ABSTRACT The influence of glutamate intake on growth and appetite, and the mechanisms of preference and aversion for monosodium L-glutamate (MSG) solutions were investigated in rats. Food intake, but not weight gain, was reduced significantly in rats fed a glutamate + glutamine (Glx)-deficient diet compared with those fed a control diet. Increase in the voluntary intake of Glx solutions was more rapid in rats fed the Glx-deficient diet. The preference and aversion for MSG solutions were distinctly different in 14 rat strains tested. Brown-Norway rats showed a strong preference for 60 mmol/L MSG and did not show aversive behavior toward solutions containing up to 600 mmol/L MSG. Sprague-Dawley (SD) rats showed a moderate preference for 60 mmol/L MSG and a weak aversion for MSG concentrations higher than 240 mmol/L; Long-Evans Agouti rats showed a moderate preference for 60 mmol/L MSG and a marked aversion for MSG concentrations higher than 120 mmol/L. Aversion was not due to nonspecific hyperosmotic effects. After section of gastric branches of the vagus nerve, MSG became aversive to SD rats. Aversion to 240 mmol/L MSG was reduced by 23–39% when combined with proline, alanine, glycine and glucose. These results show that the preference and aversion for MSG are determined by genetic factors, as well as vagus nerve function, and that the aversion to high MSG concentrations is reduced by the presence of other glucogenic amino acids and sugars. J. Nutr. 130: 966S–970S, 2000.

KEY WORDS: ● taste preference ● taste aversion ● monosodium L-glutamate ● vagotomy ● rat strains

Animals and humans can detect the quality and quantity of protein ingested during a meal and use this information, via cephalic relays, to initiate digestion. In addition, they must have a means to monitor and satisfy the body’s requirement for protein over longer time periods. Results from preference tests indicate that the ingestion of monosodium L-glutamate (MSG), L-glutamine (Gln) and L-arginine is correlated with dietary protein intake, to facilitate urea formation in the liver (Mori et al. 1991). Data on the taste perception of MSG and its synergistic enhancement by 5′-ribonucleotides in mammals strongly suggest that such “umami” taste stimuli describe a basic taste category for protein intake (Brand et al. 1991, Ninomiya et al. 1991, Sato and Akaike 1965, Torii and Cagan 1980, Yamaguchi and Kimizuka 1979). This characteristic of taste is similar to saltiness (a taste category for mineral intake) (Torii 1980) and sweetness (a taste category for energy intake) (Torii et al. 1986 and 1987).

Animals change their preference for diets and liquids when one or more components of the diet are changed. For example, when an L-lysine–deficient diet is offered, rats become anorexic and begin ingesting an L-lysine solution previously perceived to be aversive (due to a bitter taste). After the rats have been exposed to a diet deficient in an essential amino acid, the concentration of the essential amino acid in the brain, as well as in plasma, decreases rapidly (Torii et al. 1987). Electrophysiologic data from behavioral preference tests suggest that the responses of neurons in the lateral hypothalamic area to the oral ingestion of solutions containing MSG, other amino acids or NaCl change in lysine-deficient rats, perhaps resulting in or from an altered preference for these nutrients (Tabuchi et al. 1991). Such results suggest that the central nervous system, especially the lateral hypothalamic area, may modulate amino acid and protein metabolism and the homeostatic levels of each amino acid.

These studies were undertaken to investigate the nutri-
tional significance of MSG and Gln, and the mechanisms of preference for and aversion to MSG solutions using various strains of rats.

Experiment I

Body weight gain, appetite, and preference for Glx (MSG + Gln) solutions were compared in rats given free access to a nutritionally complete, defined diet or a diet lacking Glx, to investigate the physiologic role of glutamate on rat growth and behavior.

MATERIALS AND METHODS

Subjects. Male Sprague-Dawley (Crj:SD, SD) rats (n = 20; 4 wk old, Charles River Japan, Atsugi, Japan) were used. The rats were divided into four groups (n = 5/group) and treated as follows: the first group had free access to water and a nutritionally complete control diet containing (in lieu of protein) an amino acid mixture (15 g/100 g dry weight) of composition similar to that of whole-egg protein (a high quality protein) (Torii et al. 1987). The second group had free access to water and a diet similar to the control diet, except that L-glutamic acid (Glu) and Gln were replaced with the same amount of an amino acid mixture that did not contain Glu and Gln (Glx-deficient diet). The third and fourth groups had free access in a choice paradigm to 13 solutions (in bottles with drinking tubes) of the deficient diet. The third and fourth groups had free access in a choice paradigm to 13 solutions (in bottles with drinking tubes) of the deficient diet. The third and fourth groups had free access in a choice paradigm to 13 solutions (in bottles with drinking tubes) of the deficient diet. The third and fourth groups had free access in a choice paradigm to 13 solutions (in bottles with drinking tubes) of the deficient diet.

Procedure. The four groups were fed the experimental diets for 8 wk; body weights and food and water intakes were measured daily. Daily consumption of each of the 13 solutions was also recorded for those rats that had access to these solutions in the choice paradigm.

Data analysis. Differences in weight gain, food intake and intake of Glx solutions (the sum of intakes of 0.15 mol/L MSG and 0.2 mol/L Gln solutions) between the control and Glx-deficient groups were analyzed by one-way ANOVA. The statistical criterion was P < 0.05. All data are shown as means ± SEM.

RESULTS

Body weight gain and food intakes were compared in rats fed the control and Glx-deficient diets (1st and 2nd groups, Fig. 1A). As shown in Figure 1A, the weight gain during the 8-wk period in the Glx-deficient group tended to be lower than that in the control group (352.6 ± 13.3 and 381.7 ± 18.5 g, respectively). The average daily food intake during the latter half of the experimental period (between wk 5 and 8) in the Glx-deficient group was slightly but significantly lower (P < 0.05) than that in the control group (23.1 ± 0.1 and 24.4 ± 0.3 g/d, respectively).

The consumption of Glx solutions increased gradually and reached maximum levels (~60 mL/d/rat) in both the control and Glx-deficient groups (3rd and 4th groups, Fig. 1B). The percentage of intake of Glx solutions was as high as 80% of the total solution intake from the 13 bottles in the control and Glx-deficient groups. The increase in intake of Glx solutions in the Glx-deficient group tended to occur more rapidly than that in the control group.

Experiment II

To investigate the mechanisms of preference and aversion for MSG solutions, intakes of solutions of MSG at various concentrations were tested in 14 rat strains as well as in vagotomized rats. The influence of other chemicals on MSG preference and aversion was also tested.

MATERIALS AND METHODS

Subjects. Fourteen strains of male rats (n = 6 rats/group) weighing 250–320 g at the start of the experiments, were studied: Sprague-Dawley (Crj:SD, SD), Brown-Norway (BN/Crj, BN), Donryu (Crj: Donryu), Wistar-Kyoto (WKY/Ncrj, WKY), Wistar-Lewis (LEW/ Crj, LEW), Fisher (F344/DuCrj, F344), Long-Evans Cinnamon (Crj: LEC, LEC), spontaneously hypertensive (SHR/Ncrj, SHR) and Wistar (Crj; Wistar) rats were obtained from Charles River Japan (Atsugi, Japan); Wistar (Slc;Wistar) rats were obtained from Japan.
TABLE 1

Percentage of intakes of monosodium glutamate (MSG) solutions in 14 rat strains1,2

<table>
<thead>
<tr>
<th>Strain of rats</th>
<th>60</th>
<th>120</th>
<th>240</th>
<th>480</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD</td>
<td>126.66 ± 7.27**</td>
<td>112.73 ± 4.45*</td>
<td>97.37 ± 8.67</td>
<td>83.29 ± 8.52</td>
</tr>
<tr>
<td>BN</td>
<td>156.95 ± 7.57***</td>
<td>124.58 ± 8.47</td>
<td>102.62 ± 9.81</td>
<td>101.47 ± 8.35</td>
</tr>
<tr>
<td>LEW</td>
<td>137.76 ± 7.34**</td>
<td>150.28 ± 12.09**</td>
<td>103.01 ± 7.78</td>
<td>60.24 ± 5.68**</td>
</tr>
<tr>
<td>F344</td>
<td>131.57 ± 5.06**</td>
<td>128.04 ± 4.38**</td>
<td>119.19 ± 3.65**</td>
<td>84.41 ± 5.48*</td>
</tr>
<tr>
<td>Hairless</td>
<td>140.06 ± 10.84**</td>
<td>130.77 ± 10.28*</td>
<td>102.70 ± 7.80</td>
<td>(42.2 ± 12.4)3</td>
</tr>
<tr>
<td>Donryu</td>
<td>143.92 ± 9.57**</td>
<td>114.88 ± 13.05</td>
<td>83.35 ± 11.06</td>
<td>62.21 ± 8.27**</td>
</tr>
<tr>
<td>Crj:Wistar</td>
<td>112.48 ± 4.18*</td>
<td>103.57 ± 19.58</td>
<td>108.19 ± 13.18</td>
<td>77.85 ± 10.73</td>
</tr>
<tr>
<td>Slc:Wistar</td>
<td>105.27 ± 5.83</td>
<td>85.95 ± 6.85</td>
<td>75.72 ± 5.72**</td>
<td>70.95 ± 3.18**</td>
</tr>
<tr>
<td>WKY</td>
<td>101.23 ± 7.29</td>
<td>90.72 ± 8.53</td>
<td>79.75 ± 6.99**</td>
<td>71.39 ± 2.68**</td>
</tr>
<tr>
<td>SHR</td>
<td>117.00 ± 12.39</td>
<td>79.73 ± 13.81</td>
<td>75.83 ± 5.60**</td>
<td>77.50 ± 3.74**</td>
</tr>
<tr>
<td>LE</td>
<td>109.78 ± 6.64</td>
<td>118.00 ± 9.15</td>
<td>91.98 ± 4.64</td>
<td>58.19 ± 6.17**</td>
</tr>
<tr>
<td>LEC</td>
<td>99.69 ± 4.37</td>
<td>90.50 ± 3.76*</td>
<td>68.77 ± 3.78**</td>
<td>57.70 ± 4.42**</td>
</tr>
<tr>
<td>LEA</td>
<td>126.77 ± 7.98**</td>
<td>92.67 ± 2.23**</td>
<td>36.91 ± 4.28**</td>
<td>21.88 ± 3.31**</td>
</tr>
<tr>
<td>F1 (SD × LEA)</td>
<td>134.32 ± 10.05**</td>
<td>113.81 ± 12.27</td>
<td>74.03 ± 3.92**</td>
<td>57.92 ± 5.59**</td>
</tr>
</tbody>
</table>

1 MSG intake was expressed as a percentage of intake relative to water.
2 Abbreviations: SD, Sprague-Dawley; BN, Brown-Norway; LEW, Wistar-Lewis; WKY, Wistar-Kyoto; SHR, spontaneously hypertensive rats; LE, Long-Evans; LEC, Long-Evans Cinnamon; LEA, Long-Evans Agouti.
3 n = 2, because 4 hairless rats were dead as a result of water deprivation.
* P < 0.05 and ** P < 0.01, significance compared with water intake by paired t test.

RESULTS

Preference and aversion for MSG solutions in 14 rat strains. Patterns of MSG concentration-solution intakes were investigated in 14 rat strains (Table 1). Intakes of 60 mmol/L MSG, the most preferred concentration among the rat strains, varied from 157% in BN rats to 100% in LEC rats. The intakes of 60 mmol/L MSG were significantly higher (P < 0.05 or P < 0.01) than water intakes in SD, BN, LEW, F344, Hairless, Donryu, Crj:Wistar, LEA and F1 rats, whereas those of the Wistar strains (Slc:Wistar, WKY, and SHR) and Long-Evans strains (LE and LEC) were not significant.

At higher concentrations of MSG (240 and 480 mmol/L), the intake was reduced in most rats. However, MSG intake in BN rats was comparable to water intake. Compared with other strains of rats, LEC and LEA rats showed a specific pattern. Their intakes of MSG solutions (120–480 mmol/L) were greatly reduced, especially in LEA rats (P < 0.01). The F1 rats showed an intermediate amount of MSG intake compared with that of their parent strains.

To investigate the mechanisms of high MSG sensitivity in LEA rats, we selected SD rats as the comparison group and examined their behavior in the following experiments for these reasons: 1) the SD strain is among the most common; 2) in contrast to LEA rats, SD rats showed a preference for 60 mmol/L MSG solution in SD rats was as high as that in LEA rats; and 3) in contrast to LEA rats, SD rats showed only a weak aversion for higher concentrations of MSG.

Preference and aversion for several amino acid solutions in SD and LEA rats. Intakes of various amino acid solutions at various concentrations were compared in SD and LEA rats. The intake patterns of MSA were similar to those of MSG in SD and LEA rats.

Hepatic branch (HVX), gastric branch (GVX) and subdiaphragmatic trunks (TVX), aortic (free base), L-arginine HCl, L-lysine HCl, L-proline, L-alanine, L-serine, glycine and L-threonine. One test chemical, only at the above concentrations, was presented to each rat. The pH of the solutions was not controlled. In a separate series of experiments, a single concentration (300 mmol/L of proline, alanine, glycine or glucose) was added to MSG solutions (of varying concentrations). The fluid intake from each bottle was measured at the end of the test session.

Data analysis. Intakes of MSG and other amino acids were expressed as a percentage of intake relative to water intake. Water intake was determined by averaging the intakes on d 8, 9 and 10. The difference between each solution intake and water intake was compared by paired t test. The differences in the intakes of each solution among the groups tested were analyzed by one-way ANOVA. Post-hoc tests employed Fisher’s protected least significant difference test.
Effects of glucogenic amino acids and glucose on monosodium glutamate (MSG) intake in Long-Evans Agouti (LEA) rats.

TABLE 3

<table>
<thead>
<tr>
<th>Addition to MSG solution</th>
<th>60</th>
<th>120</th>
<th>240</th>
<th>480</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>126.77 ± 7.98</td>
<td>92.67 ± 2.23</td>
<td>36.91 ± 4.28</td>
<td>21.88 ± 3.31</td>
</tr>
<tr>
<td>Proline (300 mmol/L)</td>
<td>106.61 ± 7.07</td>
<td>88.00 ± 4.78</td>
<td>59.66 ± 7.26**</td>
<td>21.56 ± 4.21</td>
</tr>
<tr>
<td>Alanine (300 mmol/L)</td>
<td>82.55 ± 7.93**</td>
<td>81.23 ± 2.04</td>
<td>66.37 ± 6.09**</td>
<td>19.07 ± 5.54</td>
</tr>
<tr>
<td>Glycine (300 mmol/L)</td>
<td>92.61 ± 7.38**</td>
<td>90.10 ± 11.77</td>
<td>63.75 ± 4.71**</td>
<td>31.16 ± 6.65</td>
</tr>
<tr>
<td>Glucose (300 mmol/L)</td>
<td>115.54 ± 8.41</td>
<td>117.32 ± 8.92*</td>
<td>75.49 ± 6.83**</td>
<td>28.25 ± 7.94</td>
</tr>
</tbody>
</table>

1 MSG intake was expressed as a percentage of intake relative to water.

* P < 0.05 and ** P < 0.01, significance compared with MSG-alone (None) group by ANOVA.
tions of MSG with the greatest aversion for higher concentrations. Significant preferences for lower concentrations of MSG were observed in SD, BN, LEW, F344, Hairless, Donryu, Crl:Wistar, LEA and F1 rats, but not in rats tracing their origin to the Wistar (Slc:Wistar, WKY, and SHR) and Long-Evans colonies (LE and LEC). On the other hand, the extent of aversion for higher concentrations of MSG varied remarkably among rat strains, falling into three groups as follows: 1) rats showing no aversion (BN rats); 2) rats showing a moderate aversion (SD, LEW, F344, Donryu, Crl:Wistar rats, Slc: Wistar, WKY, SHR, LEC and F1 rats); and 3) rats showing a marked aversion (LEA rats). Such results suggest that the extent of aversion for higher concentrations of MSG may be controlled at least in part by genetic factors. This conclusion is supported by the evidence showing that the F1 rats (the first generation of matings consisting of male SD × female LEA rats) showed an intermediate aversion compared with that seen in their respective parent strains.

LEA and LEC rats are mutant strains established from LE rats (Nakajima et al. 1994). LEC rats display hereditary hepatic and spontaneous hepatocellular carcinoma, but LEA rats do not develop liver diseases. Nakajima et al. (1993 and 1994) demonstrated that the hepatic activity of low Km aldehyde dehydrogenase (ALDH2), an enzyme related to ethanol metabolism, is suppressed because of a point mutation in the ALDH2 gene in LEA and LEC rats. The results thus suggest that the preference and aversion for MSG might be related to the activity of ethanol metabolism–related enzymes in the liver. In contrast, BN rats did not show aversive responses to MSG. Ethanol preference in BN rats was much higher than that in WKY and F344 rats (Li and Lumeng 1984). In this study, WKY and F344 rats showed moderate aversion to higher concentrations of MSG.

Significant reductions in the intakes of basic amino acid solutions (arginine, arginine HCl and lysine HCl) were also observed in the LEA rats. These aversive symptoms could be coupled to the induction of a disorder in acid-base balance, even though these amino acids were present as sodium or hydrochloride salts. Because of these facts, we hypothesize that the homeostatic control of the excretion of the above-mentioned chemicals may have been less efficient in LEA than in SD rats.

It is well known that plasma and brain L-glutamate concentrations vary little; they remain low throughout a given 24-h period and are independent of dietary protein intake. Because the consumption of highly concentrated MSG solutions was greatly reduced in vagotomized rats, signals normally arising from the vagus might contribute to the suppression of unpleasant sensations caused by the consumption of concentrated MSG solutions. These results thus suggest that the vagus nerve could contribute to the behavioral expression of aversion for higher concentrations of MSG. The contribution of the gastric branches was the greatest, whereas that of the celiac branches was intermediate and that of the hepatic branch was negligible. After the dissection of the subdiaphragmatic trunks or gastric branches in SD rats, the preference and aversion for MSG solutions were similar to those in intact LEA rats. These results suggest that the vagus nerve may play a role in the modulation of MSG ingestive behavior.

Finally, the aversion for higher concentrations of MSG was reduced by coadministering other nutrients such as proline, alanine, glycine and glucose. Inhibition of an MSG “sensor” function and/or of MSG absorption in the digestive tract may explain these results. The maximal homeostatic control by the alimentary organs may be regulated primarily by the small intestine and liver. Coexisting nutrients in the digestive tract may play an important role in reducing the aversive stimulation during and after the meal whenever MSG is used appropriately as a food additive to create a palatable taste sensation.

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LITERATURE CITED


