Effect of aspartame and sucrose loading in glutamate-susceptible subjects

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ABSTRACT It has been postulated that individuals reporting an idiosyncratic symptom response after glutamate ingestion might also experience such symptoms after aspartame ingestion. Such sensitive subjects might have been missed in earlier studies of aspartame. In the present study, six subjects reporting various symptoms after glutamate ingestion, but not after placebo, were administered aspartame (34 mg/kg body weight) or sucrose (1 g/kg body weight) dissolved in orange juice in a randomized, cross-over, double-blind study. No subject reported symptoms typical of a glutamate response after either sucrose or aspartame loading. One subject reported slight nausea approximately 1.5 h after aspartame ingestion, but indicated that the symptoms were not those of a glutamate response. Plasma phenylalanine and aspartate levels were similar to those noted in normal subjects administered identical doses of aspartame. The data indicate no effect of aspartame loading in glutamate-susceptible subjects. Am. J. Clin. Nutr. 34: 1899-1905, 1981.

KEY WORDS Aspartame, glutamate, Chinese restaurant syndrome

Introduction

The ingestion of large amounts of monosodium L-glutamate (MSG) has been reported to produce a variety of symptoms in sensitive individuals (1-29). The best known characterization of symptoms is the so-called Chinese restaurant syndrome, although this term is used to describe a wide variety of responses. The link between MSG and the symptoms of Chinese restaurant syndrome was initiated by Kwok in 1968 (1). He reported that ingestion of Chinese food produced "... numbness at the back of the neck, gradually radiating to both arms and the back, general weakness and palpitation." Kwok's observations were expanded by Schaumburg and coworkers (2-4) who suggested that MSG was the causative ingredient in Chinese food. Schaumburg and Byck (3) first reported the symptoms as a burning sensation in the back of the neck, forearms, and anterior thorax, and a feeling of infrarobital pressure and tightness. In later studies, these investigators (4) reported three types of symptoms: a burning sensation, facial pressure, and chest pain, while also noting that headache is a consistent complaint in some individuals. Other, more anecdotal reports expanded the list of symptoms to include numbness of the jaw, lacrimation, periorbital fasciculation and syncope, temporal headache, or vice-like pounding in the head, as well as sweating about the face and armpits (5-12). This variety of symptoms has produced some confusion about the precise symptom grouping required to fit a diagnosis of Chinese restaurant syndrome. A number of investigators insist that subjects classified as having Chinese restaurant syndrome must manifest all of the symptoms (burning sensation, facial pressure, and chest pain) reported by Schaumburg et al. (4).

The incidence of subjects in the general population who experience symptoms after glutamate ingestion is not clear, and widely differing rates have been reported (4, 14-17, 19-25, 28). This variation probably relates to differences in test methods, dose of MSG administered, study conditions, the vehicle used to administer the MSG, and the symptom criteria. As pointed out by Kerr et al. (15-17), particular care must be exercised in interpreting studies using questionnaire methods.

Recently, several individuals have claimed...
to be acutely sensitive to the presence of added free MSG in the diet, while apparently not responding to protein-bound glutamate (26, 27). Unfortunately, these reports are in the form of letters to the editor, and contain little data obtained under controlled conditions. Nonetheless, these reports resulted in increased concern about reactions to dietary glutamate and similar compounds.

Aspartame (L-aspartyl-L-phenylalanyl methyl ester) is a dipeptide which is 180 to 200 times sweeter than sucrose (30). Because of its aspartate content, Olney (31, 32) and Reif-Lehrer (13, 14) have expressed concern about the interaction of this peptide with MSG in food systems. Indeed, Reif-Lehrer (13) suggested that aspartame might cause symptoms in subjects sensitive to MSG because of the structural similarity between glutamate and aspartate. Although we had not noted symptoms typical of a glutamate-induced response in some 49 subjects studied after receiving large doses of aspartame (33), it is possible that glutamate-susceptible subjects were not studied, since many studies resulted in increased concern about reactions to dietary glutamate and similar compounds.

The present study reports a direct test of Reif-Lehrer’s hypothesis (13) that glutamate sensitive subjects would also be aspartame sensitive. Six subjects who reported one or more symptoms after glutamate ingestion were administered aspartame or sucrose in a randomized, double-blind, cross-over design to determine whether aspartame elicited a response. Plasma amino acid levels were measured to determine whether such subjects metabolized aspartame differently than from normal subjects.

### Materials and methods

Six fasted subjects, known to respond to glutamate ingestion were tested. Each subject reported one or more symptoms (Table 1) after ingestion of MSG at 150 mg/kg body weight in tomato juice, but did not respond to a placebo (tomato juice containing NaCl at 10 mg/kg body weight) when the solutions were administered in a double-blind manner. Five of the six subjects reported similar symptoms of less intensity after ingesting soup providing MSG at 50 mg/kg body weight. Four subjects (B, C, D, E) did not report symptoms after ingesting soup providing either 0 or 25 mg/kg MSG. One subject (F), did not respond to soup providing either 0, 25, or 50 mg/kg body weight of MSG. Subject A reported symptoms (headache, warmth of extremities, eyes out of focus, increased auditory acuity) after ingestion of MSG at 25 mg/kg body weight in soup. However, this subject also reported symptoms (unusual feeling in eyes, but no problem with focus) after ingesting a placebo dose of soup providing no MSG in a follow-up blinded study. Later, subject A was reported to be a user of “street drugs.” In our experience, a symptom response to glutamate administration at 25 mg/kg body weight is unusual. Thus, this subject’s response to a low glutamate dose may reflect either a placebo response, or a response due to simultaneous drug usage. Unfortunately, this subject was lost to the study soon after drug use was established, and follow-up studies could not be carried out.

The proposed study was fully explained to each subject and informed, written consent obtained. The protocol of the study was reviewed and approved by the Committee on Research Involving Human Subjects of the University of Iowa.

The subjects were screened before entry into the study. This included a physical examination, complete blood count, urinalysis, a pregnancy test (female subjects), SMA 6/60 and SMA 12/60 profiles (serum: total protein, albumin, calcium, inorganic phosphorus, cholesterol, glucose, urea nitrogen, uric acid, alkaline phosphatase, lactate dehydrogenase, total bilirubin, glutamate-oxaloacetate transaminase, sodium, potassium, chloride, carbon dioxide, and creatinine) and fasting plasma amino acid analysis. All subjects had values within normal limits for the laboratory.

### Table 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>Test substance administered</th>
<th>Glutamate*</th>
<th>NaCl†</th>
<th>Aspartame‡</th>
<th>Sucrose§</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Headache, nausea</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>Headache, facial pressure, and tightness in temples</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>Headache, tightness in chest, facial pressure</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>D</td>
<td>Headache, facial pressure</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>E</td>
<td>Tightness in chest, burning, and tingling sensation in arms, pressure in face, nausea</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>F</td>
<td>Headache, light headed, stomach ache</td>
<td>None</td>
<td>None</td>
<td>Slight nausea</td>
<td>None</td>
</tr>
</tbody>
</table>

* Administered at 150 mg/kg body weight dissolved in tomato juice.
† Administered at 10 mg/kg body weight dissolved in tomato juice.
‡ Administered at 34 mg/kg body weight dissolved in orange juice.
§ Administered at 1 gm/kg body weight dissolved in orange juice.
Each subject received both aspartame (34 mg/kg body weight) and sucrose (1 g/kg body weight) in a cross-over design. Test doses were dissolved in 300 ml of cold orange juice and administered to fasted subjects (8 to 10 h) at 0800 h. Test compounds were administered at least 1 wk apart in a randomized double-blind manner.

Plasma amino acid levels were measured at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, and 4 h after the test load. The subjects received nothing by mouth for 4 h after the load, except water. Normal activity and meals were allowed after 1200 h.

Each subject was separated from the others during the study, and was asked to record any symptoms noted after administration of the test compounds using a specific form. The form listed 17 symptom categories: abdominal cramps; burning sensation in face or chest; chest pain; diarrhea; dizziness or light-headedness; flushing sensation in face or chest; headache; heartburn; nausea or vomiting; numbness or loss of feeling in any part of the body; palpitation; unusual perspiration or sweating; unusual thirst; a feeling of tightness around the face, neck, or chest; tingling in some part of the body; weakness; or “other symptoms” (to be specified by the subject). Each category listed a space for: time of symptom onset, the time when symptoms were mostly gone, and the time when symptoms had totally disappeared. All subjects were acquainted with the symptoms they experienced after glutamate ingestion.

Heparinized blood samples for amino acid analysis were centrifuged immediately to separate plasma and erythrocytes. The plasma was deproteinized with sulfosalicylic acid as previously described (34), and either analyzed immediately or stored at -70°C to prevent loss of glutamine and cystine (35, 36). Amino acid analyses were carried out on automated amino acid analyzers (Beckman 12 1 M, Beckman Instruments Company, Palo Alto, CA).

Aspartame was obtained from Searle Laboratories (Skokie, IL) and sucrose from the Mallinckrodt Chemical Company (St. Louis, MO).

Statistical analysis used the dependent or independent t test as appropriate (37).

Results

No subject reported symptoms typical of a glutamate-type response after ingesting either sucrose or aspartame. One subject (F) reported slight nausea 1.5 h after the aspartame dose, but not after sucrose loading. However, the subject clearly indicated that this response differed from that experienced after glutamate ingestion (headache, light headed, stomach ache). In addition, the time of symptom onset (1.5 h) was later than the time of symptom onset after MSG ingestion (12 to 40 min) as noted in both our studies and those of other investigators. This subject was the individual who reported symptoms only at 150 mg/kg body weight MSG and did not respond to soup providing MSG at 0, 25, or 50 mg/kg body weight.

Plasma aspartate, glutamate, phenylalanine, and tyrosine concentrations in these subjects are shown in Table 2. Plasma aspartate concentrations were slightly, but not significantly higher, after aspartame loading than after sucrose loading. Plasma aspartate

<table>
<thead>
<tr>
<th>Time</th>
<th>Aspartate</th>
<th>Glutamate</th>
<th>Phenylalanine</th>
<th>Tyrosine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>±0.16</td>
<td>±0.24</td>
<td>±0.70</td>
<td>±1.58</td>
</tr>
<tr>
<td>15</td>
<td>1.03</td>
<td>0.62</td>
<td>6.57</td>
<td>4.86</td>
</tr>
<tr>
<td>30</td>
<td>±0.84</td>
<td>±0.41</td>
<td>±1.01</td>
<td>±1.84</td>
</tr>
<tr>
<td>45</td>
<td>0.62</td>
<td>0.74</td>
<td>6.07</td>
<td>5.45</td>
</tr>
<tr>
<td>60</td>
<td>±0.25</td>
<td>±0.42</td>
<td>±1.50</td>
<td>±1.87</td>
</tr>
<tr>
<td>90</td>
<td>0.60</td>
<td>0.62</td>
<td>6.12</td>
<td>5.27</td>
</tr>
<tr>
<td>120</td>
<td>±0.34</td>
<td>±0.47</td>
<td>±1.49</td>
<td>±1.37</td>
</tr>
<tr>
<td>150</td>
<td>0.55</td>
<td>0.53</td>
<td>5.72</td>
<td>5.58</td>
</tr>
<tr>
<td>180</td>
<td>±0.27</td>
<td>±0.32</td>
<td>±1.73</td>
<td>±2.05</td>
</tr>
<tr>
<td>240</td>
<td>0.37</td>
<td>0.67</td>
<td>4.26</td>
<td>5.56</td>
</tr>
<tr>
<td>0</td>
<td>±0.22</td>
<td>±0.40</td>
<td>±1.07</td>
<td>±1.43</td>
</tr>
<tr>
<td>120</td>
<td>±0.43</td>
<td>±0.24</td>
<td>±1.42</td>
<td>±1.90</td>
</tr>
<tr>
<td>150</td>
<td>0.48</td>
<td>0.48</td>
<td>3.56</td>
<td>3.81</td>
</tr>
<tr>
<td>180</td>
<td>±0.28</td>
<td>±0.28</td>
<td>±0.84</td>
<td>±0.95</td>
</tr>
<tr>
<td>240</td>
<td>±0.38</td>
<td>±0.30</td>
<td>±0.96</td>
<td>±0.98</td>
</tr>
</tbody>
</table>

TABLE 2
Mean (±SD) plasma aspartate, glutamate, phenylalanine, and tyrosine concentrations (μmol/dl) after aspartame or sucrose loading in glutamate-susceptible subjects (n = 6)
concentrations in these individuals were similar to values noted in apparently normal subjects administered this dose of aspartame in a previous study (34). Plasma glutamate concentrations increased slightly after both aspartame and sucrose loading in all subjects, but values did not differ statistically from zero time concentrations.

Plasma phenylalanine concentrations decreased significantly \((p = 0.01)\) from base-line levels 90 min after sucrose loading, and returned toward base-line values 4 h after loading. After aspartame loading, plasma phenylalanine concentrations increased significantly \((p = 0.001)\) from fasting levels to the range seen postprandially in normal infants and adults fed protein meals (38, 39). Similarly, plasma tyrosine concentrations decreased after sucrose loading, but increased after aspartame loading, presumably reflecting conversion of phenylalanine to tyrosine. Plasma phenylalanine and tyrosine concentrations in glutamate sensitive individuals were similar to those noted in 12 normal subjects studied earlier at this aspartame dose (34).

Plasma concentrations of alanine and proline increased significantly \((p = 0.01)\) after both aspartame and sucrose loads (Table 3). This effect undoubtedly is due to the orange juice base.

Plasma concentrations of the branched chain amino acids (leucine, isoleucine, and valine) decreased significantly (Table 3) after both aspartame and sucrose loading. The decrease noted was similar to that observed in normal subjects administered either aspartame (34 mg/kg body weight) or aspartate (13 mg/kg body weight) dissolved in orange juice, and presumably reflects the carbohydrate content of the orange juice.

**Discussion**

These data demonstrate that subjects experiencing idiosyncratic symptoms after glutamate ingestion do not experience similar symptoms after ingestion of either aspartame (34 mg/kg body weight) or sucrose (1 g/kg body weight). Similarly, no differences in plasma aspartate, glutamate, or phenylalanine levels were noted after aspartame ingestion between these subjects and the 12 normal subjects studied earlier (34). These data argue against Reif-Lehrer's suggestion (13) that aspartame would evoke symptoms in glutamate-susceptible individuals. Our data are consistent with those of Schaumburg et al.

**TABLE 3**

Mean (±SD) plasma alanine, proline, leucine, isoleucine and valine concentrations (μmol/dl) after aspartame or sucrose loading in glutamate-susceptible subjects (n = 6)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Alanine (Aspartame)</th>
<th>Alanine (Sucrose)</th>
<th>Proline (Aspartame)</th>
<th>Proline (Sucrose)</th>
<th>Leucine (Aspartame)</th>
<th>Leucine (Sucrose)</th>
<th>Isoleucine (Aspartame)</th>
<th>Isoleucine (Sucrose)</th>
<th>Valine (Aspartame)</th>
<th>Valine (Sucrose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>30.4 ± 6.11</td>
<td>31.3 ± 7.66</td>
<td>25.9 ± 7.96</td>
<td>25.7 ± 9.32</td>
<td>16.0 ± 4.25</td>
<td>13.1 ± 4.75</td>
<td>8.46 ± 3.01</td>
<td>7.42 ± 2.72</td>
<td>27.1 ± 5.74</td>
<td>23.1 ± 4.18</td>
</tr>
<tr>
<td>15</td>
<td>32.3 ± 7.69</td>
<td>38.2 ± 7.77</td>
<td>26.3 ± 9.46</td>
<td>30.5 ± 10.00</td>
<td>15.1 ± 3.37</td>
<td>14.0 ± 2.60</td>
<td>8.56 ± 2.62</td>
<td>7.34 ± 1.34</td>
<td>25.8 ± 4.50</td>
<td>24.2 ± 7.08</td>
</tr>
<tr>
<td>30</td>
<td>43.8 ± 7.83</td>
<td>45.7 ± 8.37</td>
<td>27.6 ± 8.37</td>
<td>31.6 ± 11.3</td>
<td>13.1 ± 4.33</td>
<td>11.7 ± 4.73</td>
<td>6.96 ± 3.46</td>
<td>6.18 ± 2.31</td>
<td>23.1 ± 2.31</td>
<td>23.1 ± 6.82</td>
</tr>
<tr>
<td>45</td>
<td>46.9 ± 8.45</td>
<td>46.7 ± 8.38</td>
<td>27.9 ± 8.37</td>
<td>31.1 ± 12.4</td>
<td>12.4 ± 4.36</td>
<td>10.2 ± 4.81</td>
<td>6.92 ± 2.44</td>
<td>5.47 ± 2.12</td>
<td>21.2 ± 19.8</td>
<td>22.1 ± 7.89</td>
</tr>
<tr>
<td>60</td>
<td>43.2 ± 8.57</td>
<td>44.3 ± 7.62</td>
<td>27.2 ± 7.95</td>
<td>27.9 ± 9.95</td>
<td>9.95 ± 2.07</td>
<td>9.22 ± 3.75</td>
<td>4.99 ± 2.44</td>
<td>5.16 ± 1.44</td>
<td>21.2 ± 3.38</td>
<td>19.8 ± 5.24</td>
</tr>
<tr>
<td>90</td>
<td>35.3 ± 7.62</td>
<td>41.5 ± 5.44</td>
<td>25.1 ± 6.64</td>
<td>28.2 ± 9.09</td>
<td>7.60 ± 2.33</td>
<td>7.60 ± 3.26</td>
<td>4.48 ± 1.48</td>
<td>3.76 ± 2.08</td>
<td>20.8 ± 3.76</td>
<td>17.4 ± 3.30</td>
</tr>
<tr>
<td>120</td>
<td>35.5 ± 7.62</td>
<td>41.5 ± 5.44</td>
<td>23.1 ± 7.26</td>
<td>26.6 ± 9.93</td>
<td>7.61 ± 2.67</td>
<td>7.61 ± 5.75</td>
<td>5.75 ± 4.02</td>
<td>4.02 ± 1.98</td>
<td>19.8 ± 17.6</td>
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<td>150</td>
<td>35.5 ± 6.64</td>
<td>40.1 ± 7.50</td>
<td>25.3 ± 6.44</td>
<td>26.7 ± 10.8</td>
<td>7.47 ± 2.33</td>
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<td>180</td>
<td>34.6 ± 6.40</td>
<td>43.1 ± 7.34</td>
<td>24.4 ± 7.94</td>
<td>26.8 ± 3.81</td>
<td>8.47 ± 2.64</td>
<td>8.47 ± 1.90</td>
<td>6.45 ± 2.43</td>
<td>4.43 ± 22.3</td>
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<td>240</td>
<td>32.6 ± 9.52</td>
<td>37.2 ± 7.34</td>
<td>22.6 ± 7.92</td>
<td>27.0 ± 3.73</td>
<td>12.6 ± 1.77</td>
<td>12.6 ± 2.65</td>
<td>6.45 ± 2.43</td>
<td>4.43 ± 22.3</td>
<td>22.3 ± 19.3</td>
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<td></td>
<td>±8.83 ± 6.58</td>
<td>±7.67 ± 7.63</td>
<td>±7.63 ± 3.36</td>
<td>±1.97 ± 2.41</td>
<td>±1.12 ± 2.48</td>
<td>±2.48 ± 4.22</td>
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</tbody>
</table>
They noted that subjects reporting symptoms after glutamate ingestion did not report symptoms after ingesting 5-g loads of monosodium aspartate, that portion of aspartame postulated by Reif-Lehrer (13) as likely to produce symptoms.

Because of the large differences in reported incidence rates for individuals with glutamate-induced symptoms, aspartame effects were studied directly in subjects considered reactive to glutamate. As noted in Table 1, only one subject (E) reported all three symptoms considered typical of classical Chinese restaurant syndrome as described by Schaumburg et al. (4). The other subjects reported symptoms similar to those of the subjects studied by Ghadimi et al. (19). Our experience, like that of Ghadimi et al. (19), indicates that headache is a common symptom in sensitive individuals.

Although no subject reported symptoms considered typical of a glutamate-type response after aspartame ingestion, one subject did report slight nausea 1.5 h after aspartame loading. Although nausea was not listed by Schaumburg et al. (4) as one of the three major symptoms produced in glutamate-sensitive subjects (burning sensation, facial pressure, chest pain), nausea is reported by some individuals ingesting large doses of glutamate. Subjects A and E report nausea as well as other symptoms after ingesting 150 mg/kg MSG in tomato juice. These subjects did not experience nausea after ingesting lower doses of MSG (50 mg/kg), although most of the other symptoms are experienced at the lower dose. Nausea and vomiting have been associated with the marked elevation of blood glutamate concentrations after intravenous administration of glutamate-containing solutions (40-43). However, these symptoms may reflect other factors, such as hyperosmolality. Vinnars et al. (44) reported nausea and vomiting in subjects infused with amino acid solutions containing no glutamate or aspartate.

Some normal subjects ingesting high doses of aspartame in previous studies have found the extreme sweetness unpleasant. This is not surprising, since a 34 mg/kg aspartame dose administered to a 70-kg person has a sweetness equivalent to 1 lb of sucrose. At the highest dose of aspartame studied (200 mg/kg body weight), five of six subjects reported nausea (45). However, we do not believe that this response is a glutamate-type reaction due to aspartame's aspartate content, since plasma aspartate levels increased only slightly. By contrast, blood glutamate levels are significantly elevated by glutamate loads producing symptoms. The nausea experienced by these subjects probably reflects the extreme sweetness of the solution administered. A 70-kg individual ingesting 200 mg/kg aspartame receives the sweetness equivalent of 5.5 lb of sucrose in a single serving—obviously an unpleasant experience.

The dose of aspartame administered to these subjects was considerable, and should represent a reasonable test of whether susceptible subjects will react to the compound under normal use conditions. If aspartame sweetness were to replace all sucrose sweetness in the typical American diet, daily aspartame ingestion would be 7.5 to 8.5 mg/kg body weight, with the 99th percentile of projected daily intake of 34 mg/kg body weight (34). Similar projected intake values have been calculated by the Food and Drug Administration (46) and the Market Research Corporation of America (47). The aspartame dose studied closely approximates the Allowable Daily Intake value (40 mg/kg body weight) recently established by the FAO/WHO (48). Administration of aspartame at 34 mg/kg in a single bolus neither increased plasma aspartate levels nor produced a glutamate-type response. The administration of a single bolus dose of a specific compound at a level approximating its Allowable Daily Intake should be an adequate test for sensitivity. Monosodium glutamate administered as a single bolus dose to sensitive subjects at its Allowable Daily Intake (150 mg/kg body weight) produces a high symptom incidence in test populations (19) and elevates plasma glutamate levels (49).

References
44. Vinnars E, Furist P, Hermanson IL, Josephson B, Lindholmer B. Protein catabolism in the postoperative state and its treatment with amino acid solution.


