Published in final edited form as:

Physiol Behav. 2012 June 25; 106(4): 457–461. doi:10.1016/j.physbeh.2012.03.008.

Flavor Preferences Conditioned by Intragastric Glucose but not Fructose or Galactose in C57BL/6J Mice

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Abstract

The present study determined if mice, like rats, differ in their flavor conditioning responses to intragastric (IG) infusions of three common monosaccharide sugars. In experiment 1, C57BL/6J mice were trained to drink a flavored saccharin solution (the CS+) paired with intragastric (IG) self-infusions of 16% glucose, fructose or galactose and a different flavored solution (the CS-) paired with IG water infusions during 22 h/day training sessions. The glucose infusions increased CS+ intakes during training and produced a strong CS+ preference (~87%) in two-bottle choice tests. In contrast, the fructose and galactose infusions reduced CS training intakes and did not condition a CS+ flavor. Experiment 2 determined if reducing fructose and galactose concentration would enhance conditioning. However, IG infusions of 8% sugar also failed to condition CS+ preferences. The robust conditioning response to IG glucose confirms results obtained with rats, but the indifference of mice to IG fructose and galactose contrasts with preference and avoidance responses observed in rats. The effectiveness of glucose to condition preferences suggests an important role for glucose-specific sensors rather than gut “sweet” taste receptors in the postoral modulation of carbohydrate appetite.

Keywords

Postoral sugar conditioning; sweet flavors; sugar concentration

1. Introduction

The attraction to sugar and sugar-rich foods is driven by sweet taste receptors in species as diverse as flies and humans [26]. Sugar appetite is also enhanced by the post-oral actions of the nutrient [13]. This has been extensively documented in laboratory rats using the conditioned flavor preference procedure in which one arbitrary flavor (the conditioned stimulus, or CS+) is paired with an intragastric (IG) infusion of sugar and another flavor (the CS-) is paired with an IG infusion of water. In a subsequent two-bottle choice test, the rat displays a strong preference for the CS+ flavor over the CS- flavor even in the absence of IG infusions [5,10,15]. In recent studies we adapted the IG conditioning procedure to mice to take advantage of the availability of inbred mouse strains with different sugar preferences (e.g., C57BL/6J vs. 129P3/J) and genetically modified knockout (KO) strains with impaired

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sweet taste signaling (e.g., T1R3 KO). These studies revealed that, like rats, mice develop strong preferences for flavors paired with IG infusions of sucrose, glucose or glucose polymer (maltodextrin) [17,18,19,28].

Prior studies using a variety of test paradigms demonstrate that glucose and glucose polymers are very effective in conditioning flavor preferences in food deprived and non-deprived rats [3,15,16,21,27]. Fructose, on the other hand, produces mixed results in rats. IG fructose infusions produced no or only weak conditioned preferences in rats trained with unsweetened CS solutions (e.g., grape Kool-Aid) but conditioned moderate to strong preferences (~70% to 90%) for a saccharin-sweetened CS in rats trained 22 h/day [2,3,15]. Yet, food-restricted rats trained 30 min/day failed to develop a preference for a sweetened CS+ paired with IG fructose infusions [3,16]. In contrast to glucose and fructose, IG galactose infusions conditioned a significant flavor avoidance in rats (30 min/day sessions) [16]. Whether mice also vary in their flavor conditioning response to IG infusions of different monosaccharides is not known. However, a recent study reported that IG infusions of glucose and galactose were equally effective in conditioning a place preference in mice [9], which suggests that galactose may also condition a flavor preference in mice.

The present study, therefore, compared the flavor conditioning response of B6 mice to glucose, fructose and galactose. In Experiment 1, separate groups had the CS+ flavor paired with an IG self-infusion of one of the three sugars at a 16% concentration. The mice were trained 22 h/day with chow available ad libitum. Saccharin-sweetened CS solutions were used because it facilitates flavor conditioning by IG maltodextrin and sucrose in mice [17,18,19] and fructose conditioning in rats [2]. Experiment 2 further investigated fructose and galactose conditioning using 8% sugar infusions. A prior study revealed that fructose conditions stronger preferences in rats at a lower concentration [2], suggesting that stronger preferences might be observed in mice trained with 8% fructose and/or galactose infusions.

2. Experiment 1

2.1. Method

2.1.1. Subjects—Adult male C57BL/6J mice (10–16 weeks old) from the Jackson Laboratory (Bar Harbor, ME) were used. They were housed singly in plastic cages with ad libitum access to chow (5001, PMI Nutrition International, Brentwood, MO) and water or flavored saccharin solutions. The mice were kept in a room maintained at 22°C with a 12:12 h light-dark cycle. Experimental protocols were approved by the Institutional Animal Care and Use Committee at Brooklyn College, and were performed in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

2.1.2. Surgery—The mice were anesthetized with isoflurane (2%) inhalation and fitted with a gastric catheter as described previously [18,28]. To facilitate recovery, the animals were given rations of a palatable liquid diet, both 2 days before and 3 days after surgery (3 ml/day, Chocolate Ensure, Abbott Laboratories, Abbott Park, IL) in addition to their chow diet. Eight to 12 days after surgery, the animals were transferred to the infusion test cages. Four days later the mice were briefly (5 min) anesthetized with 2% isoflurane, fitted with a harness and spring tether (CIH62; Instech Laboratories, Plymouth Meeting, PA). The mice were then returned to the test cages and the tether was attached to an infusion swivel mounted on a counterbalanced lever (Instech Laboratories) positioned at the top of the cage.

2.1.3. Apparatus—Testing occurred in infusion cages (15 × 15 × 32 cm high) described previously (18). Fluid was available from one or two stainless steel sipper spouts attached to 50 ml plastic tubes. The sipper spouts were interfaced via electronic lickometers (Med Electronics, St. Albans, VT) to a computer that operated a syringe pump (model A-99; Razel

Scientific, Stamford, CT), which infused liquid into the gastric catheters as the animals licked. The pump rate was nominally 0.5 ml/min but the animal controlled the overall infusion rate and volume by its licking response; oral intake to infusion ratio was maintained at ~1:1 by computer software. In two bottle tests, two infusion pumps were attached via a 20 gauge Y connector to the gastric catheters. Daily intakes were measured to the nearest 0.1 g, and IG infusions were recorded to the nearest 0.5 ml.

2.1.4. Test solutions—The CS solutions contained 0.2% (w/w) sodium saccharin (Sigma Chemical, St. Louis, MO) and were flavored with 0.05% (w/w) cherry or grape Kool-Aid flavor mix (General Foods, White Plains, NY). The IG infusates were water and 16% (w/w) glucose (Tate & Lyle, Honeyville Food Products, Rancho Cucamonga, CA), fructose (Tate & Lyle), or galactose (Sigma). For half the mice, cherry-saccharin was the CS+ paired with IG sugar infusion and grape-saccharin was the CS- paired with water infusion; the flavor-infusate pairs were reversed for the remaining animals. The orally consumed CS+ mixed with the IG sugar infusion in the stomach so that the carbohydrate concentration in the gut was ~8%.

2.1.5. Procedure—The mice (n=10 per group) were adapted to drink water paired with matched IG water infusions for 5 days (22 h/day). They were then given 6 one-bottle training days with the CS- solution paired with IG water infusions (Days 1, 3, 5) and the CS+ solution paired with IG sugar infusions (Days 2, 4, 6). This was followed a two-bottle choice test with the CS+ vs. CS- for four days. This was a “reinforced” test with the intakes of the CS+ and CS- paired with IG infusions of sugar and water, respectively. A “nonreinforced” two-bottle test was then conducted for 2 days with both the CS+ and CS- now paired with IG water infusions. The left-right position of the CS+ and CS- solutions were alternated throughout training and testing. Chow was available ad libitum throughout the experiment.

2.1.6. Data analysis—Total fluid intake (oral intake plus IG infusate) during each of the one-bottle training days and two-bottle test days was calculated. The training data for each group were evaluated with a two-way ANOVA, using CS solution (CS+ vs. CS-) and training days as within factors. The two-bottle test data were averaged over the 4 reinforced days and 2 nonreinforced days and analyzed in a two-way ANOVA with CS solution and test type as within factors. Additional between group analyses compared the mean CS+ and CS- intakes of the three groups during training (Group $\times$ CS (CS+ vs. CS-)) and two-bottle tests (Group $\times$ Test (reinforced vs. nonreinforced) $\times$ CS (CS+ vs. CS-)). The two bottle intakes of the individual mice were also expressed as percent CS+ intakes (CS+ intake/total intake $\times$ 100) and evaluated with within group (Reinforced vs. Nonreinforced test) t-tests and a between group ANOVA (Group $\times$ Test). In all statistical comparisons, the null hypothesis was rejected when $P < 0.05$.

2.2. Results

Figure 1 presents total daily intakes of the mice in the Glucose, Fructose and Galactose groups across the six days of one-bottle training and during the two-bottle tests. During one-bottle training, the Glucose mice consumed more CS+ than CS- ($F(1,9) = 13.1, P < 0.01$) and increased their CS intakes over days ($F(2, 18) = 6.6, P < 0.01$). Although the CS $\times$ Day interaction was not significant ($P = 0.09$), post-hoc tests indicated that only CS+ intakes increased ($P < 0.01$) over days and the mice consumed more ($P < 0.01$) CS+ than CS- during the last 4 training days. In the two-bottle tests the Glucose mice consumed substantially more CS+ than CS- in both the reinforced and nonreinforced tests ($F(1,9) = 30.1, P < 0.001$). Intake across the two tests differed only in that CS+ intake increased from the reinforced to

the nonreinforced test (32.6 to 37.1 g/day, CS $\times$ Test interaction: $F(1,9)=12.4$, $P<0.01$). The percent CS+ preferences were 86% and 89% in the two tests and did not significantly differ.

The results were quite different for the Fructose group. The mice consumed less CS+ than CS- during training with significant differences ($P<0.01$) for the first and last pairs of days (CS $\times$ Day, $F(2,16)=6.3$, $P<0.01$). CS+ intake was suppressed on the first training day and remained low, while the CS- intakes declined from day 1 to days 3 and 4 (CS $\times$ Day interaction, $F(2,18)=6.3$, $P<0.01$). The mice did not differ in their CS+ and CS- intakes during the two-bottle tests and total intakes (CS+ plus CS-) increased from the reinforced to the nonreinforced test (18.9 to 21.2 g/day, $F(1,9)=11.1$, $P<0.01$). Percent CS+ preferences did not significantly differ in the two tests and remained just above 50% (Figure 1).

In the case of the Galactose mice, training intakes of the CS+ exceeded those of the CS- ($F(1,9)=6.9$, $p<0.05$) and intakes of both solutions declined over training ($F(2,18)=36.3$, $P<0.001$). The mice did not differ in their CS+ and CS- intakes during the two-bottle tests and intakes in the reinforced and nonreinforced tests were similar. Percent CS+ preferences also did not significantly differ in the two tests and remained just under 50% (Figure 1).

Separate analyses compared the training and choice test intakes among the three groups. During training, the Glucose group consumed more of both CSs than did Fructose and Galactose groups, with the difference being most pronounced for the CS+ (CS $\times$ Group interaction, $F(2,27)=27.3$, $P<0.001$); the training intakes of the Fructose and Galactose groups did not significantly differ. In the reinforced preference tests, the Glucose group consumed more CS+ than the Fructose and Galactose groups; the CS- intakes did not significantly differ ($F(2,27)=20.2$, $P<0.001$). The results were similar for the nonreinforced test (Group $\times$ CS interaction ($F(2,27)=24.2$, $P<0.001$). The groups also differed in their percent CS+ preferences in the reinforced and nonreinforced tests; overall, the CS+ glucose preference was much greater than that for CS+fructose or CS+galactose ($87.4\% > 55.6\% = 44.7\%$, $F(2,27)=22.90$, $P<0.001$).

3. Experiment 2

This experiment determined if pairing a CS+ with self-infusions of 8% fructose or galactose would enhance flavor conditioning in B6 mice. This seemed possible because we previously observed strong IG fructose conditioning (90% CS+ preference) in rats trained with 7.2% rather than 16% sugar infusion; 7.2% fructose was used to match the caloric density of 5% ethanol [1,2]. Glucose was not tested at the lower concentration because in a prior study we reported ~90% CS+ preference in mice infused with 8% maltodextrin, which is rapidly digested to glucose in the gut [18].

3.1. Method

Adult male C57BL/6J mice were trained as in Experiment 1 except that the CS+ solution was paired with IG infusions of 8% fructose ($n=10$) or 8% galactose ($n=13$).

3.2. Results

Figure 2 presents the training and test data for the 8% Fructose and 8% Galactose groups. During training, the Fructose group drank similar amounts of CS+ and CS- and intakes did not vary over days. In the two-bottle reinforced and nonreinforced tests CS+ and CS- intakes did not significantly differ. The percent CS+ intakes in the two tests also did not significantly differ and remained close to 50%.

The 8% Galactose group drank slightly but significantly less CS+ than CS- during training (17.9 vs. 19.7 g/day, $F(1,12)=14.2$, $P<0.01$) and the intakes of both solutions declined over

training days ($F(2,24)=16.5$, $P<0.001$). In the two-bottle reinforced and nonreinforced tests CS+ and CS- intakes did not significantly differ. The percent CS+ intakes in the two tests also did not differ and remained close to 50%. Between group analyses indicated that the 8% Fructose and 8% Galactose did not significantly differ in their CS training and test intakes or in their percent CS+ preferences (50.0% and 49.0%, respectively).

4. Discussion

The present results demonstrate that the monosaccharides glucose, fructose and galactose differ greatly in their post-oral conditioning effects in B6 mice. Whereas IG 16% glucose self-infusions conditioned a strong CS+ preference, fructose and galactose infusions failed to do so. In addition, only the glucose self-infusions significantly increased the one-bottle intake of the CS+ during training.

The robust conditioning response of the B6 mice to the IG glucose is similar to that observed with IG infusions of maltodextrin and sucrose in this strain [17,18,19]. As in the present study, the maltodextrin and sucrose infusions increased one-bottle training intake of the saccharin-sweetened CS+ and produced ~90% CS+ preferences. In all cases the conditioned preferences were observed in both reinforced and nonreinforced tests, demonstrating that the mice had acquired a true preference for the CS+ flavor. That is, their elevated CS+ intake in the choice test was not driven by concurrently infused carbohydrate. Rats also develop ~90% preferences for CS+ flavors paired with IG infusions of glucose, maltodextrin or sucrose [5,15,15,21].

In contrast to glucose, IG infusion of fructose did not condition a CS+ preference; instead the mice were indifferent to the CS+ and CS- solutions in the two-bottle tests. Prior studies reported that IG fructose is considerably less effective than glucose in conditioning flavor preferences in rats [2,3,15,16]. Nevertheless, rats trained 22 h/day with saccharin-sweetened CS solutions acquired moderate (~70%) to strong (90%) preferences for CS+ flavors paired with IG infusions of 16% or 7.2% fructose, respectively [2]. The present findings indicate that the post-oral actions of fructose are less reinforcing for B6 mice than for rats. A recent oral conditioning study revealed that B6 mice also did not acquire a preference for a CS+ flavor added to a 16% fructose solution over a CS- flavor added to a 0.05% saccharin solution (2 h/day sessions). Yet, seven of eight other mouse strains tested displayed preferences for the fructose-paired CS+ [12]. The CS+ preference displayed by these other strains may have been reinforced by the sweet taste and/or postoral actions of the 16% fructose solution. It is possible, therefore, that IG fructose may condition flavor preferences in mouse strains other than B6.

In Experiment 1, the IG fructose but not IG glucose or galactose suppressed CS+ intake on day 2 compared to CS- intake on day 1. Conceivably, the intake inhibitory (satiating) action of the 16% fructose infusion may have counteracted any potential reinforcing effect of the sugar and blocked preference conditioning; prior rat studies indicate that overly satiating infusions reduce preference conditioning [14]. However, this does not explain the failure of IG 8% fructose to condition a flavor preference in Experiment 2; CS+ and CS- training intakes were very similar in the second experiment.

Like fructose, galactose infusions did not condition flavor preferences when infused at 16% or 8% concentrations. Both concentrations suppressed CS+ intakes during training, although the mice consumed slightly more CS+16% galactose and slightly less CS+8% galactose, relative to the CS-, in Experiments 1 and 2, respectively. The indifference (~50% preference) the mice displayed for the CS+ paired with IG 16% galactose is in marked contrast to the significant CS+ avoidance (21% preference) observed in an earlier study with

food-restricted rats trained 30 min/day [16]. We also observed a galactose conditioned avoidance in food-restricted rats trained with flavored sugar solutions [22]. It may be that B6 mice would also avoid a galactose-paired CS+ flavor if trained and tested food-restricted in short sessions, but preliminary findings indicate that this is not the case (Zukerman & Sclafani, unpublished observations). The flavor avoidance produced by IG galactose was attributed to the limited ability of rats to metabolize the sugar due to the postweaning decline in the required enzymes [16], and it may be that galactose metabolism is less impaired in mice than in rats. Nevertheless, other findings indicate that mice are limited in their ability to utilize high-galactose diets [23] and B6 mice avoid a 32% galactose solution in 24-h sugar vs. water choice tests (Zukerman & Sclafani, unpublished observations).

Whereas IG glucose but not galactose conditioned a flavor preference, a recent study reported that the two sugars conditioned similar place preferences (CPP) in mice [9]. In the CPP study, mice were trained to drink a palatable, noncaloric fat substitute (sorbitol fatty acid ester, SFE) and water in different sides of a test chamber. The SFE by itself did not condition a place preference but did so when paired with IG intubation of glucose or galactose, as well as with IG corn oil, sucrose, or maltodextrin. On the other hand, IG fructose did not produce a CPP, consistent with the failure of fructose to condition a flavor preference in the present study. The differential conditioning results obtained with galactose in the present and prior study may be due to several factors including the different training tasks (flavor vs. place conditioning) and mouse strains (B6 vs. ddY). Another potentially important factor is that the mice in the CPP study were infused with a relatively small amount of galactose (0.2 ml of 20% sugar) in each SFE training session. Perhaps at this low dose, impaired sugar metabolism is not a factor that limits the rewarding action of galactose. We are currently investigating flavor conditioning in mice given limited access to galactose.

There is evidence that glucose may act at both intestinal and hepatic-portal sites to condition preferences [4,11,24]. With regards to the intestine, the recent discovery of sweet “taste” receptors in the gut suggested the possibility that the same receptor responsible for sugar taste preference may also mediate post-oral sugar conditioned preferences [6]. However, the present and other findings showing that IG fructose is much less effective than IG glucose in conditioning flavor preferences argue against this interpretation given that the two sugars appear to be about equally sweet (or palatable) as measured in brief taste tests [7,8,20,21,28]. Furthermore, we recently reported that knockout mice missing the T1R3 component of the sweet taste receptor in mouth and gut show a normal preference conditioning response to IG sucrose [17]. Together, these data indicate that other intestinal sugar sensors mediate post-oral preference conditioning. Two potential candidates include SGLT1 and SGLT3, which are thought to function as glucose sensors in addition to being, in the case of SGLT1, an intestinal glucose transporter [25]. SGLT1 and 3 are of particular interest because they bind to glucose but not fructose, although neither protein has as yet been implicated in the postoral glucose conditioning. They differ, in that SGLT1 but not SGLT3 also binds to galactose [25]. Thus, the differential effectiveness of glucose and galactose in conditioning flavor preferences, if confirmed in subsequent studies would implicate SGLT3 in postoral glucose conditioning.

In summary, the present findings demonstrate that intragastric infusions of glucose are much more effective than fructose or galactose in conditioning flavor preferences in B6 mice, as is the case in rats. However, the B6 mice differed from rats in failing to prefer the fructose-paired CS+ as well as failing to avoid the galactose-paired CS+. This might not be true of other inbred mouse strains, given strain differences observed in fructose-conditioned preferences using an oral training procedure [12]. The differential conditioning actions of the monosaccharide sugars in mice and rats argue against the involvement of gut sweet “taste” receptors but rather implicate a primary role for glucose-specific sensors.

Acknowledgments

This research was supported by grant DK-31135 from the National Institute of Diabetes and Digestive and Kidney Diseases. The authors thank Kwame McCartney and Martin Zartarian for their expert technical assistance.

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Highlights

Mice learned to prefer a flavor paired with intragastric infusions of 16% glucose

Intragastric infusions fructose or galactose did not condition a flavor preference

Postoral sugar conditioning is mediated by glucose-specific sensors

Figure. 1.

Experiment 1. Flavor-sugar conditioning in B6 mice. Intake of the CS+ solution was paired with IG infusions of either 16% glucose (left), 16% fructose (middle) or 16% galactose (right). Intake of the CS- solution was paired with IG infusions of water. The left side of each panel shows total daily fluid intake (oral CS intake plus IG infusate) during each of the six 1-bottle training days. The CS- solution was offered on days 1, 3, and 5, and the CS+ solution was offered on days 2, 4, and 6. The right side of each panel shows mean total daily intake during the reinforced (Rein) two-bottle preference test, in which the CS+ was paired with IG sugar infusion, and mean daily intake during the nonreinforced (NR) two-bottle test, in which the CS+ was paired with IG water infusion. Values are mean (+ S.E.) total daily intakes. Numbers atop bars represent mean percent preference for the CS+ solutions. Significant differences (*P < 0.05) between CS+ and CS- intakes during 1-bottle training and 2-bottle test are shown.

Figure 2.

Experiment 2. Flavor-sugar conditioning in B6 mice. Intake of the CS+ solution was paired with IG infusions of either 8% fructose (left) or 8% galactose (right). Intake of the CS- solution was paired with IG infusions of water. The left side of each panel shows total daily fluid intake (oral CS intake plus IG infusate) during each of the six 1-bottle training days. The CS- solution was offered on days 1, 3, and 5, and the CS+ solution was offered on days 2, 4, and 6. The right side of each panel shows mean total daily intake during the reinforced (Rein) two-bottle preference test, in which the CS+ was paired with IG sugar infusion, and mean daily intake during the nonreinforced (NR) two-bottle test in which the CS+ was paired with IG water infusion. Values are mean (+ S.E.) total daily intakes. Numbers atop bars represent mean percent preference for the CS+ solutions.