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Amino acid and carbohydrate preferences in C57BL/6ByJ and 129P3/J mice

Alexander A. Bachmanov and **Gary K. Beauchamp**
Monell Chemical Senses Center, Philadelphia, PA 19104, USA

Abstract

Compared with mice from the 129P3/J (129) inbred strain, mice from the C57BL/6ByJ (B6) inbred strain have higher consumption of several sweet-tasting amino acids and carbohydrates. To examine the relative contribution of taste and nutritive properties in these strain differences, we measured responses of B6 and 129 mice to eight sweet and non-sweet amino acids and carbohydrates in two-bottle preference tests with water. Mice from the two strains did not differ in consumption of non-sweet L-valine and L-histidine. Compared with 129 mice, B6 mice had higher consumption and lower preference thresholds for sweet amino acids L-glutamine, L-alanine and L-threonine, monosaccharides glucose and fructose, and maltooligosaccharide. These data suggest that differences in gustatory responsiveness are an important factor underlying higher consumption of some amino acids and carbohydrates by B6 mice compared with 129 mice. It is likely that in B6 mice, higher sweet taste responsiveness results in increased consumption of sweet-tasting amino acids and sugars, and higher taste responsiveness to complex carbohydrates results in increased consumption of maltooligosaccharide. However, postingestive processes also influence nutrient consumption and may be responsible for higher intake of carbohydrates compared with sweet-tasting amino acids. Results of this study set the stage for genetic analysis of differences between B6 and 129 mice in taste responsiveness and macronutrient consumption.

Keywords

inbred mice; genetics; nutrient; intake; consumption; appetite; sweet; taste

1. Introduction

Variation among inbred mouse strains provides a tool to detect genetic loci underlying variable traits and to identify corresponding polymorphic genes. Mouse strains differ in consummatory responses to various taste stimuli and nutrients, including sweeteners, carbohydrates and amino acids [1–10]. Mice from the C57BL/6 and 129 inbred strains have been extensively studied for differences in sweetener and nutrient consumption [5–7,11–15]. Compared with 129 mice, C57BL/6 mice have higher consumption of several different sweet-tasting amino acids and carbohydrates [2,3,5,6,11–13,16].

Ingestive responses to amino acids and carbohydrates depend on both their taste properties and their postingestive effects. The goal of the study was to examine the relative contribution of

Correspondence to be sent to: Alexander A. Bachmanov, Monell Chemical Senses Center, 3500 Market Street, Philadelphia, PA 19104, USA., Tel.: +1-267-519-4760; fax: +1-267-519-4760. E-mail address: bachmanov@monell.org.

taste and nutritive properties in differential ingestive responses of C57BL/6ByJ (B6) and 129P3/J (129) mice. To achieve this, we compared responses of B6 and 129 mice to sweet and non-sweet amino acids and carbohydrates in two-bottle preference tests. We hypothesized that if mice from these two strains differ in postingestive responses to nutrients, then they will differ in consumption of nutrients regardless of their sensory properties. If these strains differ in sweetness perception, then they will differ in consumption of only sweet-tasting nutrients.

We have chosen for this study 8 compounds that include five amino acids and three carbohydrates. To humans, three of the amino acids (L-glutamine, L-alanine and L-threonine) have a prominent sweet taste, while two other amino acids (L-valine and L-histidine) lack a strong sweet component [17–21]. This is consistent with available data on preferences, conditioned taste aversion generalization, and single fiber recordings from gustatory nerves for these compounds in rodents [22–29]. Sweet L-threonine and non-sweet L-valine and are essential amino acids. Sweet L-glutamine and L-alanine, and non-sweet L-histidine are nonessential amino acids.

The three carbohydrates were glucose, fructose and maltooligosaccharide. To humans, the monosaccharides glucose and fructose taste sweet [21], and are qualitatively very similar to sucrose [30,31]. Behavioral and neurophysiological data in mice also support sucrose-like taste of glucose and fructose [27,28]. Maltooligosaccharides are glucose polymers containing 2 to 10 glucose units. The maltooligosaccharide used in this study contains predominantly polymers with 3 to 6 glucose units, no glucose monomers, and only 2% maltose and polymers with greater than 7 glucose units. Another commonly used maltodextrin preparation, Polycose, contains a higher proportion of sugars (9% of glucose and maltose) and polymers with greater than 7 glucose units (43%). Behavioral and neurophysiological studies in rats have suggested that that the taste of polysaccharides is qualitatively different from the taste of sugars or starch [32–35]. We have found no published data on human perception of maltooligosaccharide taste.

2. Materials and methods

2.1. Animals

Male mice from the C57BL/6ByJ (B6, n = 17) and 129P3/J (129, n = 26) inbred strains were obtained from the Jackson Laboratory (Bar Harbor, ME). Group 1 included 10 B6 and 18 129 mice that were 8.7 – 11.1 months old (10.6 ± 0.9 months, M ± SD) when testing began. Group 2 included 7 B6 and 8 129 mice that were 3.7 – 4.2 months old (4.0 ± 0.2 months, M ± SD) when testing began. Although mice from these two groups differed in age, it is unlikely that age variation affected results because in our previous experiments taste preferences of B6 and 129 mice remained stable over a period spanning more than two years [36]. During the experiments, the mice were housed in individual cages in a temperature-controlled room at 23° C on a 12-h light: 12-h dark cycle (7:00 a.m. on, 7:00 p.m. off). They had free access to Teklad Rodent Diet 8604 (Harlan Teklad, Madison, WI; 24.5% protein, 50.3% carbohydrate and 4.4% fat; 3.93 Kcal/g gross energy; 0.31 % sodium, 0.99 % potassium and 1.46 % calcium).

2.2. Taste solutions

Taste solutions were prepared in deionized water. All chemicals were purchased from Sigma Chemical Company (St. Louis, MO), except for maltooligosaccharide purchased from Pfanstiehl Laboratories, Inc. (Waukegan, IL). The maltooligosaccharide used in this study contains no measurable glucose, 1.5% maltose, 97% polymers with 3 to 6 glucose units, and 0.5% polymers with greater than 7 glucose units, with an average degree of polymerization of 4.4 [32].

2.3. Two-bottle preference tests

Construction of the drinking tubes has been described previously [37] and is given in detail on the Monell Mouse Taste Phenotyping Project web site (www.monell.org/MMTPP; [36]). Individually housed mice were presented with one tube containing a taste solution in deionized water, and the other tube containing deionized water. Daily measurements were made in the middle of the light period by reading fluid volume to the nearest 0.1 ml. Each concentration of a taste solution was tested for 48 h, with the positions of the tubes containing taste solution and water switched after 24 h to control for side preferences. The solutions were tested in the increasing order of concentration, with the concentrations changing by approximately half log-steps. There were no breaks between testing different concentrations of the same compound, but between testing different compounds the mice received deionized water in both drinking tubes for at least three days.

Mice from Group 1 were tested with 0.1, 0.3, 1, 3, 10, 30, 100 and 300 mM L-valine and 0.1, 0.3, 1, 3, 10, 30, 100 and 300 mM L-histidine, in the order listed. Mice from Group 2 were tested with 1, 3, 10, 30, 100 and 300 mM L-glutamine; 1, 3, 10, 30, 100 and 300 mM L-alanine; 1, 3, 10, 30, 100 and 300 mM L-threonine; 0.1, 0.3, 1, 3, 10 and 30% maltooligosaccharide; 10, 30, 100, 300 and 1000 mM glucose; and 10, 30, 100, 300 and 1000 mM fructose, in the order listed. Body weight (BW) was measured (to the nearest 0.1 g) at the beginning of each taste solution concentration series, and at the end of the experiment.

2.4. Data analyses

Average daily (24-h) fluid intakes were calculated for each mouse for each solution concentration. Preference scores were calculated as the ratio of the average daily solution intake to the average daily total fluid (solution + water) intake, in percent.

The B6 mice were heavier than were 129 mice: the average body weight measured throughout the experiment in Group 1 was 33.1 ± 0.9 g for B6 mice and 27.1 ± 0.3 g for 129 mice (M ± SE; $p < 0.001$, t-test); in Group 2 it was 32.9 ± 1.4 g and 28.6 ± 0.5 g, respectively ($p < 0.05$). To account for the strain difference in body size, and to make results comparable with our previous publications [5–7], solution intakes were expressed per 30 g BW (the approximate weight of an adult mouse) using average individual BW values obtained before and after corresponding concentration series of taste solutions.

Normality of data was assessed for each strain, concentration and index (intake or preference) separately using the Kolmogorov-Smirnov Tests. With the exception of preferences for 1000 mM fructose in 129 strain ($p < 0.05$), no deviations from the normal distribution were detected. The data for each compound intakes and preferences were analyzed separately using two-way repeated measures ANOVAs with strain as the between-group factor and concentration as the within-group factor. Fisher LSD planned comparison tests were used to evaluate strain differences between individual means. These statistical tests used a criterion for significance of $p < 0.05$.

A preference threshold was defined as the lowest solution concentration for which a preference score was above 75%. An avoidance threshold was defined as the lowest solution concentration for which a preference score was below 25%. Thresholds of preference and avoidance can also be determined using statistical tests (e.g., comparing solution and water intakes or comparing preference scores with the 50% indifference level). Because the numbers of experimental animals used and the numbers of solutions tested differed between the experimental groups, the power to detect significant differences and effects of multiple comparisons also differed between groups. Using defined threshold levels allowed us to avoid a complication of differential sensitivity of statistical tests in different groups. The 25% and 75% threshold levels

were chosen as midpoints between complete indifference (50%) and complete avoidance (0%) or preference (100%). These threshold levels approximate the 50% level of correct responses often used in psychophysics as a threshold value (e.g., [38,39]). In all cases when a preference score was above preference threshold or below avoidance threshold, intakes of water and a taste solution were significantly different ($p < 0.01$, paired t-tests).

3. Results

3.1. L-valine

L-valine intakes and preference scores were not significantly affected by solution concentration and did not differ between strains (Table 1). Significant interactions between effects of strain and concentration are attributed to a tendency of B6 mice to have lower intakes and preferences at 0.3 and 1 mM concentrations and higher intakes and preferences at 300 mM concentration compared with 129 mice (Fig. 1). However, strain differences in responses to these concentrations were not significant in planned comparisons tests. Mice were indifferent to all L-valine concentrations: preference scores were within the range between 25% and 75% thresholds of avoidance and preference, respectively.

3.2. L-histidine

L-histidine intakes and preferences significantly decreased with increasing solution concentration. However, even for the highest concentration tested, 300 mM, preference scores did not drop below threshold of avoidance. There were no strain differences in responses to L-histidine.

3.3. L-glutamine

L-glutamine intakes and preferences significantly increased with increasing solution concentration and were overall higher in B6 mice than in 129 mice. B6 mice had a lower preference threshold than did 129 mice (Table 2).

3.4. L-alanine

L-alanine intakes and preferences significantly increased with increasing solution concentration and were overall higher in B6 mice than in 129 mice. B6 mice had a lower preference threshold than did 129 mice.

3.5. L-threonine

L-threonine intakes and preferences significantly increased with increasing solution concentration. Intakes were overall higher in B6 mice than in 129 mice. Although effects of strain and strain × concentration interaction on preference scores were not significant, B6 mice had a lower preference threshold than did 129 mice.

3.6. Maltooligosaccharide

Maltooligosaccharide intakes and preferences were significantly affected by solution concentration and were overall higher in B6 mice than in 129 mice. B6 mice consumed the largest amount of solution when it was presented at 10% concentration, while for 129 mice the highest intake was at 30%, the highest concentration tested. B6 mice had a lower preference threshold than did 129 mice.

3.7. Glucose

Glucose intakes and preferences were significantly affected by solution concentration and were overall higher in B6 mice than in 129 mice. B6 mice consumed the largest amount of solution

when it was presented at 300 mM concentration, while for 129 mice the highest intake was at 1000 mM, the highest concentration tested. Preference scores for the lowest concentration tested, 10 mM, were above 75% preference threshold in both strains, but significant strain differences in preferences for the lower glucose concentrations (10 and 30 mM) and different slopes of concentration-preference curves (evident from significant strain × concentration interaction) suggest that preference threshold for glucose is lower in B6 mice than in 129 mice.

3.8. Fructose

Fructose intakes and preferences were significantly affected by solution concentration and were overall higher in B6 mice than in 129 mice. B6 mice consumed the largest amount of solution when it was presented at 300 mM concentration, while for 129 mice intakes were similarly high at 300 and 1000 mM concentrations. B6 mice had a lower preference threshold than did 129 mice.

4. Discussion

In this study, we used 48-h two-bottle tests to examine differences in consumption of amino acid and carbohydrate solutions between mice from the B6 and 129 strains. We found that B6 and 129 mice did not differ in consumption of L-valine and L-histidine. For L-glutamine, L-alanine, L-threonine, maltooligosaccharide, glucose and fructose, B6 mice had higher consumption and lower preference thresholds compared with 129 mice.

In this study, we tested more than one tastant in the same group of mice. Repeated testing of nutritive solutions may alter solution intakes and preferences, and even attenuate strain differences in consumption [12,13]. It is thus possible that absolute values for intakes, preferences or preference thresholds obtained in this study would be different from those obtained in naive mice. However, it is unlikely that repeated testing had impact on presence and direction of strain differences reported in our study. Repeated testing with nutritive sweeteners was reported to reduce differences between B6 and 129 mice [12,13]. However, we have found that strain differences in consumption of L-glutamine, L-alanine and L-threonine (tested in the beginning of the experiment) were smaller than strain differences in consumption of maltooligosaccharide and glucose tested next (Fig. 1). Thus, instead of expected attenuation of strain differences with repeated testing, we observed larger strain differences for the solutions tasted later. The most likely explanation for this increase is the difference between the properties of amino acids and carbohydrates (see details in section 4.3.). The strain difference in consumption of fructose appears to be smaller than the strain differences in consumption of maltooligosaccharide and glucose, which were tested before fructose. If this were due to effects of previous exposure, we would expect that attenuation of strain differences would result from an elevated consumption by 129 mice. However, consumption of fructose by both B6 and 129 mice was actually lower than the consumption of the two previously tested carbohydrates. The most likely explanation for the lower consumption of fructose is the difference between postingestive effects of fructose compared with glucose or its polymer, maltooligosaccharide (see details in section 4.3.).

4.1. Strain differences in amino acid consumption

Mice from the B6 and 129 strains differed only in consumption of sweet-tasting amino acids (L-glutamine, L-alanine and L-threonine), but the two strains did not differ in consumption of non-sweet amino acids (L-valine and L-histidine). The presence or absence of strain differences in amino acid consumption did not depend on whether an amino acid is essential or nonessential. This suggests that B6 and 129 mice do not differ in a generalized amino acid appetite, and that strain differences in amino acid consumption depend on differential sweet

taste responsiveness. Consistent with this, B6 mice had lower preference thresholds for the sweet-tasting amino acids compared with 129 mice.

4.2. Strain differences in carbohydrate consumption

Compared with 129 mice, B6 mice had higher consumption of both types of carbohydrates tested: monosaccharides glucose and fructose, and maltooligosaccharide. Several lines of evidence indicate that differential mono- and oligosaccharide intakes of B6 and 129 mice depend on strain differences in taste perception rather than in postingestive mechanisms. B6 and 129 mice did not differ in consumption of starch [6], a carbohydrate with nutritive value equivalent to that of sugars and maltooligosaccharide. Postingestive reinforcing properties of sucrose were similar in B6 and 129 mice [15]. At the same time, for all three carbohydrates tested, there was indication of lower preference thresholds in B6 mice relative to 129 mice, suggesting higher taste sensitivity of B6 mice. Consistent with this, chorda tympani responses to maltooligosaccharide, as well as to sugars and Polycose, were higher in B6 mice than in 129 mice [40].

It is unlikely that glucose, fructose and maltooligosaccharide share the same taste quality. Maltooligosaccharide has a negligible amount of maltose (1.5%) and no measurable glucose. A solution of 1% maltooligosaccharide, strongly preferred by B6 mice (98 ± 1%, M ± SE), contains only 0.015% (0.4 mM) maltose, which is well below maltose preference threshold for B6 mice (28 mM) [5]. The percentage of sugars derived from maltooligosaccharide may increase in the oral cavity as a result of salivary amylase activity, but this is unlikely to explain similar responses to equivalent weight/volume concentrations of maltooligosaccharide and glucose. Studies with rats suggested that glucose polymers and sugars have qualitatively different tastes [32–35]. If this is also true for mice, this would suggest that although taste perception of the sugars and maltooligosaccharide involves distinct mechanisms, both mechanisms are more responsive in B6 mice compared with 129 mice.

Consistent with this hypothesis, mouse taste perception of glucose and fructose involves a T1R3-containing taste receptor [41–43], but allelic variation of the *Tas1r3* gene encoding the T1R3 protein does not affect taste responsiveness to maltooligosaccharide [43]. Thus, B6 and 129 mice are likely to differ in two gustatory mechanisms: a T1R3-dependent mechanism involved in reception of sugars, and a T1R3-independent mechanism involved in reception of glucose polymers.

4.3. Differences between consumption of amino acids and carbohydrates

In mice from both strains, consumption of carbohydrate solutions reached higher levels than did consumption of amino acid solutions. The highest intakes for the three carbohydrates tested ranged in B6 mice from 10.0 ml/30 g BW (strain mean) for 300 mM fructose to 18.6 ml/30 g BW for 300 mM glucose, and in 129 mice from 6.8 ml/30 g BW for 300 and 1000 mM fructose to 11.4 ml/30 g BW for 1000 mM glucose. The highest intakes of the three preferred amino acids ranged in B6 mice from 5.0 ml/30 g BW for 300 mM L-threonine to 6.1 ml/30 g BW for 300 mM L-glutamine, and in 129 mice from 3.4 ml/30 g BW for 300 mM L-threonine to 5.2 ml/30 g BW for 300 mM L-glutamine.

One possible reason for this difference is that we did not test as high weight/volume concentrations of amino acids as we did for carbohydrates. Consistent with this, in some cases intakes of similarly concentrated solutions of amino acids and carbohydrates were similar. For example, intakes of 300 mM (3.5%) L-threonine and 3% maltooligosaccharide were respectively 5.0 and 5.1 ml/30 g BW in B6 mice, and 3.4 and 2.7 ml/30 g BW in 129 mice. However, in some other cases intake of carbohydrates substantially exceeded intake of amino acids at similar concentrations. For example, intakes of 300 mM (4.4%) L-glutamine and 300

mM (5.4%) glucose were respectively 6.1 and 18.6 ml/30 g BW in B6 mice, and 5.2 and 6.9 ml/30 g BW in 129 mice.

Both sensory and postingestive properties of these nutrients may be responsible for their differential consumption. On one hand, chorda tympani nerve responses overall tend to be higher in response to carbohydrates compared with sweet amino acids, but there is also a substantial variation in responses within each class of nutrients [40,43,44]. In humans, the sweetness potency of fructose is higher compared with sucrose, but the sweetness potency of L-alanine, L-glutamine and L-threonine tends to be lower compared with sucrose [21]. Besides sweet taste, many amino acids have additional aversive taste components [17,19], which could decrease amino acid consumption relative to consumption of carbohydrates that have relatively pure sweet taste [21]. On the other hand, although amino acids and carbohydrates have similar caloric value, they have different metabolic pathways and thus may differ in postingestive rewarding effects. It is also possible that excess consumption of some amino acids has negative postingestive effects that limit their intake compared with consumption of carbohydrates.

Differences in metabolism of individual carbohydrates might have also contributed to their differential consumption. Although relative to glucose, fructose has higher sweetness potency in humans [21] and tends to evoke stronger responses in the mouse chorda tympani nerve [43], intake of fructose was lower than intake of glucose. This may be due to differences in metabolism of glucose and fructose [45]. On the other hand, although glucose monomers and polymers are likely to differ in sensory properties, their intakes were similar.

It is possible that an interaction between gustatory and postingestive mechanisms is responsible for differential consumption of amino acids and carbohydrates, as it was suggested to be responsible for differences between B6 and 129 strains [15,46].

4.4. Conclusions

Results of this study suggest that differences in gustatory responsiveness are an important factor underlying higher consumption of some amino acids and carbohydrates by B6 mice compared with 129 mice. It is likely that in B6 mice, higher sweet taste responsiveness results in increased consumption of sweet-tasting amino acids and sugars, and higher taste responsiveness to complex carbohydrates results in increased consumption of maltooligosaccharide. However, postingestive processes also influence nutrient intake and may be responsible for higher intake of carbohydrates compared with sweet-tasting amino acids.

Results of this study set the stage for genetic analysis of differences between B6 and 129 mice in taste responsiveness and macronutrient consumption. These two strains carry different alleles of the *Tas1r3* gene encoding a taste receptor protein, T1R3, involved in reception of sweeteners and amino acids [8,44,47]. However, *Tas1r3* polymorphisms do not explain all differences in sweet taste responsiveness among mouse strains [43,44,48,49]. Our ongoing studies are aimed at elucidating the role of *Tas1r3* and other genes in mouse behavioral responses to tastants and nutrients.

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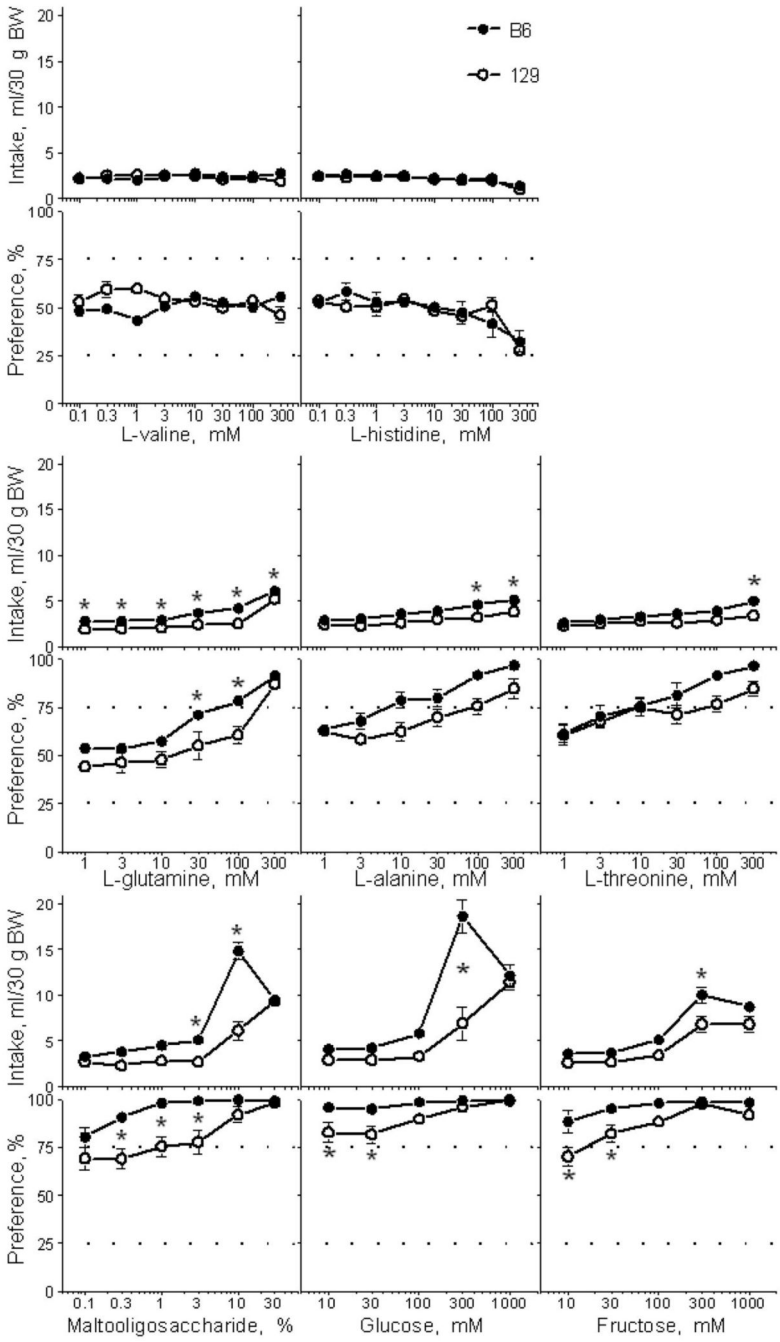

Fig. 1.

Sweetener intakes and preferences by B6 and 129 mice. Values are means ± SE. *Significant difference between B6 and 129 mice, $p < 0.05$, Fisher LSD planned comparison tests.

Table 1

ANOVA results for two-bottle preference tests of B6 and 129 mice

Taste compound	Effect	d.f.	F values	
			Solution intake/30 g BW	Preference score
L-valine	Strain	1, 26	0.1	0.7
	Concentration	7, 182	1.8	0.5
	Strain × concentration	7, 182	4.6*	3.4*
L-histidine	Strain	1, 26	0.4	0.1
	Concentration	7, 182	13.6*	10.0*
	Strain × concentration	7, 182	0.6	1.1
L-glutamine	Strain	1, 13	58.8*	18.9*
	Concentration	5, 65	68.6*	32.7*
	Strain × concentration	5, 65	1.3	0.9
L-alanine	Strain	1, 13	18.6*	10.4*
	Concentration	5, 65	50.0*	27.0*
	Strain × concentration	5, 65	3.1*	1.8
L-threonine	Strain	1, 13	10.3*	2.4
	Concentration	5, 65	31.2*	18.4*
	Strain × concentration	5, 65	4.6*	1.6
Maltooligosaccharide	Strain	1, 13	29.6*	12.2*
	Concentration	5, 65	117.3*	17.2*
	Strain × concentration	5, 65	24.9*	4.5*
Glucose	Strain	1, 13	14.2*	8.4*
	Concentration	4, 52	67.1*	12.7*
	Strain × concentration	4, 52	17.1*	4.8*
Fructose	Strain	1, 13	10.6*	14.9*
	Concentration	4, 52	61.7*	6.5*
	Strain × concentration	4, 52	1.8	1.3

*$P < 0.05$, ANOVA.

Table 2

Preference thresholds[a] of B6 and 129 mice

Taste compound	B6	129
L-glutamine, mM	100	300
L-alanine, mM	10	100
L-threonine, mM	30	100
Maltooligosaccharide, %	≤ 0.1	3
Glucose, mM	≤ 10	≤10
Fructose, mM	≤ 10	30

[a] The lowest solution concentration for which a preference score was above 75%.