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Comparative Metabolism of Glutamate in the Mouse, Monkey, and Man

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The mouse and monkey are often used as animal models to study the potential toxicity of glutamate salts for man. However, these species vary in apparent susceptibility to glutamate-induced neuronal necrosis. It is now generally accepted that the administration of large quantities of glutamate or aspartate to the neonatal rodent produces a variety of toxic effects (see review in ref. 27). However, even the rodent's susceptibility is partially strain dependent, some strains showing greater sensitivity than others to these amino acids (16). The potential for glutamate salts to produce toxic effects in the neonatal primate is controversial. Original reports associated the administration of large doses of glutamate salts with hypothalamic neuronal necrosis in the neonatal primate (23,25). However, at least four independent research groups have not been able to reproduce the lesion in the primate (1,2,17,26,32,36). These same research groups have no difficulty in inducing the rodent lesion.

Our research groups have focused on studies evaluating the effect of added glutamate salts in food systems on the plasma levels of amino acids. These data have been accumulated in an attempt to supplement the neuropathology data evaluating the safety of glutamate salts. Our premise has been the following: although the neonatal rodent is clearly susceptible to glutamate-induced neuronal necrosis (16,20), plasma glutamate levels must be substantially elevated prior to the occurrence of such lesions (33). In addition, the so-called blood-brain barrier of the species must be susceptible. Thus, our data indicate that plasma glutamate levels must be greater than six times normal in the infant mouse before neuronal necrosis is observed (33). Even the acutely sensitive neonatal mouse tolerates plasma glutamate plus aspartate levels under 60 μmoles/dl and develops neuronal necrosis only when plasma levels exceed this apparent threshold.

It has been suggested that the inability of research groups other than Olney's to induce lesions in the neonatal primate with glutamate reflected a failure to elevate plasma glutamate levels (25). However, this is not the case. Our combined research

groups have studied animals in which plasma glutamate levels were grossly elevated without finding evidence of the hypothalamic lesion (32). These data clearly demonstrate that the neonatal primate and rodent differ in their susceptibility to glutamate-induced neuronal necrosis at equivalent plasma glutamate levels.

We have presented preliminary data (7,27) suggesting that glutamate metabolism might differ in the rodent and in the primate. These data were based on the radioactivity found in glutamate-derived metabolites after the administration of ^{14}C-labeled glutamate. The major metabolites in the neonatal primate were glucose and lactate, whereas the neonatal rodent accumulated α-ketoglutarate and acetoacetate as well. These studies led us to further comparisons of the absorption and metabolism of glutamate in mice, monkeys, and humans after ingestion of monosodium glutamate (MSG) either with meals or dissolved in water.

Our first experiment focused on plasma glutamate levels following the addition of MSG to meal systems. It had been suggested that MSG added to food might be absorbed more rapidly and metabolized less well than protein-bound glutamate, yielding markedly elevated plasma glutamate levels (21,22). To determine the appropriate experimental levels of MSG ingestion, we used the data of the Committee on GRAS List Survey—Phase III (9). The data in Table 1, taken from Appendix E of the Committee's report, show estimated daily intakes of MSG for individuals living in the United States. These data show an expected mean daily intake of 6.8 mg/kg body weight in the 12- to 23-month-old infant. This age group has the highest estimated daily intake of MSG in the United States. In this age group, 30 mg MSG/kg body weight represents the 90th percentile of total daily ingestion.

In our first study, we added MSG at a level of 34 mg/kg body weight to a high-protein meal and measured plasma amino acid levels with time (4). Normal adult subjects were fed a hamburger-milk shake meal providing 1 g protein/kg body weight. The composition of the meal is shown in Table 2. One group of six individuals ingested the meal alone, whereas a second group of six subjects ingested

TABLE 1. *Expected daily intake of MSG based on person-days*

	Total sample Intakes (mg/kg/day)			
		Percentile		
Age	Mean	90th	99th	99.9th
0–5 months	0.3	0	11	25
6–11 months	1.9	1.9	36	46
12–23 months	6.8	30	43	61
2–5 years	5.5	23	37	56
6–17 years	2.7	10	25	40
18+ years	1.5	7	12	19

From Committee on GRAS List Survey—Phase III, ref. 9.

TABLE 2. *Composition of the hamburger-milk shake test meal for a 70-kg adult*[a]

Component	Quantity (g)	Protein[b] (g)	Fat (g)	Carbohydrate (g)	Energy (kcal)
Hamburger	222	61	25.5	0	346
Bun	50	4.5	1.5	25.5	133
Milk	100	3.5	3.5	5	66
Ice cream	50	2	5	11	95
Total	442	71	35.5	72	640

[a] The quantity of the hamburger in each meal was varied with each individual so as to provide a uniform protein level of 1 g/kg body weight (4).
[b] Protein, 38% of total energy.

an identical meal to which MSG had been added at a level providing 34 mg/kg body weight. The plasma glutamate and aspartate levels in these subjects are shown in Fig. 1. These data demonstrate that the addition of MSG to the meal had no effect on plasma glutamate and aspartate levels beyond that of the meal itself.

The results from this study led us to evaluate the effects of higher MSG loads ingested with meals on plasma amino acid levels. The Acceptable Daily Intake (ADI) set for MSG by the WHO/FAO is 150 mg/kg body weight/day. We elected to study the effects of 100 and 150 mg MSG/kg added to a single meal on plasma glutamate levels. In addition, we wished to compare the effect of these dosages on mice, monkeys, and humans.

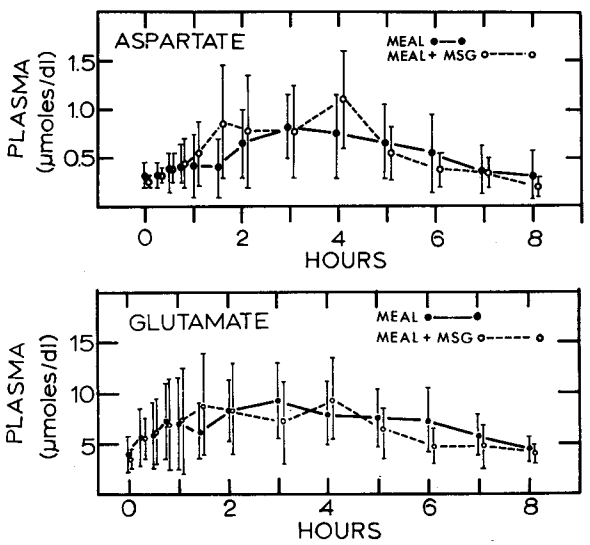

FIG. 1. Plasma glutamate and aspartate levels (mean ± SD) in normal adult subjects after ingestion of a high-protein meal (1 g protein/kg) with or without added MSG (34 mg/kg). (From Baker, et al., ref. 4.)

TABLE 3. *Composition of the Sustagen[a] meal system used*

Component	Quantity (g/kg)	Energy (kcal/kg)
Protein	0.40	1.6
Fat	0.059	0.53
Carbohydrate	1.12	4.48
Water	4.2	0
Total	5.78	6.61

[a] Mead-Johnson; formula also contains appropriate vitamins and minerals.

A Sustagen meal system was chosen for these studies. Sustagen (composition shown in Table 3) is a liquid, ready-to-feed solution that can be fed to mice, monkeys, and man. The Sustagen solution was fed to adult animals or humans at 4.2 ml/kg. This level provides 0.4 g protein, 1.12 g carbohydrate, and 1.6 kcal/kg body weight. The MSG was dissolved in Sustagen to give a 2.4% (w/v) solution when the dose was 100 mg/kg, and to give a 3.6% solution (w/v) when MSG was administered at 150 mg/kg body weight.

The data in Fig. 2 show mean plasma glutamate levels in adult mice (Webster Swiss albino strain) administered Sustagen meals providing 0, 100, or 150 mg MSG/kg body weight. Glutamate values at each time point represent plasma levels from pooled blood of five animals. The administration of the Sustagen meal alone resulted in a slight increase in plasma glutamate levels. The addition of MSG to the meal resulted in further, small, highly variable increases in plasma glutamate levels. Maximum levels of 15 μmoles/dl were observed at 1 hr after administration of the Sustagen meal providing 150 mg MSG/kg body weight.

The data in Fig. 3 show mean plasma glutamate levels in adult rhesus monkeys (*Macaca mulatta*) administered Sustagen meals providing MSG at 0, 100, or 150 mg/kg body weight. In each experiment, four adult animals were administered the Sustagen meals by stomach tube. Sequential blood samples were obtained from each animal after dosing as described previously (31,32). Plasma glutamate levels were essentially unchanged in the animals administered the Sustagen meal alone or

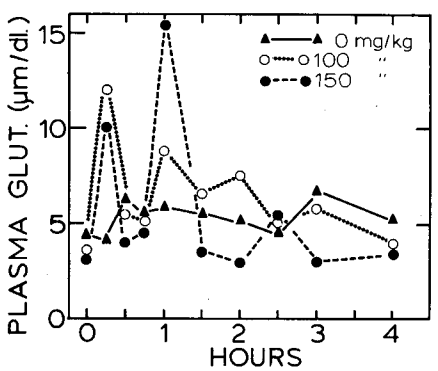

FIG. 2. Mean plasma glutamate (GLUT) levels in adult mice administered a Sustagen meal (0.4 g protein/kg) with and without added MSG (100 and 150 mg/kg body weight).

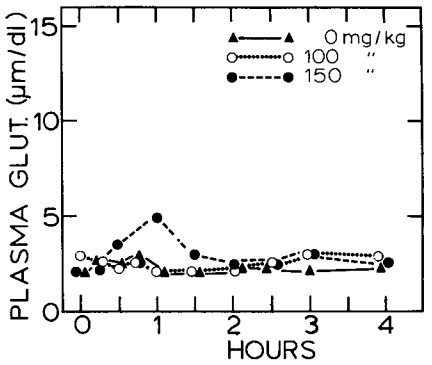

FIG. 3. Mean plasma glutamate (GLUT) levels in adult rhesus monkeys administered a Sustagen meal (0.4 g protein/kg) with and without added MSG (100 and 150 mg/kg body weight).

the Sustagen meal providing MSG at 100 mg/kg body weight. Ingestion of the Sustagen meal providing MSG at 150 mg/kg body weight resulted in a slight increase in glutamate levels at 1 hr after ingestion.

The data in Fig. 4 show plasma glutamate in normal human subjects fed the Sustagen meals (5). Six normal adult subjects (3 male, 3 female) were studied using a Latin Square Design (8) for the administration of the three meal systems studied (Sustagen alone, Sustagen providing 100 mg MSG/kg, and Sustagen providing 150 mg MSG/kg). The addition of MSG to the Sustagen meal produced slightly higher and broader plasma glutamate curves than observed after the ingestion of the Sustagen meal alone. However, peak plasma glutamate levels after ingestion of the meal providing 150 mg MSG/kg were no greater than those noted in subjects ingesting a high-protein meal (1 g protein/kg) without added glutamate (Fig. 1). These data demonstrate the excellent metabolism of MSG added to meals and show that added MSG is *not* absorbed preferentially to protein-bound glutamate as suggested by Olney (21,22).

The data in Fig. 5 compare plasma glutamate levels in adult mice, monkeys, and humans after the ingestion of the Sustagen meal providing MSG at a level of 150

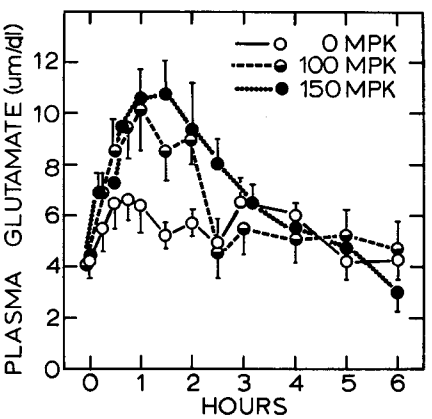

FIG. 4. Plasma glutamate levels (mean ± SEM) in six normal adult subjects administered a Sustagen meal (0.4 g protein/kg body weight) with and without added MSG (100 and 150 mg/kg body weight).

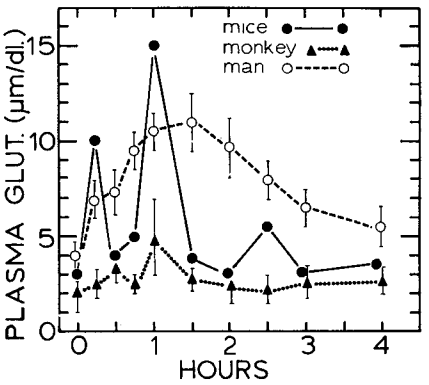

FIG. 5. Comparison of plasma glutamate (GLUT) levels in adult mice (mean) monkeys (mean ± SEM) and humans (mean ± SEM) administered a Sustagen meal providing 150 mg MSG/kg body weight.

mg/kg body weight. These data suggest that adult humans metabolize glutamate less rapidly than do adult mice or monkeys, since they show a broader curve. This was surprising, since we expected adult humans and monkeys to metabolize glutamate more rapidly than mice.

The MSG meal data led us to compare glutamate absorption-metabolism curves when MSG is administered to these three species in water. Adult mice, monkeys, and human subjects were administered MSG dissolved in water at levels providing 150 mg/kg body weight. The glutamate was dissolved to provide a 3.6% solution, and the solution was administered at 4.2 ml/kg body weight. The percentage of MSG in solution and the volume per kg administered were identical to those used in the Sustagen study. The data in Fig. 6 compare plasma glutamate levels in mice, monkeys, and human subjects after ingestion of MSG dissolved in water (150

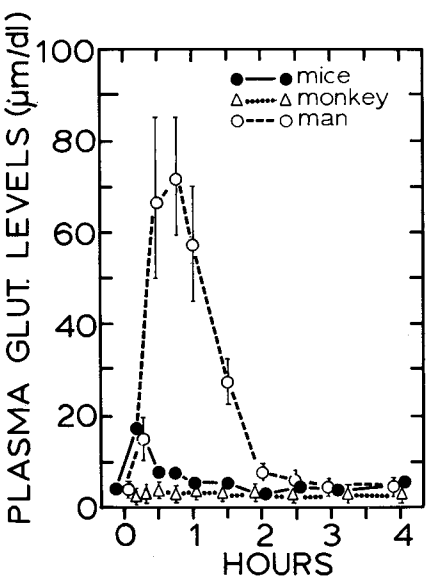

FIG. 6. Plasma glutamate (GLUT) levels in adult mice (mean), monkeys, and humans (mean ± SEM) administered 150 mg MSG/kg body weight dissolved in water.

mg/kg body weight). These data, like the Sustagen data, suggest that adult humans metabolize glutamate less rapidly than adult mice or monkeys. The levels seen in adult mice and monkeys were consistent with the levels observed in the neonatal pig given similar doses of MSG (28).

The data shown in Fig. 7 compare plasma glutamate levels in human subjects administered MSG at 150 mg/kg body weight either with the Sustagen meal or dissolved in water. These data demonstrate the modulating effect of food on MSG metabolism and absorption. The administration of the MSG in water produced much higher plasma glutamate levels than did the equivalent dose administered with a meal. Thus, MSG metabolism varies depending on the vehicle used to administer the dose. Most importantly, it becomes clear that MSG added to a meal is not preferentially absorbed.

The results obtained from mice and monkeys given MSG in water were puzzling when compared to the data obtained in man. Marked elevations in plasma glutamate levels were not obtained in either mice or monkeys given MSG at 100 or 150 mg/kg body weight. Failure to elevate plasma glutamate levels when MSG was administered with Sustagen was not surprising, since we had noted only small changes in plasma glutamate levels in humans under these conditions. However, the low plasma glutamate levels observed in monkeys and mice when MSG was administered in water was puzzling, since plasma glutamate levels had risen in humans under comparable conditions.

These results led us to consider possible causes for these low levels, especially the possibility that gastric emptying had failed to occur in these animals. To evaluate this possibility, loading studies in adult mice and monkeys were carried out using increasing doses of MSG dissolved in water. We wished to obtain a dose-

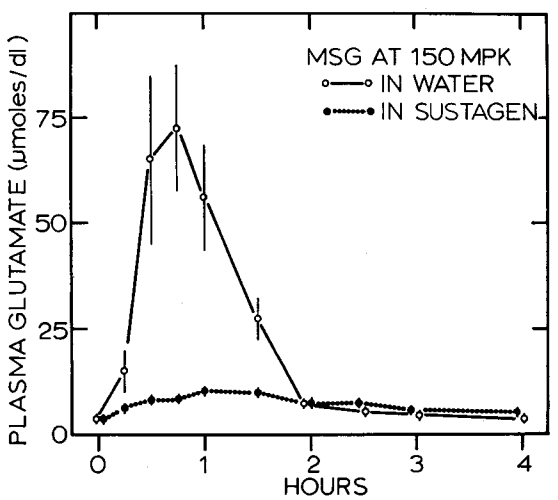

FIG. 7. Plasma glutamate levels in normal adult humans administered MSG at 150 mg/kg body weight either dissolved in water, or as part of a Sustagen meal. Data shown as mean ± SEM.

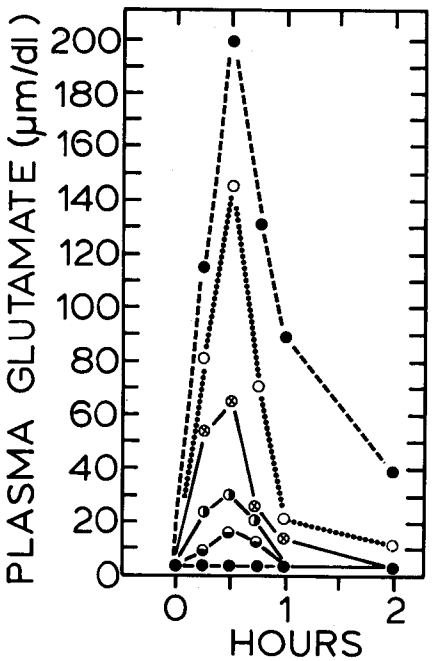

FIG. 8. Mean plasma glutamate levels in adult mice administered MSG dissolved in water at 0 (—●—), 150 (—○—), 250 (—◑—), 500 (—⊗—), 1,000 (···○···), and 2,000 (--●--) mg/kg body weight.

response curve for plasma glutamate levels with MSG dose. These data would allow us to determine if plasma glutamate levels measured in mice and monkeys were appropriate to the dose of MSG administered.

The data in Fig. 8 show mean plasma glutamate levels in adult mice administered MSG dissolved in water. The glutamate doses studied were 0, 250, 500, 1,000, 2,000, and 4,000 mg MSG/kg body weight. A 5% MSG solution was used for animals dosed at 250 and 500 mg/kg, a 10% solution was used for animals dosed at 1,000 mg/kg, a 20% solution was used for animals dosed at 2,000 mg/kg, and a 40% solution was used for animals dosed at 4,000 mg/kg. The data in Fig. 8 show a reasonable response of plasma glutamate levels to increasing doses of MSG and indicate that the plasma levels obtained at the 150 mg/kg dose are reasonable.

The data in Fig. 9 show similar results in adult monkeys administered MSG in water at doses of 150, 500, and 1,000 mg/kg body weight. In these studies, apparent delayed gastric emptying was observed in the two animals studied at 500 mg/kg dose. However, allowing for this shift, the overall response observed after MSG loading at 150 mg/kg is appropriate. The data shown in Figs. 8 and 9 support those data shown in Fig. 6 and indicate that adult humans metabolize glutamate less efficiently than either adult mice or monkeys.

Although peak plasma glutamate levels in adult mice and monkeys showed a reasonable response to increasing doses of MSG, the peak values observed were lower than expected, based on data available for the neonatal rodent and primate. This difference led us to speculate whether younger animals metabolize glutamate less well than adults.

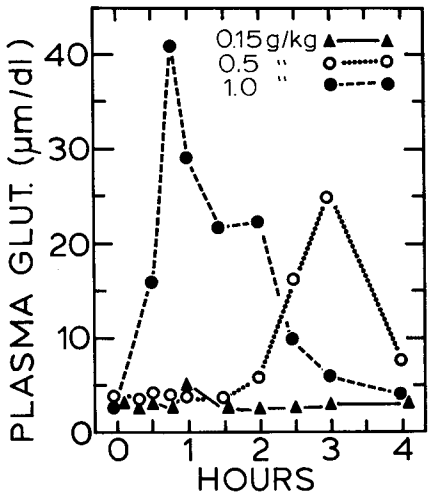

FIG. 9. Mean plasma glutamate (GLUT) levels in adult rhesus monkeys administered MSG dissolved in water at 150, 500, and 1,000 mg/kg body weight.

In 1974 we studied the plasma threshold levels of dicarboxylic amino acids required to produce neuronal necrosis after ingestion of protein hydrolysate solutions (33). Neonatal mice were injected with glutamate- and aspartate-containing solutions, and plasma amino acid levels were measured with time. As shown in Fig. 10, a series of dose-related curves of plasma glutamate and aspartate levels was

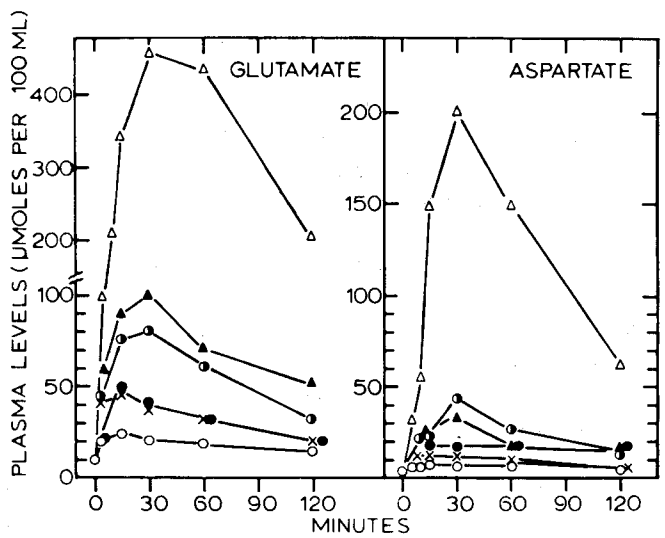

FIG. 10. Plasma glutamate and aspartate levels in 9- to 11-day-old mice injected with protein hydrolysate solutions containing glutamate and aspartate: Amigen at 20 μl/g (×), 50 μl/g (▲), or 100 μl/g (△), or Aminosol at 20 μl/g (○), 50 μl/g (●), or 100 μl/g (◑). (From Stegink et al., ref. 33, with permission.)

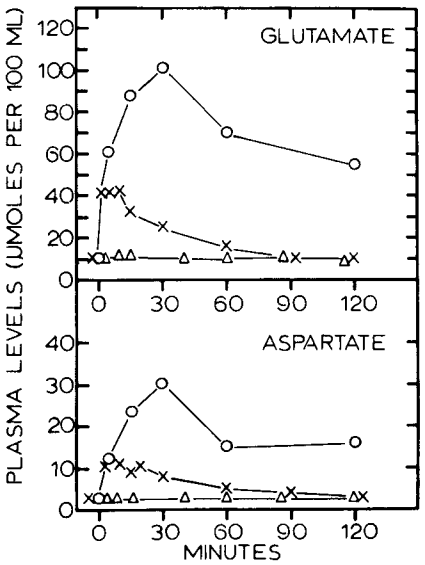

FIG. 11. Plasma glutamate and aspartate levels in 9- to 11-day-old mice following subcutaneous injection with either isotonic saline at 50 μl/g body weight (△) or glutamate and aspartate containing protein hydrolysate (Amigen) at 50 μl/g body weight (○). Plasma glutamate and aspartate levels in 25-day-old mice injected with Amigen at 50 μl/g body weight (×). (From Stegink et al., ref. 33, with permission.)

obtained. Comparison of these data to the degrees of neuronal necrosis observed by Olney et al. (24) in animals injected with these solutions indicated a plasma dicarboxylic amino acid threshold level of about 60 μmoles/dl was required for neuronal damage in the neonatal mouse.

Since the adult mouse is known to be more resistant to dicarboxylic amino acid-induced neuronal necrosis than the neonate (16,20), we compared plasma levels in infant and adult mice. The data in Fig. 11 show plasma glutamate and aspartate levels in 9- to 11-day-old and 25-day-old mice following subcutaneous injection with either isotonic saline or protein hydrolysate solutions at 50 μliters/gm body weight. Comparison of plasma glutamate and aspartate levels indicate that older animals metabolize injected glutamate and aspartate more rapidly than the younger animals.

These animals had been studied, however, after subcutaneous injection of glutamate rather than oral administration and with a glucose-protein hydrolysate solution rather than glutamate alone. To eliminate these differences, we studied neonatal mice that had received an orally administered solution of MSG in water. Nine- to ten-day-old mice were treated with 0, 250, 500, 1,000, and 2,000 mg MSG/kg body weight. The percentage of MSG in the solutions used was the same as that utilized for the adult animals shown in Fig. 8. The data in Fig. 12 show mean plasma glutamate levels in these animals. These data indicate much higher plasma glutamate levels are obtained in neonatal mice than in adult mice given equivalent oral doses of MSG in water.

These data indicate a plasma glutamate threshold for neuronal necrosis that is close to the one obtained in our studies with the protein hydrolysate (33). Reynold's data (*this volume*) indicate an absence of neuronal necrosis in neonatal mice given

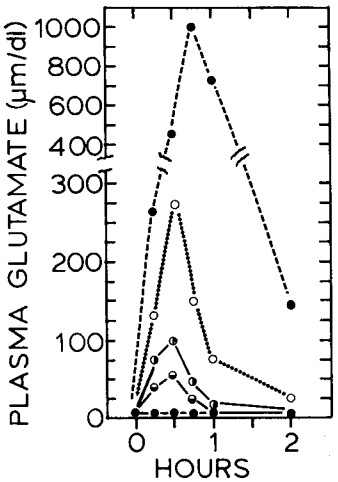

FIG. 12. Plasma glutamate levels in 9- to 11-day-old mice administered oral loads of glutamate dissolved in water: 0 (—●—), 250 (—○—), 500 (—◦—), 1,000 (···○···), or 2,000 (--●--) mg/kg.

MSG at a dose of 250 mg/kg body weight. However, 22% of the neonatal mice administered MSG at 500 mg/kg show neuronal necrosis. The data in Fig. 12 show plasma levels of 40 μmoles/dl in animals given 250 mg/kg and levels of 80 to 100 μmoles/dl in animals given 500 mg/kg. This suggests a plasma glutamate threshold level of approximately 80 μmoles/dl, in good agreement with our value of 60 μmoles/dl obtained in the casein hydrolysate studies (33), where the osmotic load was high.

The peak plasma glutamate values obtained in these infant mice are similar to those reported by other investigators (Table 4). However, the peak plasma levels observed in our adult mice are significantly lower than values reported by other investigators (Table 5), although the values reported by others vary considerably, ranging from 208 to 344 μmoles/dl for an equivalent dose (6,15,18,19). These investigators (6,18,19) report little, or no, age-related effect on the metabolism of orally administered glutamate.

The available data confirm that the infant rodent metabolizes *injected* glutamate less well than the adult rodent. O'hara et al. (18,19) and Takasaki et al. (34) also report an age-related effect of subcutaneously injected glutamate, confirming our earlier report (33). O'hara et al. (18,19) reported peak plasma glutamate levels of 1,058 μmoles/dl in infant mice, 760 μmoles/dl in weanling mice, and 539 μmoles/dl in adult animals injected subcutaneously with MSG at a dose of 1 g/kg body weight. When the dose was given intraperitoneally rather than subcutaneously, this age-related effect was smaller. Our data are also consistent with data reported by Cresteil and Leroux (10) on the metabolism of injected glutamate by neonatal and adult rodents. They report a strong age-related effect in the conversion of injected ^{14}C-glutamate to $^{14}CO_2$. The rate of $^{14}CO_2$ production from injected glutamate increased from 130 nmoles/hr in the zero-hour neonatal rat to 2,000 nmoles/hr in the 21-day-old animal, indicative of an increased ability to metabolize glutamate.

TABLE 4. *Mean peak plasma glutamate levels in 7- to 11-day-old mice after oral administration of MSG dissolved in water*

Dose (mg/kg)	Plasma glutamate levels (μmoles/dl)		
	Iowa	Bizzi et al. (6)	O'hara et al. (18,19)
0	8	—	17
250	40	72	—
500	88	108	62
1,000	282	210	314
2,000	1,050	—	—

Since all laboratories report age-related effects on the metabolism of injected glutamate, the failure of other laboratories to note an age-related effect after oral administration was puzzling. These differences could reflect the differences in the strains of animals studied. In addition, it is possible that our mice had more residual food in their gut than those studied by other investigators. The simultaneous availability of food, particularly carbohydrate, has a marked effect on plasma glutamate levels after an oral glutamate load (30). In our studies, adult and infant mice were fasted from 2 to 4 hr prior to glutamate loading. However, adult and infant animals ingested diets of differing composition (mouse milk versus chow), and this difference could affect the quantity of food remaining in the gut at the time of glutamate loading. Such differences could account for the large variation in peak plasma glutamate levels reported by other investigators in adult mice after oral glutamate loads. For example, O'hara et al. (18,19) report higher levels than either Bizzi et al. (6) or James et al. (15) after equivalent glutamate loads (Table 5). However, O'hara et al. (18,19) fasted animals for 10 hr prior to dosing, whereas other groups apparently did not.

To test this point, adult mice were fasted for 24 hr prior to oral administration of MSG (1 g/kg body weight administered as a 10% solution). A comparison of plasma glutamate levels in adult mice fasted for 2 to 4 hr and those fasted for 24 hr is shown in Fig. 13. These data demonstrate that the length of fasting prior to dose has a

TABLE 5. *Mean peak plasma glutamate levels in infant, weanling, and adult mice after oral doses of MSG at 1 g/kg body weight using 10% solutions*

Age of animal	Peak plasma glutamate levels (μmoles/dl)			
	Iowa	Bizzi et al. (6)	O'hara et al. (18,19)	James et al. (15)
Infant	282	210	314	—
Weanling	—	—	219	—
Adult	145[a]	208[b]	344[c]	210[b]

[a] Animals fasted 2 to 3 hr.
[b] Animals not fasted.
[c] Animals fasted 10 hr prior to dosing.

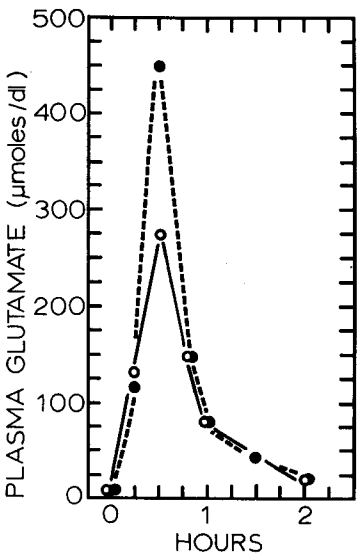

FIG. 13. Mean plasma glutamate levels in adult mice given 1 g MSG/kg body weight. Mice were fasted for 2 to 3 hr (—○—) or 24 hr (---●---) prior to dosing.

marked effect on peak plasma glutamate levels. The peak values observed in animals fasted for 24-hr were higher than those reported by O'hara et al. (18,19), where a 10-hr fast was used.

It is not certain whether the increased plasma glutamate levels noted with increasing length of fasting result entirely from a decrease in residual food in the gut. Intestinal enzymes have very short half-lives, and increased fasting will decrease the levels of intestinal enzymes needed to metabolize orally administered glutamate. However, these data support our contention of an age-related effect on glutamate metabolism in animals fasted for a standard length of time, such as 3 to 4 hr. The failure of O'Hara et al. (18,19) to observe an age-related effect with oral glutamate administration between neonatal, weanling, and adult mice probably reflects the differing fasting periods used. In their studies, adult animals were fasted for 10 hr, weanling animals for 2 hr, and infant mice were not fasted. Thus, the variables related to fasting could obscure an age effect. There are other reasons to believe that the age-related effect on glutamate metabolism observed in animals fasted 3 to 4 hr is real. Age-related effects are noted when glutamate is injected (18,19,33). Factors causing this age-related effect should also affect the metabolism of orally administered glutamate to some degree. Second, Wen and Gershoff (35) report that the levels of the two major glutamate transaminase enzymes present in rodent intestinal mucosa show a strong age-related effect. Enzyme levels are much lower in the neonatal rat than in postweanling animals. The intestinal transaminases play a major role in the metabolism of orally administered glutamate (27,30), and it is highly likely that differences in levels of mucosal glutamate transaminases would affect glutamate metabolism and clearance. Levels of these enzymes may decrease with increased fasting in adult animals, accounting for the increase in plasma glutamate levels when animals are fasted for 24 hr rather than 3 to 4 hr. Thus, the

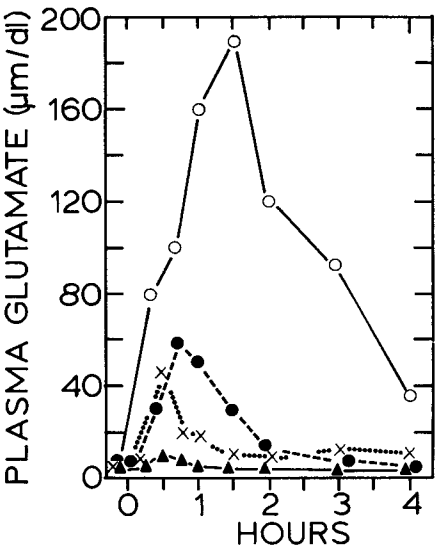

FIG. 14. Plasma glutamate levels in neonatal rhesus monkeys administered oral loads of MSG dissolved in water: 0 (—▲—), 250 (···×···), 500 (--●--), or 1,000 (—○—) mg/kg.

factors affecting glutamate metabolism and clearance are complex. The length of fasting prior to administration of the load, the simultaneous presence of food, and the age of the animal all affect peak plasma glutamate levels.

We also carried out experiments in neonatal rhesus monkeys to determine if similar age-related effects on glutamate metabolism were observed in the primate. The data in Fig. 14 show plasma glutamate levels in neonatal monkeys (1 to 2 weeks of age) given oral doses of MSG in water at 150, 250, 500, and 1,000 mg/kg body weight. Comparisons of these data with values obtained in adult monkeys (Fig. 9) indicate that the adult monkey metabolizes glutamate more rapidly than the neonate. The monkey, like man (30), may have a considerable individual-to-individual variation in the ability to metabolize glutamate. We have previously observed two neonatal monkeys who showed a marked inability to metabolize glutamate (32). However, the best interpretation of the data indicates an age-related increase in the ability of the rhesus monkey to metabolize glutamate.

The brains and retinas of the neonatal monkeys were concomitantly perfused with glutaraldehyde for future study after being prepared as thin (1-μ) plastic sections. No damage was found in the hypothalami (26,32) or the retinas (D. Apple, *personal communication*) of these newborn monkeys following MSG loads of 1 to 4 mg/g.

The role of the erythrocyte in the transport of glutamate in the blood is of considerable interest, since certain amino acids are known to be transported in the erythrocyte to a greater extent than in plasma under certain circumstances (3,11–14).

Our data differ from those reported by Bizzi et al. (6) concerning the ratio of erythrocyte to plasma glutamate in animals. They report this ratio to be about unity in both arterial and venous compartments, either in basal conditions or after oral administration of MSG. Our data (Table 6) indicate a considerable difference

TABLE 6. *Fasting plasma and erythrocyte glutamate levels in adult mice, monkeys, and humans*

Species	Plasma (μmoles/dl)	Erythrocyte (μmoles/dg)
Mice	6.8 ± 3.6[a]	21.0 ± 8.8
Monkeys	3.1 ± 0.4	59.9 ± 8.9
Humans	4.8 ± 1.6	18.9 ± 7.1

[a] Mean ± SD.

between plasma and erythrocyte levels of glutamate in fasting adult mice, monkeys, and man. This difference increases further if the erythrocyte levels are expressed as μmoles/100 ml water in the red cell, rather than as μmoles/100 g of cells. We do not see the simultaneous increase in both plasma and erythrocyte glutamate levels after glutamate loading as reported by Bizzi et al. (6). The data in Fig. 15 show plasma and erythrocyte glutamate levels in a single male adult human subject given MSG in water at 100 or 150 mg/kg body weight. Despite large increases in plasma glutamate levels, erythrocyte levels do not change. Similar results were obtained in adult mice.

The interaction between plasma glutamate and erythrocyte glutamate levels is complex. As shown in Table 6, the erythrocyte, like other tissues, maintains a considerably higher glutamate concentration within the cell than in plasma. Our data indicate that erythrocyte glutamate levels in the neonatal human and monkey are considerably higher than those in adult humans and monkeys. Our data suggest that the neonatal monkey erythrocyte may be more receptive to glutamate transfer from the plasma than the adult erythrocyte.

The data in Fig. 16 show plasma and erythrocyte glutamate levels in two neonatal monkeys administered oral doses of MSG in water. Considerable variation is noted between erythrocyte glutamate levels in these two animals. The data suggest that elevations in plasma glutamate that do not exceed the level of glutamate present in the erythrocyte do not affect erythrocyte levels. However, when plasma glutamate

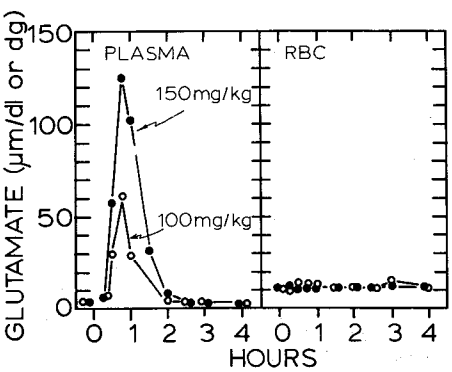

FIG. 15. Plasma (μmoles/dl) and erythrocyte (μmoles/dg) glutamate levels in a typical adult male subject ingesting MSG dissolved in water at 100 or 150 mg/kg body weight.

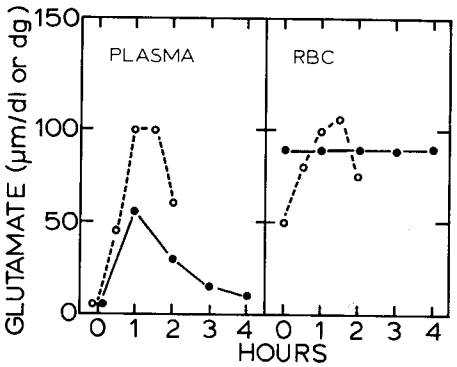

FIG. 16. Plasma (μmoles/dl) and erythrocyte (μmoles/dg) glutamate levels in two infant rhesus monkeys ingesting MSG dissolved in water: animal 1 (—●—) and animal 2 (--○--).

levels exceeded those normally present in the erythrocyte, erythrocyte glutamate levels also increased.

In summary, our data indicate that the administration of large doses of MSG with meals to humans, monkeys, and mice results in only small increases in plasma glutamate levels over those occurring with the meal alone. The data indicate that the added MSG is not absorbed preferentially to the protein-bound glutamate.

The administration of MSG dissolved in water results in higher plasma glutamate levels than when the equivalent dose is given with a meal. This effect is most obvious in humans.

Glutamate-loading studies in mice and monkeys indicate that the adult animal metabolizes glutamate more rapidly than the neonate, although many factors affect the rates of metabolism. The data suggest that adult humans metabolize glutamate less rapidly than do either adult mice or rhesus monkeys.

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