingestive Behavior, Paris, France; ³AJINOMOTO, Institute of Life Sciences, Amino Acid Basic and Applied Research Group, Kawasaki, Japan; and ⁴Avicenne Hospital, Service of Gastroenterology, Research Center for Human Nutrition-IdF, Bobigny, France

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Boutry C, Matsumoto H, Airinei G, Benamouzig R, Tomé D, Blachier F, Bos C. Monosodium glutamate raises antral distension and plasma amino acid after a standard meal in humans. *Am J Physiol Gastrointest Liver Physiol* 300: G137–G145, 2011. First published October 28, 2010; doi:10.1152/ajpgi.00299.2010.—The consumption of monosodium glutamate (MSG) is advocated to elicit physiological and metabolic effects, yet these effects have been poorly investigated directly in humans and in particular in the postprandial phase. Thirteen healthy adults were supplemented for 6 days with a nutritional dose of MSG (2 g) or sodium chloride (NaCl) as control, following a crossover design. On the 7th day, they underwent a complete postprandial examination for the 6 h following the ingestion of the same liquid standard meal (700 kcal, 20% of energy as [¹⁵N]protein, 50% as carbohydrate, and 30% as fat) supplemented with MSG or NaCl. Real-ultrasound measures of antral area indicated a significant increased distension for the 2 h following the meal supplemented with MSG vs. NaCl. This early postprandial phase was also associated with significantly increased levels of circulating leucine, isoleucine, valine, lysine, cysteine, alanine, tyrosine, and tryptophan after MSG compared with NaCl. No changes to the postprandial glucose, insulin, glucagon-like peptide (GLP)-1, and ghrelin were noted between MSG- and NaCl-supplemented meals. Subjective assessments of hunger and fullness were neither affected by MSG supplementation. Finally, the postprandial fate of dietary N was identical between dietary conditions. Our findings indicate that nutritional dose of MSG promoted greater postprandial elevations of several indispensable amino acids in plasma and induced gastric distension. Further work to elucidate the possible sparing effect of MSG on indispensable amino acid first-pass uptake in humans is warranted. This trial was registered at clinicaltrials.gov as NCT00862017.

monosodium glutamate; circulating amino acids; gastric antral area; postprandial metabolism; gastric emptying

MONOSODIUM GLUTAMATE (MSG) is a worldwide-used flavor enhancer with a level of consumption that has increased 2.5 times between 1995 and 2007. In this context, it seems important to fully characterize the potential physiological and metabolic effects of this compound. Glutamate is extensively metabolized by enterocytes so dietary glutamate hardly appears in the portal vein (46). Glutamate is a major substrate in enterocytes (4) for energy production and protein metabolism (7). This amino acid is the precursor of metabolites that play important physiological roles, such as

glutathione (oxidative stress modulator) or *N*-acetylglutamate (metabolic regulator) (47, 55). In addition, L-glutamic acid is an excitatory neurotransmitter in the central nervous system and could represent an amino acid with signaling function like leucine that stimulates protein synthesis (17). MSG has been shown to stimulate brush-border membrane-associated enzymatic activities (36) and pancreatic secretions in duodenum (40). Some studies also suggest that glutamate enhances insulin secretion (1, 43) and glucose tolerance (1), although this point is controversial (34).

The possible effect of free glutamate on intestinal physiology is suggested by the existence of glutamate receptors in the gastric (41) and intestinal tracts, as well as in the hepatoportal area (42). Glutamate receptors have also been identified in Langerhans islets (20), in the myenteric plexus of the small intestine (50), or in the submucosal plexus in jejunum (31). Thus MSG could have an effect on gastric emptying through these receptors before significant amounts of glutamate are endogenously released through hydrolysis of dietary proteins. The blockade of *N*-methyl-D-aspartate receptors (glutamate receptor) by specific antagonists administered intraperitoneally accelerated gastric emptying (11). An interesting study has reported that MSG supplementation added to a high-energy, high-protein liquid diet accelerated gastric emptying in humans (58). However, a separate study failed to evidence any influence of MSG added to a high-protein meal on satiety in humans (33). Thus no comprehensive set of data is available in humans on the possible effects of MSG supplementation to a standard meal on gastric emptying and on the related effects in terms of satiety and postprandial metabolism.

The aim of this study was then to measure the effects of nutritional doses of MSG in healthy subjects adapted to a standard diet. The known effects of glutamate on the digestive tract principally arise from *in vitro* or *in vivo* (animal) studies, making extrapolation of these findings to humans difficult. We chose to study gastric distension as a main outcome because it may represent a determinant of intestinal nutrient delivery and also one of the parameters of intestinal physiology for which validated methods are available. Dietary amino acid appearance kinetics and metabolism, hormonal profiles, and subjective evaluation of hunger and fullness sensation were also studied in parallel to the digestive response. We particularly examined the postprandial metabolism of dietary amino acid because it is closely linked to absorption kinetics (6, 12, 15).

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MATERIALS AND METHODS

Subjects. The clinical study was performed in the Research Center for Human Nutrition (CRNH) Ile de France in Avicenne Hospital (Bobigny, France). The study protocol received the approval of the Institutional Review Board of Saint-Germain-en-Laye Hospital. Thirteen healthy subjects (7 female, 6 male) were recruited based on the following inclusion criteria: good health status, age between 30 and 50 yr, and body mass index between 23 and 28 kg/m². They were included after a thorough medical examination and a routine blood test. All subjects received detailed information on the protocol and gave their written informed consent to participate in the study. All subjects were studied under both the experimental and control conditions following a crossover design. The characteristics of the subjects are depicted on Table 1. The trial was registered at clinicaltrials.gov (NCT00862017).

Adaptation diets and test meals. The subjects were instructed to follow at home a standard diet providing adequate levels of energy in quantity and quality (33 kcal·kg⁻¹·day⁻¹, with 15% of energy as protein, 35% as fat, and 50% as carbohydrate) for two consecutive periods of 7 days. They received detailed menus depicting the nature and amounts of food for each of the three daily meals. This diet was supplemented daily in MSG (2 g) or in an equivalent load of sodium (Na) provided as sodium chloride (NaCl, 0.87 g) that was provided to the subjects in two daily doses. They were instructed to spread each capsule of powder on their food at lunch and dinner but were not informed if capsules were containing MSG or NaCl. The subjects were asked to ensure strict compliance with their diets and to complete daily record sheets regarding their food consumption. The rate of compliance was 100% during all experimental periods. At the end of each dietary adaptation, the subjects attended the CRNH clinical facility at 0900 for a whole experimental day, after an overnight fast. On that day, they received the test meal, composed of 38 g milk protein (19 g of casein and 19 g of milk soluble protein), 27 g fat (27 g of commercial oil combining rapeseed, sunflower, grapeseed oils, and Oléisol), 99 g carbohydrate (79 g of maltodextrin and 20 g of saccharose), and water to reach a final volume of 600 ml. The test meal provided 700 kcal (20% energy as protein, 35% as fat, and 45% as carbohydrate). The milk proteins were ¹⁵N-labeled, as used previously (25, 39). The global ¹⁵N isotopic enrichment was 0.5380 atom%. The test meal was supplemented with MSG (2 g) after the 7-day MSG adaptation period or with NaCl (0.87 g) after the 7-day adaptation control period.

Experimental protocol. Each subject was studied the last day of each dietary adaptation (supplemented with MSG or with a NaCl supplement) following a crossover design. The subjects arrived at the hospital after an overnight fast. After baseline collections of blood and urine samples, they ingested the standard liquid test meal. Blood was sampled at 30-min intervals for the first 3 h and then at 60-min intervals for the next 3 h. Total urine was collected every 2 h after the meal ingestion. Transabdominal real-time ultrasound measures of the antral diameter were performed by the same trained experimenter before the meal, just after the subject had finished drinking the meal (10 min), and then every 30 min for the first 3 h and every hour for the last 3 h. Subjective assessment of hunger, satiety, fullness, and desire to eat was made using 100-mm visual analog scales (VAS) adapted from Hill and Blundell (19). The clinician and the investiga-

tors involved in the measurement of gastric area and in the assessment of hunger and satiety were blinded regarding the dietary treatment. Briefly, subjects were instructed to rate themselves by marking how they felt at the moment of completing the following questions: Are you hungry? (no-yes); How does your stomach feel? (empty-very full); How many foods can you eat? (nothing-a large amount); and Would you like to eat? (no-yes). The VAS was presented to the subjects before the meal and every hour after the meal. Ratings on the scales were converted to a score (mm) for statistical analysis of their sensations of satiety, fullness, and hunger. Blood samples were centrifuged for 15 min at 1,500 g, and plasma was separated into aliquots for further analyses. Antiproteases were added to the plasma samples spared for the determination of hormone concentrations. Urine specimens were weighed and separated into aliquots. All the samples were stored at -20°C until analysis.

Measurement of antral gastric distension. The measurement of antral area was used as a parameter related to gastric emptying compared with the standard method scintigraphy (22, 37). Measures were performed throughout the experimental day by real-time ultrasound (Logiq Book XP; GE Medical Systems, Velizy, France) in subjects lying down in a supine position. A baseline measure was done just before the meal ingestion at time 0, and a second measure was performed after the completion of the meal, which slightly varied among subjects (time = 9.5 ± 4.0 min). The antral cross section was then determined every 30 min for the first 3 h following the meal ingestion and every hour for the three following hours by a blind trained experimenter. The lower border of the liver and the pancreas served as internal landmarks to determine the longitudinal section (*d*₁) of the antrum. The lower border of the liver, the aorta, the vena cava, and the gallbladder served to determine the cross section of the antrum (*d*₂). Antral diameters were computed to determine the antral area, according to the following formula: $\pi \times d_1 \times d_2 / 4$. The antral distension was calculated as the antral area at each time expressed as a percentage of the maximal retention measured just after the meal ingestion. Nonlinear regression was applied to determine the half-time of complete distension. The equation used for calculation is given by $y = y_0 + a \times \exp(-b \times x)$ where *y* is the antral distension, *x* is time in min after the meal, and *y*₀, *a*, and *b* are constants.

Assessment of the postprandial kinetics of dietary N. The postprandial metabolic fate of ¹⁵N-labeled dietary protein was determined through the measures of ¹⁵N enrichment in all of the accessible N pools: plasma amino acids, protein and urea, urinary urea, and ammonia. The kinetics of appearance of dietary N in plasma amino acid and urea pools has been shown to directly reflect intestinal absorption kinetics (6, 13). Urea and ammonia were isolated from urine and urea, and protein and amino acids were extracted from plasma as previously described (6). The ¹⁵N enrichment was measured by isotope ratio mass spectrometry (Isoprime; GV Instruments, Manchester, UK) coupled to an elemental analyzer (Euro Elemental Analyser 3000; EuroVector, Redavalle, Italy) with atropine as the standard. The metabolic fate of dietary N (expressed as a percentage of the ingested amount) in the different body N pools monitored (serum proteins and free amino acids, body urea, urinary urea, and ammonia) was calculated as detailed. The incorporation of dietary N (*N*_{inc}, %ingested) in samples was calculated as $N_{inc} = [(E_{sample} - E_{basal}) / (E_{meal} - E_{basal}) \times N_{total}] / (N_{ing} \times 100)$ where *E* refers to enrichment (atom%), *N*_{total} refers to nitrogen concentration, and *N*_{ing} refers to ingested nitrogen, as previously detailed (13).

Other analytical methods. Urea concentrations in plasma and urine were assayed using a commercial kit (Bio-Mérieux, Marcy l'Etoile, France). Plasma glucose was measured by using a glucose oxidase method (Glucose GOD-DP kit; Kone, Evry, France). Urinary creatinine was assayed by an enzymatic method (Dimension Automate; Dupont de Nemours, Les Ulis, France), and urinary ammonia was measured with an enzymatic method (Kone Automate; Kone). Plasma insulin, glucagons-like peptide (GLP)-1, and ghrelin concentrations were analyzed by using a human endocrine panel (Linco Research, St.

Table 1. Baseline characteristics of the subjects

	Females	Males
Age, yr	41.9 ± 3.7	41.8 ± 4.8
Height, cm	160 ± 2	174 ± 4
Body wt, kg	61.9 ± 5.0	77.8 ± 5.3
BMI, kg/m ²	24.2 ± 1.9	25.7 ± 1.6

Results are expressed as means ± SD. BMI, body mass index.

Fig. 1. Effect of monosodium glutamate (MSG) supplementation on time course of antral area (A) and on antral distension (B) after ingestion of a test meal containing NaCl or MSG in humans ($n = 13$, crossover design). Values are means $\pm$ SD. Time is given as hours from ingestion of the test meal. The main statistical effects [time (T), diet (D), and their interaction ($T \times D$)] from a mixed model for repeated measures over time are reported for each variable when $P < 0.1$. *Significant difference between NaCl and MSG at specific time points (post hoc Tukey's test): $P < 0.05$.

Charles, MO) on a Bioplex 200 system (Bio-Rad Laboratories, Hercules, CA). Plasma amino acids were analyzed by ion exchange chromatography after protein precipitation, with addition of nor-leucine as an internal standard (Biotech Instrument, St. Quentin-en-Yvelines, France).

Statistics. Data are expressed as means $\pm$ SD. Differences in summarized indexes of gastric emptying, area under the curve (AUC), and dietary N metabolism were tested by using paired t -tests. Differences between MSG and NaCl supplementations concerning the antral area, metabolite and hormonal postprandial profiles, and postprandial kinetics of dietary N were analyzed using mixed models for repeated-measure analysis, with the treatment and the time as independent, fixed factors and the subject as a random factor (version 9.1; SAS Institute, Cary, NC). For each variable, the most appropriate matrix of covariance structures for random statements was selected. Post hoc tests were performed by using contrast analysis. A P value < 0.05 was considered as being statistically significant.

RESULTS

Dietary adaptation and body weight. There was a good compliance of the subjects (100%) to the periods of dietary standardization and supplementation with MSG or NaCl. The body weight of the subjects remained stable after both periods (69.2 ± 10.2 and 69.1 ± 10.2 kg after NaCl and MSG supplementations, respectively). The fasting urea concentration, a marker of protein intake, also remained stable whatever the dietary adaptation (5.52 ± 1.90 and 5.52 ± 1.13 mmol/l after NaCl and MSG supplementations, respectively).

Gastric antral area. Gastric antral area as estimated using the ultrasonographic measurement method was significantly influenced by MSG supplementation. Basal antral areas before the test meal were similar after NaCl and MSG supplementation, averaging, respectively, 3.50 ± 0.83 and 3.30 ± 1.06 cm². The antral area after the test meal containing MSG was significantly larger than after the control test meal containing NaCl (diet effect: $P < 0.05$) (Fig. 1A). The difference between NaCl and MSG meals was significant between 30 and 90 min. There was also an effect of MSG addition to the meal on antral distension (diet effect: $P < 0.05$), significantly at 30 min (Fig. 1B). The increase of antral area at 30 min with MSG compared with NaCl (54% increase) when NaCl was first ingested (7 subjects) was not vastly different from the MSG-induced increase of antral area when MSG was first ingested (44% increase in 6 subjects). AUC for antral area was significantly increased after

MSG compared with NaCl for the six postprandial hours, with a particularly pronounced effect for the first 3 h following the meal ingestion (Table 2). Half-time of complete distension was significantly higher after MSG supplementation compared with NaCl (+72%) (Table 2).

Plasma amino acids. MSG supplementation elicited a significant increase in the AUC of plasma concentrations of glutamate, serine, cysteine, isoleucine, leucine, tyrosine, and ornithine (Table 3). There was a trend ($0.1 > P > 0.05$) for asparagine, alanine, citrulline, valine, and lysine. These increases were in the range of 10–25% above the AUC measured in control (NaCl) conditions. For amino acids such as branched-chain amino acids, lysine, tryptophan, tyrosine, or alanine, MSG induced higher plasma concentrations at 60 or 120 min postmeal, and the time course of plasma amino acids was very similar between MSG and NaCl conditions afterward (Fig. 2). For amino acids such as glutamate or cysteine, the higher AUC observed after MSG supplementation compared with NaCl was more constant throughout the postprandial period. Glutamine concentrations were not significantly modified by the dietary treatment.

Transfer of dietary N into plasma amino acids, urea, and proteins, and urinary ammonia and urea. The MSG supplementation had no significant effect on kinetics of dietary N in plasma, since there was no significant difference in the time course of appearance of dietary N into plasma amino acids after MSG or NaCl supplementation, which peaked in both

Table 2. Effect of MSG supplementation on the AUC obtained after measure of antral area by real-time ultrasound

	NaCl	MSG	Stat Effect*
Antral area, cm ²			
AUC ₀₋₁₈₀	1,134 $\pm$ 198	1,334 $\pm$ 356	$P = 0.05$
AUC ₀₋₃₆₀	1,724 $\pm$ 209	1,984 $\pm$ 403	$P < 0.05$
Antral area, %baseline value			
AUC ₀₋₁₈₀	504 $\pm$ 241	739 $\pm$ 366	$P < 0.05$
AUC ₀₋₃₆₀	463 $\pm$ 324	795 $\pm$ 487	$P < 0.05$
$T_{1/2}$ complete distension, min	52.7 $\pm$ 32.0	90.6 $\pm$ 41.9	$P < 0.05$

Results are expressed as means $\pm$ SD; $n = 13$ subjects, crossover design. MSG, monosodium glutamate; AUC, area under the curve; 0–180, 0–180 min; 0–360, 0–360 min; $T_{1/2}$, half-time. *Paired Student's test.

Table 3. AUC of plasma amino acid concentrations after ingestion of a test meal containing NaCl or MSG in humans

	NaCl	MSG	Change, %	Stat Effect*
Tau	394 ± 107	441 ± 114	11.9	NS
Asp	104 ± 37	107 ± 37	2.6	NS
Thr	909 ± 354	1,021 ± 396	12.3	NS
Ser	648 ± 256	728 ± 258	12.3	<i>P</i> < 0.05
Asn	1,059 ± 376	1,180 ± 428	11.5	<i>P</i> = 0.09
Glu	407 ± 106	451 ± 109	10.8	<i>P</i> < 0.005
Gln	1,656 ± 436	1,802 ± 611	8.8	NS
Gly	1,020 ± 368	1,107 ± 398	8.5	NS
Ala	2,197 ± 563	2,483 ± 721	13.0	<i>P</i> = 0.09
Cit	165 ± 49	180 ± 58	9.3	<i>P</i> = 0.08
Cys	99 ± 34	124 ± 46	24.9	<i>P</i> < 0.005
Val	1,427 ± 262	1,542 ± 316	8.1	<i>P</i> = 0.07
Met	146 ± 39	160 ± 45	9.5	NS
Ile	448 ± 81	513 ± 119	14.4	<i>P</i> < 0.05
Leu	956 ± 189	1,064 ± 231	11.3	<i>P</i> < 0.05
Tyr	384 ± 88	449 ± 106	16.7	<i>P</i> < 0.05
Phe	316 ± 78	333 ± 70	5.2	NS
His	402 ± 118	421 ± 133	4.8	NS
TrpP	339 ± 112	368 ± 97	8.3	NS
Orn	360 ± 115	411 ± 137	14.1	<i>P</i> < 0.05
Lys	1,253 ± 322	1,374 ± 367	9.6	<i>P</i> = 0.06
Arg	556 ± 185	584 ± 161	5.0	NS
Pro	1,505 ± 427	1,596 ± 554	6.0	NS
Total AA	16,752 ± 3,608	18,438 ± 4,411	10.1	<i>P</i> = 0.06
Indispensable AA	6,197 ± 1,326	6,795 ± 1,579	9.6	<i>P</i> < 0.05
Dispensable AA	10,555 ± 2,359	11,643 ± 2,886	10.3	<i>P</i> = 0.08
Neoglucogenic AA†	6,837 ± 1,815	7,591 ± 2,162	11.0	<i>P</i> = 0.08
Branched-chain AA‡	2,831 ± 516	3,119 ± 643	10.2	<i>P</i> < 0.05

Results are expressed as means ± SD; *n* = 13 subjects, crossover design. Values are expressed in μmol/6 h. AA, amino acid; NS, not significant. *Paired Student's test. †Sum of glutamate, glutamine, alanine, serine, threonine, and glycine concentrations. ‡Sum of valine, leucine, and isoleucine concentrations.

cases 4 h after the meal at 0.37–0.40% of the ingested dose (Fig. 3A). Consistently, the incorporation of dietary nitrogen into plasma urea was not influenced by MSG supplementation (Fig. 3B). There was also no significant difference in the incorporation of dietary nitrogen into other N-accessible pools (plasma proteins, urinary ammonia, and urea). The transfer of dietary N 6 h after the meal to plasma protein was $12.8 \pm 4.4\%$ of ingested and $11.7 \pm 1.7\%$ of ingested for NaCl and MSG, respectively. For urinary ammonia, it was 0.30 ± 0.19 and $0.29 \pm 0.15\%$ of ingested for NaCl and MSG, respectively, and for urinary urea it was 10.5 ± 4.4 and $11.9 \pm 3.2\%$ of ingested for NaCl and MSG, respectively. Deamination of dietary amino acids was not affected by MSG supplementation.

Plasma glucose and hormones and hunger-related perceived sensations. There was no significant effect of MSG supplementation on glycemia (Fig. 4A). Plasma insulin (Fig. 4B), GLP-1 (Fig. 4C), and ghrelin (Fig. 4D) concentrations were not significantly influenced by MSG supplementation during 6 h after the meal in humans. Following the ingestion of the standard meal, the MSG supplementation had no significant effect on the perception of hunger and fullness, despite a trend toward a significant interaction between time and treatment on hunger sensation (Fig. 5). The prospective food consumption and perceived pleasure curves were similar to that obtained for hunger (data not shown).

DISCUSSION

This randomized cross-over trial in dietary-controlled, healthy subjects revealed that MSG added at nutritional doses to a standard diet elicited an antral distension and an elevation of plasma concentrations of several amino acids, including

branched-chain amino acids, in the early postprandial phase. These physiological and metabolic effects were not associated with significant change in the metabolic fate of dietary N, the postprandial glucose and hormonal responses, and the gastrointestinal sensations of hunger and fullness.

The gastric distension following ingestion of a liquid, balanced meal providing approximately one-third of the daily energy intake was more pronounced in subjects receiving MSG at doses close to that commonly consumed than an equivalent dose of NaCl as control. The monitoring of antral area by two-dimension real-time ultrasound before and at regular intervals following the ingestion of the test meal has been proposed to represent a method to assess gastric emptying (5, 22), and the specific ultrasonographic monitoring of the antrum cross-sectional area is known to accurately detect variations in gastric volume (44, 48). MSG ingestion elicited an 18% higher AUC of antrum for the first 3 h after the meal ingestion. However, it is not obvious that the antral distension observed in our study after the MSG-supplemented meal really reflected a change in meal gastric emptying. Indeed, our results may rather be explained as a MSG-induced enhanced gastric secretion without increased gastric emptying resulting in increased antral distension. Our results are in contrast with that of the only available study that has evaluated the effect of MSG supplementation on gastric emptying using an oral dose of [^{13}C]sodium acetate (58). Using this latter method, the authors reported an acceleration of gastric emptying after MSG supplementation added to a protein-rich liquid diet, but no effect was observed when MSG was added to a carbohydrate-rich diet or to the same volume of water. Different hypotheses can be

Fig. 2. Plasma concentrations of total amino acids (AA), glutamate, glutamine, leucine, lysine, and cysteine after ingestion of a test meal containing NaCl or MSG in humans ($n = 13$, crossover design). Values are means $\pm$ SD. Time is given as hours from ingestion of the test meal. The main statistical effects (T , D , and $T \times D$) from a mixed model for repeated measures over time are reported for each variable when $P < 0.1$. *Significant difference between NaCl and MSG at specific time points (post hoc Tukey's test): $P < 0.05$.

advanced to explain the discrepancy between Zai et al.'s (58) findings and the present results. We used a meal that contained more energy (700 vs. 400 kcal) and represented a larger volume (600 vs. 400 ml) than the meal used in their study, and both parameters are likely to influence gastric emptying (28). The concentration of MSG was lower in our study (16 vs. 30 mmol/l). Moreover, the protein source used in the study by Zai et al. was casein, whereas we used total milk proteins (35). Last but not least, as reported above, Zai et al. used [^{13}C]sodium acetate administration to measure gastric emptying while we used ultrasonographic monitoring of the antrum area.

Animal studies have been performed to assess the direct effect of MSG supplementation on gastric emptying or intestinal peristalsis. Toyomasu et al. (54) have shown stimulation of the upper gut motility through the vagus nerve after intragastric MSG stimulation, an effect that was associated with an acceleration of the gastric emptying rate. Furthermore, injection of MSG in stomach, duodenum, and portal vein increases gastric vagal afferent activity in rats (42, 56). However, it is worth noting that experimental conditions in animal and human studies are often very different, thus complicating comparison on the effects of MSG in these situations.

Fig. 3. Systemic utilization of dietary N. N incorporation into plasma amino acid (A) and urea (B) after ingestion of a test meal containing NaCl or MSG in humans ($n = 13$, crossover design). Values are means $\pm$ SD. Time is given as hours from ingestion of the test meal.

An interesting finding of the present study was the transient rise in plasma concentrations of many amino acids when subjects ingested the MSG-supplemented meal. This effect concerned in particular branched-chain amino acids, with significant 20–25% increases of circulating concentrations of leucine and isoleucine at 1 and 2 h after the meal. Branched-chain amino acid systemic availability has consistently been found to be increased in animals supplemented with MSG (24, 26, 30). This effect suggests a

sparing effect of MSG on branched-chain amino acid first-pass uptake, through the implication of glutamate in reducing branched-chain amino acid transamination. Recently, enterocytes isolated from pig jejunum have been shown to extensively transaminate branched-chain amino acids, a phenomenon that is stimulated by α -ketoglutarate (8). In humans, leucine first-pass uptake may represent 13–37% of the dietary leucine intake (2, 10, 21, 23, 38), and it is conceivable that decreased transamination might translate

Fig. 4. Plasma concentrations of glucose (A), insulin (B), glucagon-like peptide (GLP)-1 (C), and ghrelin (D) after ingestion of a test meal containing NaCl or MSG in humans ($n = 13$, crossover design). Values are means $\pm$ SD. Time is given as hours from ingestion of the test meal.

Fig. 5. Effect of MSG supplementation on perception of fullness (B) and hunger (A) after ingestion of a test meal containing NaCl or MSG in humans ($n = 13$, crossover design). Values are means $\pm$ SD. Time is given as hours from ingestion of the test meal. The main statistical effects (T, D, and $T \times D$) from a mixed model for repeated measures over time are reported for each variable when $P < 0.1$.

into elevation of plasma concentrations. Increased postprandial glutatemia, although of mild amplitude (11% increase of the postprandial AUC), is in line with previous results obtained in humans (51, 52).

We also found an increase in other amino acids that are derived from glutamate, including ornithine, citrulline, and alanine, in accord with other studies (24, 26, 30, 53) and with the known capacity of isolated enterocytes to convert glutamate into ornithine and citrulline and to allow pyruvate transamination into alanine (3). In contrast, this study did not demonstrate a significant increase in glutamine, aspartate, proline, or arginine as previously reported (24, 51). Last, since the catabolism of cysteine and tyrosine involves transamination with α -ketoglutarate being converted to glutamate, it is conceivable that glutamate through a mere mass-action phenomenon would participate in the sparing of these amino acids and thus in their increased plasma concentration. Data obtained in pigs from arteriovenous differences in tyrosine plasma concentrations suggest that this amino acid is little degraded by the intestine in this experimental model (57). Regarding cysteine catabolism, from the low appearance of this amino acid in the portal blood ($<20\%$ of dietary intake), it has been suggested that piglet intestine extensively utilizes cyst(e)ine (49), a suggestion that is in line with the capacity of isolated enterocytes to catabolize this amino acid (9).

By contrast with the effects on aminoacidemia, we could not evidence any detectable difference in the postprandial metabolic fate of dietary proteins, whether the subjects ingested the meal with or without MSG. The ^{15}N -labeled protein was used in the experimental meals because we have previously shown that the postprandial appearance of dietary N in pools such as plasma amino acids or urea is very sensitive to the kinetics of intestinal delivery of dietary proteins (6, 13, 16, 29). Because the measure of postprandial dietary N retention gives a global picture of protein metabolism, we cannot infer from our results that protein synthesis and/or degradation rates were unaffected by the dietary treatment but only that the net utilization of dietary N was similar. The discrepancy between the MSG-induced increase in plasma amino acids and the absence of effect of MSG on dietary N appearance in plasma amino acids and urea indicates that the improved systemic availability of amino acids may rather be the result of a modified first-pass

uptake than the result of changes in protein fluxes. However, it would be necessary to perform studies with tracers to clarify this point.

GLP-1 and ghrelin are two gastrointestinal hormones that are potent regulators of gastric emptying (18). However, in this study, postprandial GLP-1 and ghrelin concentrations were not significantly influenced by dietary MSG, and there was no clear association between these hormones and the functional response observed at the gastric level. The glucose and insulin postprandial responses were also unaffected by MSG, which is in accord with the GLP-1 results. Collectively, our results are in agreement with the only study that has assessed the effect of MSG (0.6%) administration to a high-protein meal on satiety, energy intake, and hormone circulating concentrations in humans (33). Accordingly, the MSG ingestion was not associated with any changes to the postprandial gastrointestinal sensations (fullness, hunger). Despite crossover design, our study may have lacked power to detect subtle changes in such sensations because visual analog scales represent a technique with high intersubject variability. Moreover, if modifications of the gastric volume are one component that intervenes in the sensations of fullness and hunger after a meal, they are not always sufficient to induce changes to satiety and hunger feelings (45).

In conclusion, we show that MSG supplementation at nutritional doses elicits in healthy humans a postprandial gastric distension and an elevation of several amino acid plasma concentrations that are possibly linked. These physiological and metabolic effects had, however, no measurable consequences in terms of satiety, hormone profiles, or dietary N metabolism. Thus, it can be hypothesized that the gastric distension did not translate into a delay of gastric emptying. The mechanisms involved in such distension are not known but may involve an increased water or acid secretion in the stomach in response to MSG supplementation. A recent study showing the stimulation of gastric acid secretion by MSG in dogs is in accordance with this hypothesis (59). Moreover, intraduodenal, but not intrajejunal, infusion of amino acids stimulates gastric secretion (32). Intravenous infusion of amino acids is also able to have this latter effect and acts on both acid and pepsin secretion (27). Our findings call for further studies to elucidate the mechanisms by which dietary glutamate impact systemic amino acid concentrations and the consequences of

such modulations. Last, it is worth noting that, in the present study, amino acid concentrations were measured in blood plasma but not in erythrocytes, which can contribute to the interorgan transfer of amino acids (14). However, although some amino acids are highly concentrated in erythrocytes, it is generally considered that the exchanges with plasma proceed very slowly, and thus this intracellular pool is considered to contribute poorly to interorgan fluxes.

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DISCLOSURES

None of the authors had a conflict of interest.

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