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BALB/c and SWR inbred mice differ in post-oral fructose appetition as revealed by sugar versus non-nutritive sweetener tests

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HIGHLIGHTS

- SWR and BALB/c mice initially prefer sucralose + saccharin to fructose solutions.
- SWR mice reverse this preference following experience with the two solutions.
- Ad-libitum fed and food restricted BALB/c mice fail to reverse this preference.
- Ad-libitum fed and food-restricted SWR mice prefer glucose to fructose solutions.
- Food-restricted, not ad-libitum fed BALB/c mice display this glucose preference.

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ABSTRACT

Recent studies indicate that C57BL/6J (B6) and FVB inbred mouse strains differ in post-oral fructose conditioning. This was demonstrated by their differential flavor conditioning response to intragastric fructose and their preference for fructose versus a non-nutritive sweetener. The present study extended this analysis to SWR and BALB/c inbred strains which are of interest because they both show robust flavor conditioning responses to fructose. In the first experiment, ad-libitum fed mice were given a series of 2-day, two-bottle preference tests between 8% fructose and a more preferred, but non-nutritive 0.1% sucralose + 0.1% saccharin (S + S) solution (tests 1 & 4), and fructose or S + S versus water (tests 2 and 3). In test 1, SWR mice preferred S + S to fructose, and in tests 2 and 3, they preferred both sweeteners to water. In test 4, SWR mice switched their preference and consumed more fructose than S + S. In contrast, ad-libitum fed BALB/c mice strongly preferred S + S to fructose in both tests 1 and 4, although they preferred both sweeteners to water in tests 2 and 3. Food-restricted BALB/c mice also preferred the non-nutritive S + S to fructose in tests 1 and 4. The experience-induced fructose preference reversal observed in SWR, but not BALB/c mice indicates that fructose has a post-oral reinforcing effect in SWR mice as in FVB mice. Because B6 and FVB mice prefer glucose to fructose based on the post-oral actions of the two sugars, the second experiment compared the preferences of SWR and BALB/c mice for 8% glucose and fructose solutions. *Ad-libitum* fed and food-restricted SWR mice strongly preferred glucose to fructose. In contrast, ad-libitum fed BALB/c mice were indifferent to the sugars, perhaps because of their overall low intakes. Food-restricted BALB/c mice, however, strongly preferred glucose. These findings indicate that SWR and BALB/c mice differ in their preference response to the post-oral actions of fructose.

1. Introduction

Sugar appetite in rodents depends on both stimulation of oral sweet taste receptors [1] and post-oral sugar sensors [13]. Inbred mouse strains vary in their taste response to sugars and non-nutritive sweeteners, which is attributed, in part, to genetic differences in the T1r3 component of the T1r2/T1r3 sweet taste receptor [9]. Some strains have a "sensitive" form of the receptor which results in increased preferences and intakes of a variety of nutritive and non-nutritive sweet solutions, while other strains have a "sub-sensitive" form of the receptor which produces reduced preferences and intakes of these sweetener solutions, particularly at low concentrations [1]. Sugar intake and preference are also influenced by post-oral nutritive effects via a process referred to as appetition to distinguish it from the satiation process

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that inhibits sugar intake [11,13]. Post-oral appetition is most clearly demonstrated by the intake and preference-stimulating effects produced by intragastric (IG) sugar infusions in mice and rats [13]. Conceivably, inbred strain variations in sugar preferences may be influenced by strain differences in post-oral appetition as well as by differences in sweet taste sensitivity. Sclafani and Glendinning [17] investigated this possibility in sweet-sensitive C57BL/6J (B6) mice and sub-sensitive 129 mice which differ substantially in their oral intakes of sucrose. Both strains, however, displayed similar post-oral appetition responses to IG sucrose infusions. This and other findings indicate that post-oral sugar appetition is not mediated by gut T1r3 receptors [16].

More recently, Sclafani and co-workers [18] observed a difference in post-oral sugar appetition in B6 and FVB mice, which are both sweet-sensitive strains with high oral intakes of sugar. In this case, the mice were tested with glucose and fructose. Whereas IG glucose infusions stimulated intake of, and preference for, a flavored (CS+) saccharin solution in both strains, IG fructose failed to condition preferences in B6 mice but conditioned significant CS+ preferences in FVB mice. The differential post-oral actions of fructose were also revealed in sugar vs. non-nutritive sweetener choice tests [18,19]. Like B6 mice, naïve FVB mice strongly preferred a 0.1% sucralose + 0.1% saccharin (S + S) solution to 8% fructose in an initial 2-day two-bottle test. However, after the mice had separate 2-day choice tests with S + S and fructose versus water, the FVB mice preferred fructose to S + S, whereas the B6 mice continued to prefer S + S to fructose. Taken together, these data indicate that fructose has a post-oral reinforcing action in FVB mice which conditions a preference for the initially less-preferred 8% fructose over 0.1% S + S after separate experience with both sweeteners.

The present experiment extended our analysis of post-oral fructose appetition to SWR and BALB/c inbred mice, which are sweet-sensitive and sub-sensitive strains, respectively [9]. These strains were of interest because in a survey of inbred mouse strains, they both acquired strong preferences for a CS+ flavor added to an 8% fructose + 0.2% saccharin solution over a CS- flavored 0.2% saccharin-only solution [7]. In contrast, B6 mice failed to prefer the fructose-paired CS+ flavor. At the time, the fructose-conditioned preference in the SWR and BALB/c mice was attributed to flavor-taste learning reinforced by the sugar's sweet taste since fructose was known to have little or no post-oral reinforcing actions in B6 mice or Sprague–Dawley rats [12,14,15]. However, in view of the post-oral fructose appetition recently discovered in FVB mice [18], it is possible that the fructose-conditioned flavor preferences observed in SWR and BALB/c mice were due in part to post-oral conditioning in these strains. To evaluate this possibility, Experiment 1 determined the relative preference for fructose and S + S solutions in SWR and BALB/c mice before and after they had separate experience with the two sweeteners. As noted above, unlike B6 mice, FVB mice switch their preference from S + S to fructose after experience with the sweeteners which is indicative of post-oral fructose appetition. In a second experiment we compared the preference for 8% fructose and 8% glucose in the two strains which provides an index of the differential post-oral reinforcing actions of the two sugars.

2. Experiment 1: fructose vs. sucralose + saccharin preferences

2.1. Materials and methods

2.1.1. Animals

Adult male SWR and BALB/c mice obtained from the Jackson Laboratories (Bar Harbor, ME) were adapted to the laboratory for 1 week. The starting body weights of the SWR (25.6 g) and BALB/c mice (25.7 g) were similar. The animals were singly housed in plastic tub cages in a room maintained at 22 °C with a 12:12-h light–dark cycle and given ad libitum access to chow (LabDiet Standard Laboratory Rodent Diet #5001, PMI Nutrition International, Brentwood, MO) and water except where noted. Experimental protocols were approved by the Institutional Animal Care and Use Committee at Queens College and were performed in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

2.1.2. Test solutions

Solutions of 8% fructose (Sigma Aldrich Laboratories, St. Louis, MO) and a mixture of 0.1% sucralose (Tate & Lyle, Dayton, OH) and 0.1% saccharin (Sigma Aldrich Laboratories) (S + S) were prepared with tap water on a w/w basis because intakes were measured by weight. The S + S solution was selected based on the finding that B6 mice strongly preferred it to 8% fructose or 8% glucose in 1-min two bottle tests, suggesting that it was "sweeter" than the sugar solutions [19]. The solutions were available through stainless steel sipper spouts attached to 50-ml plastic tubes that were placed on the grid top of the cage and fixed in place with springs. Fluid intakes were measured to the nearest 0.1 g by weighing the drinking bottles on an electronic balance. Spillage in this study was minimal as demonstrated by recording the change in weight of two tubes that were placed on an empty cage.

2.1.3. Procedure

SWR mice (n = 8) and BALB/c mice (n = 10) were given ad-libitum access to chow and two bottles of water for 4 days. They were then given a series of 2-day two-bottle tests as in our prior study [18]: Test 1 (days 1–2): fructose vs. S + S; Test 2 (days 3–4): fructose vs. water; Test 3 (days 5–6): S + S vs. water; Test 4 (days 8–9): fructose vs. S + S. The mice were given water vs. water for one day (day 7) between Tests 3 and 4. The left-right position of the sweetener and water bottles were switched from the first to second day of each test to control for potential position effects.

Because daily fructose and S + S intakes of the BALB/c mice were rather low, which is characteristic of this strain [6,8], a second group of nine BALB/c mice was tested which had restricted access to food to stimulate their sweetener intakes. These mice were given daily chow rations that maintained their body weights at 85–90% of their ad libitum level for two weeks prior to testing, and throughout the four 2-bottle preference test series.

2.1.4. Data analysis

Daily solution intakes were averaged over the 2 days of each test, and sweetener preferences were expressed as percent solution intakes (e.g., fructose intake / total intake × 100). Intakes were analyzed using a mixed model analysis of variance (ANOVA) with test and solution as repeated factors. One ANOVA included results from Tests 1 (naïve mice) and 4 (experienced mice), and evaluated whether relative intakes of fructose and S + S changed across the two tests within groups. A second ANOVA included results from Tests 2 and 3, and compared the intakes of each sweetener vs. water within groups. Percent sweetener intakes within groups were analyzed with t-tests. Additional between groups ANOVAs were performed as described below.

2.2. Results

2.2.1. SWR mice

The SWR mice consumed more S + S than fructose in Test 1, but more fructose than S + S in Test 4, although only the Test 4 difference was significant (Sweetener × Test interaction, $F(1,7) = 94.4$, $p < 0.0001$; Fig. 1A). Seven of the eight mice drank more S + S than fructose in the first test, whereas all 8 mice consumed more fructose than S + S in Test 4. The percent fructose intake increased from 39% in Test 1 to 66% in Test 4 ($t(7) = 7.15$, $p < 0.0001$). In Tests 2 and 3, SWR mice consumed more fructose and S + S than water ($F(1,7) = 36.0$, $p < 0.0001$) and their sweetener intakes and percent intakes did not differ.

2.2.2. BALB/c mice

The ad-libitum fed BALB/c mice consumed significantly more S + S than fructose in both Tests 1 and 4 ($F(1,9) = 112.7$, $p < 0.0001$), and their percent fructose intakes remained low in both tests (20% and