# Monosodium Glutamate: Effect on Plasma and Breast Milk Amino Acid Levels in Lactating Women[1] (36563)

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(Introduced by J. T. Bradbury)
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In 1957, Lucas and Newhouse (1) demonstrated that suckling mice injected with monosodium glutamate (MSG) at 2.2 g/kg body weight daily for 14 days developed retinal lesions. Since that time a number of investigators have confirmed the findings that suckling mice and rats injected with MSG or aspartate at these levels develop acute and irreversible retinal lesions (2–6). Adult mice were much more resistant to glutamate than newborn animals, and glutamate injection of pregnant mice produced no observable abnormalities in the offspring (1). Olney (7) and Olney and Sharpe (8) have reported that the arcuate nucleus of the hypothalamic region is particularly vulnerable to damage in the infant mouse, rat, rabbit and a single immature rhesus monkey when injected subcutaneously with MSG at doses ranging from 0.5 to 2.7 g/kg body weight. They have recently reported development of such lesions in infant mice after oral ingestion of 3 g/kg body weight of MSG, aspartate or cysteine (9). Although Arees and Mayer (10) reported the development of such lesions in adult rats when injected with large doses of MSG, several other groups of investigators have failed to induce CNS lesions in the newborn rat, monkey or dog with MSG (11–14).

Because questions have been raised on the basis of some animal studies about the safety of ingestion of MSG by lactating women, a series of MSG loading tests were carried out. This report describes the effect of the oral administration of MSG on free amino acid levels in plasma and breast milk.

*Methods and Materials.* A total of 10 women with well-established lactation patterns of 30 to 90 days duration were studied.[2] After an overnight fast the subjects received a 6 g load of MSG or lactose at 0800 hr contained in twelve 0.5 g capsules. This approximates a dose equal to 0.1 g/kg body weight, and represents considerably more than would be ingested with a meal. It is also a quantity sufficient to cause the symptoms of the Chinese restaurant syndrome in susceptible subjects (20–27). For nine tests the MSG was given in conjunction with 240 ml of Carnation Slender, for four tests MSG was given in conjunction with water. Four control subjects were given 6 g lactose in conjunction with water (Table I).

Milk samples were obtained at zero time, and at 1, 2, 3, 4, 6 and 12 hr after administration of MSG or lactose. Timed urine samples were obtained from each woman for the following intervals: 0800 to 1100 hr, 1100 to 1400 hr, and 1400 to 2000 hr. We had previously observed in animal studies that MSG was absorbed at differing rates depending on whether it was administered in conjunction with water or with food (15). Thus, blood samples were drawn at: 0, 30, 60, 120, and 180 min after administration of the MSG load with water, 0, 60, 90, 150, and 210 min after administration of MSG with Slender, and 0, 30, 60, 90, 150, and 210 min after administration of the lactose placebo.

The plasma was separated immediately from the blood samples, deproteinized with solid sulfosalicylic acid (16), and either an-

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TABLE I. Schedule of Participation in Loading Tests.[a]

| Subject | Days of lactation | | |
|---|---|---|---|
| | 30 | 60 | 90 |
| 1 | B | A | B |
| 2 | A | B | B |
| 3 | B | | B |
| 4 | B | | |
| 5 | | | A |
| 6 | B | A | B |
| 7 | C | | |
| 8 | | C | |
| 9 | | C | |
| 10 | | | C |

[a] A, MSG in water; B, MSG in Slender; C, lactose in water.

alyzed immediately or stored at —70° until analyses could be performed. Urine samples were immediately deproteinized with sulfosalicylic acid (16) and stored at —70° until analyzed. Milk samples were deproteinized by the addition of 50 mg solid sulfosalicylic acid/ml of milk. The sample was centrifuged, and the clear solution between the upper fat layer and the precipitated protein was carefully removed. If the solution was cloudy, it was centrifuged at 20,000*g* for 20 min to clear the solution prior to analysis or storage at —70°.

Amino acid analyses were carried out with Technicon NC-1 single column amino acid analyzers using the buffer system described by Efron (16) for physiological fluids.

*Results and Discussion.* Because experiments in this laboratory with newborn pigs and monkeys had demonstrated that animals given oral loads of 3,4-$^{14}$C-monosodium glutamate, in conjunction with water or an infant formula, incorporated significant quantities of radioactivity only into aspartate, glutamine, glutamate and alanine (15), the data in Tables II and III are limited to these four amino acids.

The changes noted in plasma amino acid levels in these women following the ingestion of MSG load are similar to those observed in the newborn pig or monkey given an oral dose of MSG (0.1 g/kg of body wt).

Evaluation of the plasma amino acid data in Table II indicates that plasma glutamate and aspartate levels peak approximately 30 min following ingestion of MSG with water in

TABLE II. Plasma Amino Acid Levels.

| Time (min) | Amino acid ($\mu$moles/100 ml plasma) | | | |
|---|---|---|---|---|
| | Aspartate | Glutamine | Glutamate | Alanine |
| MSG with water ($N = 4$) | | | | |
| 0 | 0.32 ± 0.16 | 61.9 ± 16.8 | 3.90 ± 1.70 | 53.1 ± 13.3 |
| 30 | 1.04 ± 0.92 | 68.0 ± 7.10 | 13.0 ± 10.1 | 50.6 ± 11.4 |
| 60 | 0.54 ± 0.31 | 62.4 ± 5.80 | 7.5 ± 4.80 | 46.6 ± 5.60 |
| 120 | 0.70 ± 0.40 | 65.9 ± 14.9 | 5.10 ± 2.70 | 47.3 ± 10.5 |
| 180 | 0.45 ± 0.25 | 62.4 ± 8.07 | 4.75 ± 2.31 | 40.5 ± 10.5 |
| MSG with Slender ($N = 9$) | | | | |
| 0 | 0.64 ± 0.27 | 61.0 ± 3.70 | 4.34 ± 0.70 | 42.5 ± 6.32 |
| 60 | 1.28 ± 1.42 | 70.5 ± 14.7 | 7.05 ± 2.70 | 68.1 ± 19.6 |
| 90 | 1.27 ± 1.24 | 72.1 ± 14.0 | 9.23 ± 5.34 | 67.3 ± 12.1 |
| 150 | 1.84 ± 1.45 | 65.0 ± 10.4 | 11.8 ± 8.20 | 50.3 ± 10.4 |
| 210 | 1.32 ± 0.80 | 59.6 ± 8.31 | 10.2 ± 7.99 | 46.8 ± 6.95 |
| Lactose with water ($N = 4$) | | | | |
| 0 | 0.43 ± 0.14 | 69.7 ± 16.6 | 4.00 ± 0.97 | 40.5 ± 6.60 |
| 30 | 0.65 ± 0.07 | 83.6 ± 8.70 | 4.10 ± 0.28 | 48.3 ± 6.70 |
| 60 | 0.39 ± 0.10 | 76.4 ± 4.60 | 3.70 ± 1.40 | 46.3 ± 10.0 |
| 90 | 0.56 ± 0.26 | 65.0 ± 16.6 | 3.80 ± 1.90 | 41.7 ± 11.4 |
| 150 | 0.61 ± 0.26 | 71.2 ± 10.9 | 5.70 ± 4.40 | 35.1 ± 3.50 |
| 210 | 0.26 ± 0.10 | 63.0 ± 14.1 | 3.20 ± 0.56 | 35.9 ± 4.00 |

most subjects, and fall rapidly to base line levels. When MSG is administered with Slender (or in the case of infant animals, an infant formula) plasma glutamate levels reach a maximum 1.5 to 2.5 hr after ingestion. The plasma glutamate elevations noted in these studies are minor when compared to the large elevations of plasma glutamate (150–250 μmoles/100 ml) noted in experimental animals ingesting MSG at 2–4 g/kg of body weight. A relatively large standard deviation is noted in plasma glutamate and aspartate values with increasing time in subjects receiving MSG with either water or Slender, which is not noted in zero time samples, or in the subjects receiving the lactose placebo. Thus, the values obtained indicate only a trend which does not withstand statistical analysis. The wide range in standard deviation in these two groups of subjects at times other than zero, is due to biological variation in the peak absorption times and handling of these amino acids following glutamate load. This is more easily seen in examining some responses in subjects administered MSG with water as shown in Fig. 1. It should be noted however that the peak times for aspartate and glutamate are identical for each individual, even though the exact time of the peak may vary. It must be emphasized that all increases in plasma amino acid levels were relatively small, with maximum glutamate elevations reaching 23 μmole/100 ml and aspartate reaching 2 μmole/100 ml.

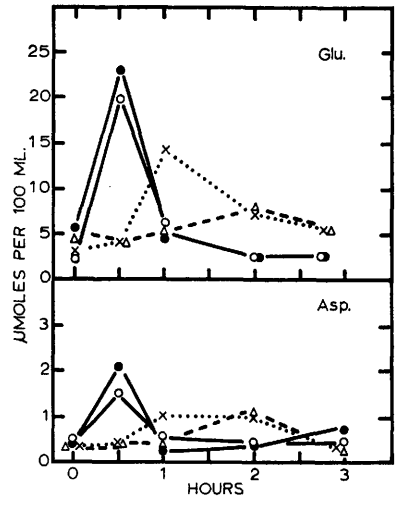


FIG. 1. Plasma glutamate (Glu.) and aspartate (Asp.) levels in individual subjects after administration of MSG with water showing variation in the overall absorption mechanism: (○) subject 1; (●) subject 2; (×) subject 5; (△) subject 6.

Plasma glutamine levels varied somewhat during the tests, but remained well within the concentrations reported for this amino acid in fasted subjects. Although plasma alanine levels were not elevated in subjects given MSG with water, increases in plasma alanine levels were noted in all subjects when MSG was administered with Slender. In the subjects receiving lactose, a slight increase in plasma alanine concentration was noted. Matthews and Wiseman (17) and Neame and Wiseman (18, 19) have reported that substantial quantities of ingested glutamate may appear in mesenteric blood as alanine. Alanine may be formed by a glutamate-dependent transamination of pyruvate, with pyruvate being formed either from carbohydrate via glycolysis, or from glutamate itself after transamination via Krebs cycle enzymes. Malate arising from the reaction, alpha-ketoglutarate to succinyl-CoA, to fumarate, to malate, can be converted to pyruvate via L-malate: NADP oxidoreductase (decarboxylating) [IUB 1.1.1.40].

Our observations on the change in serum alanine concentration following the administration of lactose or MSG with Slender suggest that carbohydrate is the source of the pyruvate carbon skeleton transaminated by glutamate. The fact that only negligible quantities of radioactivity are incorporated into alanine when 3,4-$^{14}$C-monosodium glutamate is administered in water or infant formula (15) to the infant pig or monkey also suggests that little of the carbon skeleton of this amino acid is derived from glutamate.

Free amino acid levels in milk varied considerably from individual to individual, and with the time of sampling. Glutamine levels in milk showed no change which could be correlated with the MSG load and were similar to those noted in control subjects (Table III). Small increases in aspartate and alanine levels in milk were noted with time in subjects receiving MSG with either water or

TABLE III. Free Amino Acid Levels in Breast Milk Following Administration of MSG or Lactose.

| Amino acid | Time following administration (hr) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 6 | 12 |
| | | | | ($\mu$moles/100 ml milk) | | | |
| | | | | MSG with water ($N = 4$) | | | |
| Aspartate | 2.9 ± 1.0 | 5.0 ± 3.0 | 8.0 ± 3.4 | 8.1 ± 3.9 | 7.9 ± 2.5 | 7.5 ± 3.1 | 9.1 ± 2.1 |
| Glutamine | 34.3 ± 19.1 | 35.8 ± 19.8 | 55.1 ± 20.3 | 52.5 ± 18.0 | 53.9 ± 7.70 | 51.0 ± 11.9 | 47.3 ± 12.7 |
| Glutamate | 107 ± 61.0 | 113 ± 27.3 | 126 ± 17.1 | 153 ± 66.7 | 145 ± 16.4 | 157 ± 36.0 | 181 ± 32.0 |
| Alanine | 16.5 ± 6.3 | 22.4 ± 6.8 | 30.1 ± 6.6 | 29.8 ± 7.5 | 31.0 ± 5.6 | 35.0 ± 6.1 | 35.0 ± 3.7 |
| | | | | MSG with Slender ($N = 9$) | | | |
| Aspartate | 2.5 ± 1.3 | 2.9 ± 1.6 | 5.3 ± 1.7 | 7.9 ± 2.7 | 8.0 ± 4.3 | 10.3 ± 1.5 | 5.8 ± 2.9 |
| Glutamine | 51.8 ± 27.2 | 42.4 ± 16.2 | 44.5 ± 12.7 | 57.0 ± 19.8 | 53.4 ± 22.4 | 88.1 ± 27.5 | 57.9 ± 23.0 |
| Glutamate | 146 ± 51.1 | 118 ± 39.7 | 128 ± 50.4 | 150 ± 34.1 | 161 ± 53.8 | 182 ± 28.0 | 159 ± 32.3 |
| Alanine | 16.0 ± 6.0 | 16.4 ± 4.6 | 25.8 ± 9.1 | 29.6 ± 9.8 | 27.4 ± 10.3 | 33.0 ± 7.8 | 29.2 ± 10.8 |
| | | | | Lactose with water ($N = 4$) | | | |
| Aspartate | 2.60 ± 1.6 | 3.0 ± 0.5 | 4.0 ± 1.6 | 4.3 ± 0.8 | 4.4 ± 4.5 | 4.2 ± 2.0 | 4.5 ± 2.0 |
| Glutamine | 79.5 ± 44.5 | 79.9 ± 55.1 | 68.7 ± 35.5 | 62.6 ± 34.0 | 67.3 ± 37.2 | 70.6 ± 38.0 | 85.1 ± 34.1 |
| Glutamate | 128 ± 36.6 | 147 ± 27.1 | 145 ± 16.2 | 167 ± 51.0 | 175 ± 49.2 | 158.7 ± 89.5 | 161 ± 34.1 |
| Alanine | 17.5 ± 7.4 | 22.7 ± 6.1 | 23.4 ± 5.2 | 23.4 ± 5.3 | 20.9 ± 10.9 | 26.1 ± 12.9 | 33.1 ± 10.4 |

Slender. The changes observed seemed somewhat greater than those noted in control subjects.

Glutamate is the most abundant free amino acid present in human milk thus the breast-fed infant normally receives considerable quantities of free glutamate. Glutamate levels in milk ranged from 78 to 208 μmoles/100 ml in samples obtained prior to the administration of either MSG or lactose. Similar levels (114 to 220 μmoles/100 ml) were found in the samples obtained 12 hr after ingestion of the load, when the effect of load should be minimal. Variations in breast milk amino acid levels are equally large when the data are separated and evaluated on the basis of duration of lactation.

Urinary excretion of glutamate, glutamine, alanine or aspartate was not significantly increased during any time period following ingestion of MSG when compared with the excretion of these amino acids in control subjects ingesting lactose. This is not surprising, since the increase in plasma glutamate was relatively small, and glutamate is readily metabolized by a variety of metabolic routes.

Although some changes in plasma free amino acid levels occurred following a glutamate load, the changes were of short duration as would normally follow a meal. No evidence was obtained to indicate the presence of excess glutamate in milk or plasma as the result of the ingestion of a single 6 g dose of MSG. Long-term effects on breast milk levels of glutamate following large doses of MSG remain unstudied.

None of the subjects reported symptoms associated with the so-called Chinese restaurant syndrome (20–24) at this dose. This is in agreement with the studies of most other investigators that such response is rare (21–26), but is in contrast to a recent report by Ghadimi, Kumar and Abaci (27) indicating that a dose of 0.15 g/kg of MSG produced symptoms in 12 out of 14 randomly selected adult subjects.

*Summary.* Recent studies describing the occurrence of specific neurotoxic effects in suckling animals of several species following oral or subcutaneous administration of large quantities of monosodium glutamate have raised questions regarding the safety of monosodium glutamate as a food additive for pregnant and lactating women. Plasma and breast milk free amino acid levels were measured in lactating women following ingestion of a single 6 g load of monosodium glutamate administered with either water or Slender. Small increases in plasma glutamate, aspartate and alanine levels were noted. However, little change was noted in breast milk amino acid levels. These data indicate that little, if any, of the administered load is concentrated in the milk.

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