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Genetic variance contributes to ingestive processes: A survey of 2-deoxy-D-glucose-induced feeding in eleven inbred mouse strains

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Abstract

The feeding response following administration of the anti-metabolic glucose analogue, 2-deoxy-D-glucose (2DG), is conceptualized as an experimental model of glucoprivation, which may contribute to the understanding of inter-individual differences in glucose and carbohydrate intake and, ultimately, obesity. Although variation in the intake of several nutrients as well as food and water are known to be associated with genetic variation, it is not known whether 2DG-induced feeding is similarly genotype dependent. The present study therefore examined 2DG-induced feeding in mice of 11 inbred (A/J, AKR/J, BALB/cJ, CBA/J, C3H/HeJ, C57BL6/J, C57BL10/J, DBA/2J, SJL/J, SWR/J, 129P3/J) and one outbred (CD-1) strains across a wide range of previously determined effective 2-DG doses (200, 400, 600, 800 mg/kg) and test times (1–4 h). Orderly dose-dependent increases in 2DG-induced feeding occurred after all four doses in outbred CD-1 and inbred DBA/2J mice, across the three highest doses for BALB/cJ, SJL/J and 129P3/J mice, and across the two highest doses for CBA/J and AKR/J mice. Limited instances of 2DG-induced feeding were noted only at the highest dose in A/J and C3H/HeJ mice, or at a moderate dose in C57BL/6J mice. Further, the full 2DG dose range failed to alter food intake in C57BL/10J mice, and produced significant reductions in food intake in SWR/J mice. Food intake after 2DG doses of 200–600 mg/kg, but not 800 mg/kg, displayed significant cross-correlation, suggesting that large 2DG doses may recruit non-specific effects upon food intake. There was no correlation between food intake in the absence (vehicle baseline) of and presence of 2DG, suggesting that the regulation of glucose intake in non-challenged mice does not predict subsequent responses to glucoprivic challenge. The data demonstrate genotype-dependent variability in this glucoprivic response, and may provide the basis for the subsequent identification of trait-relevant genes.

Keywords: Genetics; Glucoprivation

1. Introduction

The anti-metabolic glucose analogue, 2-deoxy-D-glucose (2DG: [67]), increases food intake following systemic [e.g., 15,56,57,61] and cerebro-ventricular [13,32] administration in rats, monkeys and humans. This ingestive response can occur in rats in the absence of other signs of glucoprivation [21,41] and reduced glucose oxidation [36], is also dependent on necessary metabolic changes [22], and displays synergistic feeding interactions with central insulin administration [17]. Further, glucoprivic feeding in rats is impaired following blockade of central glucoreceptors with alloxan [33,34,44,50,68] or stress-induced alterations in noradrenergic function ([45,47,54], but see Ref. [48]). Whereas 2DG-induced feeding is clearly delineated in outbred rats, the presence of its ingestive actions has not been universally observed in other species. Thus, 2DG-induced feeding failed to occur under similar dosing and ingestive conditions in Golden and Siberian hamsters [1,8,9,30,40,46], deermice [49] and spiny mice [18]. 2DG induces feeding in ground squirrels in only their hyperphagic, but not hypophagic phase [35], in lean, but not fatty Zucker rats

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[63], and in rats selectively bred for high, but not low saccharin intake [64].

Even within a given species, substantial inter-individual variability in ingestive responses has been demonstrated, and is often associated with genetic variance. In the mouse, for example, strain differences have been reported for the intake of salt [e.g., 2,6,7,10,62], bitter tastants [e.g., 6,14,62], fats [e.g., 5,58], saccharin [e.g., 14,16,31,39,62], sucrose [e.g., 4,14,26, 29,31,38] and food and water [3]. Recently, we reported changes in sucrose intake among 11 inbred strains across a range of sucrose concentrations (0.0001–20%) in two-bottle 24-h preference tests [29]. Our data show very wide strain-dependent sensitivities in the sucrose concentration capable of significantly increasing sucrose intake, the magnitude of such intake at different concentrations, and the kilocalories consumed as sucrose, indicating that variation in several sucrose-related measures are also genotype-dependent. In addition to assessing the contribution of genetic background in the variability of ingestive behaviors, inbred mouse strain surveys can also identify strains with highly divergent responses to serve as progenitors in quantitative trait loci (QTL) mapping, which may localize phenotype differences to chromosomal regions, and ultimately genes. This approach has been successfully applied to differences in the intake of fat, carbohydrate, bitter tastants, saccharin, sucrose, and total Kcal intake [14,58]. Identification of QTLs associated with variability in ingestive behaviors like glucoprivation is an important first step in the genetic dissection of obesity.

Although 2DG-induced food intake may reflect glucosensing mechanisms and provide insight into the regulatory control of carbohydrate intake, to our knowledge a QTL for this response has yet to be identified. In fact, in contrast to other ingestive processes, it is currently unknown whether this response is subject to response variability at all, and/or whether such potential variability is associated with genetic variability. Although studies have demonstrated a role for genes encoding Na^+-coupled glucose transporters (SGLT) and glucose transporter facilitators (GLUT) in glucosensing (see review: [53]), it is not known whether allelic frequency of these genes makes any contribution to the quantitative distribution of 2DG feeding responses. Indeed, we have previously reported on the absence of significant correlations between intake of sucrose at several concentrations and *Tas1r3* taste receptor gene polymorphisms [29].

To begin to provide for the genetic analyses of 2DG-induced feeding, the present study surveyed 11 inbred strains differences for feeding responses across a wide range of previously determined effective systemic 2DG doses (200, 400, 600, 800 mg/kg) and test times (1–4 h). Since there are no previous 2DG feeding data for inbred strains, standard outbred CD-1 mice were also tested to provide a point of comparison with other studies [e.g., 12,19,65] to confirm the efficacy of our paradigm.

2. Methods

2.1. Subjects

Outbred (CD-1, Charles River Laboratories, Wilmington, MA; $n=20$) and inbred (A/J, AKR/J, BALB/cJ, CBA/J, C3H/HeJ, C57BL6/J, C57BL10/J, DBA/2J, SJL/J, SWR/J, 129P3/J, Jackson Laboratories, Bar Harbor, ME; $n=10$ each) male mice (12 weeks of age) were initially acclimated to the Queens College vivarium for one week in group (5 per cage) housing. Then, each animal was housed individually in clear polyethylene cages ($30\times20\times15$ cm) throughout the entire study, and maintained on a 12 h light: 12 h dark cycle (lights off at 2000 h) at a constant temperature of 22 °C with chow and water available ad libitum.

2.2.2. DG intake procedure

All procedures were approved by the Queens College Institutional Animal Care and Use Committee. Each animal was moved to a test cage at 4–6 h into the light cycle and provided with a water bottle and a pre-weighed ration of Purina Mouse chow (5.3 kcal/g) placed on a stainless steel grid on the bottom of the test cage. A brown paper towel was placed below this grid to collect spillage. Animals were acclimated to this test cage prior to and during four days of baseline data collection in which pre-weighed food pellets were placed on

Table 1
Food intake difference scores ($g\pm$S.E.M., minus baseline values) relative to vehicle baseline intake, and percentage change over vehicle baseline intake 4 h following 2DG in 12 mouse strains as compared to sucrose intake (20%) and percentage of kilocalories consumed as sucrose in 12 mouse strains

2-DG dose/strain	Vehicle intake (4 h)	Measures	200 mg/kg	400 mg/kg	600 mg/kg	800 mg/kg
A/J	0.52 (0.04)	Diff. score % Veh	−0.21# (0.07) 40%↓#	+0.06 (0.06) 12%↑	+0.02 (0.08) 4%↑	+0.52* (0.08) 100%↑*
AKR/J	0.58 (0.08)	Diff. score % Veh	−0.21 (0.04) 36%↓	−0.08 (0.08) 14%↓	+0.28* (0.11) 48%↑*	+0.35* (0.15) 60%↑*
BALB/cJ	0.74 (0.05)	Diff. score % Veh	+0.12 (0.10) 16%↑	+0.61* (0.17) 82%↑*	+0.44* (0.08) 59%↑*	+0.71* (0.10) 96%↑*
C57BL/6J	0.39 (0.05)	Diff. score % Veh	−0.08 (0.06) 21%↓	+0.24* (0.10) 62%↑*	+0.20 (0.09) 51%↑	−0.12 (0.10) 31%↓
C57BL/10J	0.48 (0.09)	Diff. score % Veh	−0.12 (0.10) 25%↓	−0.08 (0.09) 17%↓	+0.11 (0.10) 27%↑	−0.18 (0.08) 32%↓
CBA/J	0.25 (0.04)	Diff. score % Veh	−0.04 (0.08) 16%↓	+0.20 (0.03) 80%↑	+0.36* (0.10) 144%↑*	+0.47* (0.07) 188%↑*
CD-1	0.69 (0.06)	Diff. score % Veh	+0.24* (0.13) 33%↑*	+0.52* (0.15) 77%↑*	+0.42* (0.19) 61%↑*	+0.55* (0.18) 80%↑*
C3H/HeJ	0.46 (0.10)	Diff. score % Veh	+0.04 (0.13) 9%↑	+0.09 (0.09) 20%↑	+0.19 (0.09) 41%↑	+0.56* (0.11) 122%↑*
DBA/2J	0.48 (0.10)	Diff. score % Veh	+0.10 (0.12) 21%↑	+0.46* (0.17) 96%↑*	+0.37* (0.15) 77%↑*	+0.39* (0.10) 81%↑*
SJL/J	0.37 (0.04)	Diff. score % Veh	+0.13 (0.07) 35%↑	+0.22* (0.07) 59%↑*	+0.30* (0.08) 82%↑*	+0.37* (0.08) 100%↑*
SWR/J	0.95 (0.03)	Diff. score % Veh	−0.40# (0.11) 42%↓#	−0.20 (0.08) 21%↓	+0.01 (0.07) 1%↑	−0.11 (0.08) 12%↓
129P3/J	0.54 (0.04)	Diff. score % Veh	−0.28# (0.05) 51%↓#	+0.22* (0.08) 41%↑*	+0.28* (0.12) 51%↑*	+0.22* (0.05) 41%↑*

*Significant increase or # decrease in 2DG-induced food intake relative to vehicle values.

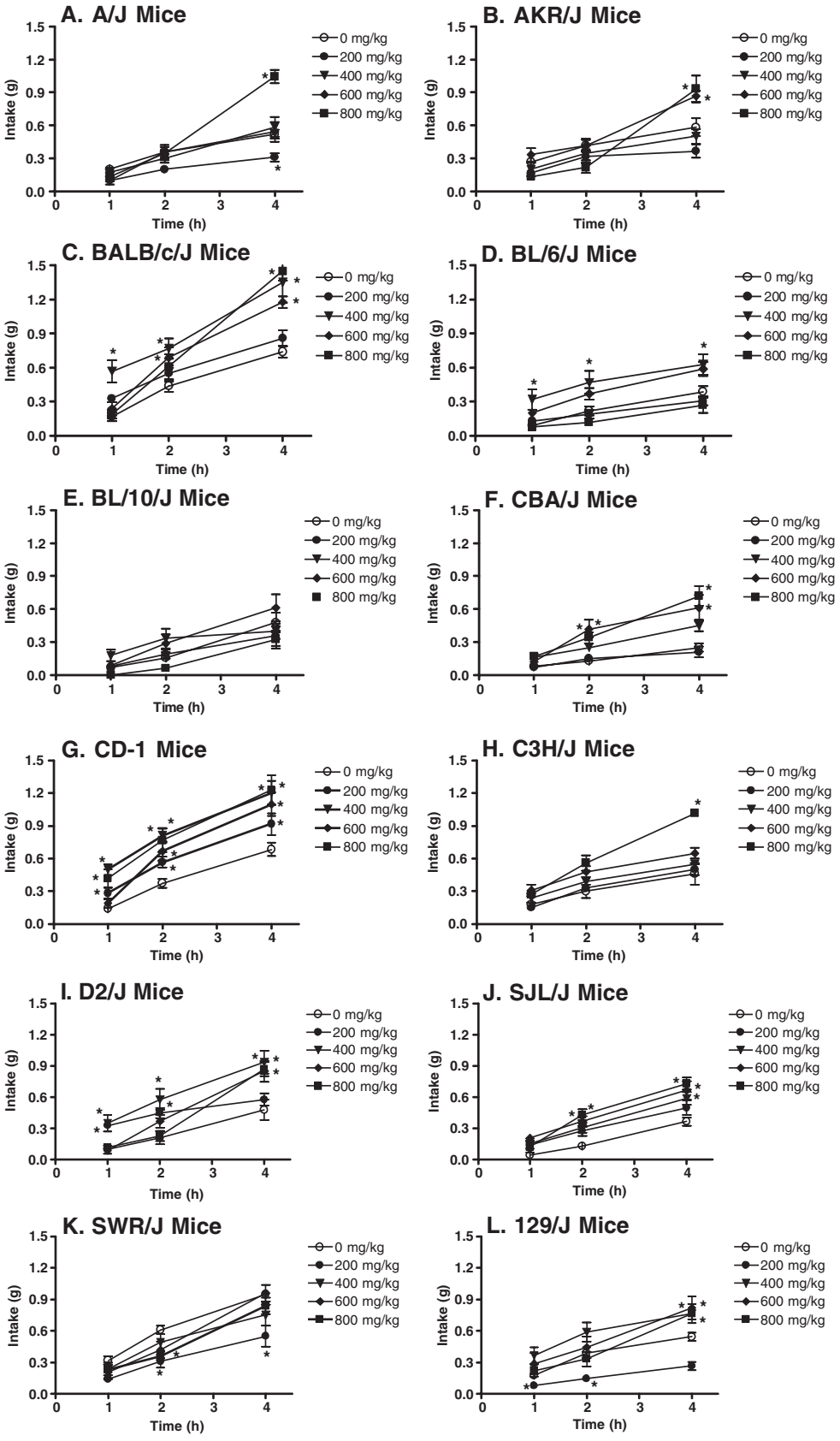

Fig. 1. Food intake ($g \pm$S.E.M.) following four doses of 2-deoxy-D-glucose (2DG) in 12 mouse strains over 4 h. Ordinates are identical to facilitate interstrain comparisons. The asterisks (*) denote significant alterations in food intake relative to the corresponding vehicle value obtained within each strain (Tukey comparisons, $P < 0.05$).

the grid floor, and intake was assessed after 1, 2 and 4 h. Food intake (+0.1 g) was assessed by weighing food pellets prior to and following each time interval, and adjusting for any spillage. After determination of stable baseline food intake, the animals were then tested with vehicle and four doses of 2DG (Sigma Chemical Company, St. Louis, MO: 200, 400, 600 and 800 mg/kg, ip). 2DG was dissolved in distilled water at concentrations of 20, 40, 60 and 80 mg/ml, and injected intraperitoneally in a 10 ml/kg volume. The interval between each injection was minimally 72 h, and maximally after one week. Half of the mice of each strain were tested in an ascending 2DG dose order, and the remaining half were tested in a descending order.

2.3. Statistics

Alterations in 2DG-induced feeding relative to vehicle baseline intake were assessed using a three-way randomized block analysis of variance with the 12 strains as the between-subject variable, the five (vehicle and 4 2DG doses) conditions as a within-subject variable, and the three intake (1, 2, 4 h) times as a second within-subject variable. Because significant strain differences were observed in baseline and vehicle food intake across the 4 h time course (Table 1), Tukey comparisons ($P<0.05$) were performed in the presence of significant effects only relative to corresponding baseline values within strains. A subsequent separate three-way randomized-block analysis of variance was performed on 2DG difference scores in which each intake value at each time point following vehicle in each animal in each strain was subtracted from each corresponding 2DG dose value with the 12 strains as the between-subject variable, the four 2DG dose conditions as a within-subject variable, and the three intake times as a second within-subject variable.

All correlations were calculated using Pearson product-moment correlation coefficients [r] subject to Bonferroni correction for multiple comparisons. Correlations were performed between mice of 11 inbred and 1 outbred strains for food intake (4 h total) during vehicle baseline testing (no 2DG) and after the four 2DG doses. Correlations were also assessed between strain glucoprivic responses of all 2G doses and the percentage of sucrose intake in the presence of sucrose concentrations of 0.01%, 2.5%, 10%, and 20% as previously reported [29]. These four concentrations were selected for correlation because they represent a wide range of sucrose concentrations, are the most preferred (10%), are not likely due to non-specific effects (0.1% and 2.5%), and constituted the highest concentration tested (20%), and thus, for some strains, peak effects.

3. Results

Significant differences in food intake were observed among strains ($F(11,209)=58.31$, $p<0.0001$), among the injection conditions ($F(4,76)=94.86$, $p<0.0001$), across test times ($F(2,38)=4476.55$, $p<0.0001$), and for the interactions between strains and conditions ($F(44,836)=12.85$, $p<0.0001$), strains and times ($F(22,418)=36.55$, $p<0.0001$), conditions and times ($F(8,152)=210.81$, $p<0.0001$), and among strains, conditions and times ($F(88,1672)=13.37$, $p<0.0001$). Significant differences in short-term vehicle baseline intake occurred across strains with SWR/J mice consuming the most followed by BALB/cJ, CD-1 and AKR/J mice, and then the other strains (Table 1). Significant differences in the difference scores for 2DG-induced intake were observed among strains ($F(11,209)=30.67$, $p<0.0001$), among 2DG doses ($F(3,57)=74.62$, $p<0.0001$), across test times ($F(2,38)=88.35$, $p<0.0001$), and for the interactions between strains and doses ($F(33,627)=9.51$, $p<0.004$), strains and times ($F(22,418)=13.06$, $p<0.0001$), doses and times ($F(6,114)=254.62$, $p<0.0001$), and among strains, doses and times ($F(66,1254)=13.52$, $p<0.0001$).

There were clear strain differences in the magnitude and pattern of 2DG-induced intake relative to corresponding vehicle conditions. 2DG produced significant dose-dependent increases in food intake following each of the four doses in the CD-1 and DBA/2J mouse strains (Fig. 1G, 1I), following the three highest doses in the BALB/cJ, SJL/J and 129P3/J mouse strains (Fig. 1C, J, L), and following the two highest doses in the CBA/J and AKR/J mouse strains (Fig. 1B, F). 2DG produced significant dose-dependent increases in food intake following only the highest dose in A/J and C3H/HeJ mice (Fig. 1A, H), and following only the 400 mg/kg dose in C57BL/6J mice (Fig. 1D). The full 2DG dose range failed to alter food intake at any time point in C57BL/10J mice (Fig. 1E). In contrast, 2DG significantly reduced food intake at the lowest and highest doses in SWR/J mice (Fig. 1K). Table 1 summarizes the food intake difference scores and the percentage changes in intake 4 h following each 2DG dose relative to vehicle treatment in the 12 tested mouse strains.

Bonferroni-corrected pairwise correlations were examined between food intake over 4 h for vehicle baseline (no 2DG) relative to each of the four 2DG doses, and then among the four 2DG doses (Table 2). Significant correlations were noted for intake across strains between the 200 and 400 mg/kg doses ($r=0.75$, $p<0.05$), the 200 and 600 mg/kg doses ($r=0.73$, $p<0.05$), and the 400 and 600 mg/kg doses ($r=0.82$, $p<0.001$). In contrast, significant correlations failed to be observed between food intake during vehicle baseline and intake after any 2DG dose, and between each of the three lower 2DG doses relative to the highest 800 mg/kg 2DG dose. Furthermore, food intake following any 2DG dose failed to

Table 2
Pearson product-moment correlation coefficients for food intake over 4 h in vehicle baseline (BL) testing and after the four 2DG doses

	BL	200 mg/kg	400 mg/kg	600 mg/kg
BL	–			
200 mg/kg	0.28	–		
400 mg/kg	0.08	*0.78	–	
600 mg/kg	0.12	*0.73	**0.82	–
800 mg/kg	0.08	0.57	0.59	0.58

Significant correlation (*$p<0.05$, **$p<0.01$) after Bonferroni corrections.

correlate significantly with previously reported [30] sucrose intake following a wide range (0.01%, 2.5%, 10%, and 20%) of effective sucrose concentrations (data not shown).

4. Discussion

Strong and systematic strain differences were observed for 2DG-induced intake as functions of dose and time. Consistent with outbred rats [e.g., 15,41,45,56] and mice [e.g., 12,19,65], outbred CD-1 mice displayed the most orderly time- and dose-dependent increases in 2DG-induced feeding. Orderly dose-dependent increases in 2DG-induced feeding for inbred mouse strains occurred across all four doses (DBA/2J), across the three highest doses (BALB/cJ, SJL/J and 129P3/J) and across the two highest doses (CBA/J and AKR/J). Some mouse strains displayed very limited instances of 2DG-induced feeding with increases noted only following the highest dose in A/J and C3H/HeJ mice or following the 400 mg/kg dose in C57BL/6J mice. Importantly, although strain-specific effects for feeding following the three lowest 2DG doses produced significant or near significant correlations, intakes following the three lower 2DG doses failed to correlate significantly with intake following the highest 800 mg/kg 2DG dose that typically produced the most pronounced ingestive effects. Just as certain species such as Golden and Siberian hamsters [1,8,9,30,40,46], deermice [49] and spiny mice [18] fail to display 2DG-induced feeding, the full 2DG dose range failed to alter food intake in C57BL/10J mice. Interestingly, 2DG actually produced significant reductions in food intake in SWR/J mice. Such strain differences should be considered vis a vis the absence of 2DG-induced feeding in mice genetically deficient in dopamine [24], the dopamine-3 receptor gene [11], dopamine beta-hydroxylase [59] or neuropeptide Y [55]. Although these findings suggest the importance of these genes in the mediation of glucoprivic feeding, the background strains of the genetically modified animals might contribute to the absence of this 2DG-mediated effect. In two cases, the knockout and wild type mice were maintained on a mixed C57BL/6J and 129/SvCPJ genetic background [24,59], while the other studies maintained their knockout mice on either pure 129/SvEv [55] or pure C57BL/6 [11] backgrounds. Thus, whereas the 129P3/J strain displayed quite robust feeding responses to 2DG across the three highest doses that were comparable to responses elicited from outbred animals, the C57BL/6J strain displayed a very limited response at only a moderate dose of 2DG. One must consider whether the absence of 2DG-induced feeding in mice with targeted deletions of dopamine [24], the dopamine-3 receptor gene [11] or dopamine beta-hydroxylase [59] would have been as robust if one used a background strain for 2DG-induced feeding other than the weakly responding C57BL/6J inbred strain. The potential confound of “hitchhiking” genes and donor strain background has been discussed at length elsewhere [28].

A common finding of 2G studies is that the presence or absence of increased 2DG feeding depends critically on the nature (e.g., type and consistency of nutrient [20,27,66]) and timing (e.g., phase of the light-dark cycle [37,60]) of vehicle baseline feeding responses. Table 1 thus provides the magnitude of 2DG feeding responses with reference to vehicle baseline values. However, significant correlations failed to occur for food intake between vehicle baseline and any dose of 2DG when all strains are considered. Indeed, inbred strains displaying low (CBA/J: 0.25 g), moderate (C3H/HeJ: 0.46 g) and high (BALB/cJ: 0.74 g) levels of vehicle baseline intake showed comparable significant increases in 2DG-induced feeding 4 h following the 800 mg/kg dose: 188%, 122% and 96%, respectively (Table 1). Thus, the present data do not indicate that the magnitude of baseline food intake is intimately related to subsequent compensatory food intake after glucoprivation. It is however possible that these discrepant results may reflect the common use of a single strain for testing. By doing so, such studies lack the statistical power afforded by assessing the relationship between vehicle baseline and 2DG-induced feeding relationships in 11 different genotypes, which may have caused this relationship to be overestimated. A more thorough examination of the putative relationship between vehicle baseline food intake and subsequent 2DG-induced feeding might consider several strains at various pre- and post-prandrial intervals.

It is important to note that 2DG administration has also been shown to produce non-specific effects upon food intake, such as lethargy as well as the fact that 2DG-induced feeding can occur in the absence of other signs of glucoprivation. Feeding induced by systemic or cerebroventricular 2DG persists 6 h after injection at which time sympathoadrenal hyperglycemia and reduced glucose oxidation have subsided (e.g., 21,36,41]). Moreover, 2DG-induced feeding is reduced by stress [45], an effect attributable in part to impairment of noradrenergic neuron function [45,47,54], but see 48]. Hence, 2DG appears to produce its ingestive effects in rats through selective activation of epinephrine-containing neurons in dorsal medulla [43], effects attenuated by either immunotoxic destruction [25,42] or prior repeated 2DG treatment [51,52]. Thus, we cannot rule out the possibility that some genetic variation in stress responding and lethargy is associated with the varying strain-specific responses to 2DG injection. Although not a directly measured variable, we did not observe any strain-specific gross motor or other impairment that might obviously confound food intake. However, such potential confounds are more likely to be pronounced following the higher 2DG doses. In the present study, we reported that there was significant cross-correlation between 2DG doses of 200, 400 and 600 mg/kg. Since the demonstration of genetic correlation between two heritable traits among isogenic (inbred) strains can be used as evidence of the existence of pleiotropic genes with a common influence on both traits [23], the data suggest that the genetic contribution to strain variance in food intake after these 2DG doses display significant overlap, and provides a genetic validation of 2DG doses across our lower testing range (200–600 mg/kg). Furthermore, the largest 2DG dose of 800 mg/kg was not significantly correlated with any of the lower doses, suggesting a genetic dissociation. It is conceivable that the highest 2DG dose could recruit potentially non-specific systems, possibly including stress and

lethargy, that vary among strains and which impact food intake. Clearly, the present data suggest that results from 2DG test doses larger than 600 mg/kg should be interpreted with caution.

Finally, we did not observe a significant correlation between sucrose intake and 2DG food intake when responses of both are considered across 11 inbred strains. Although both experimental paradigms are thought to provide insight into glucosensing processes, the present differential pattern of strain sensitivity in each suggests, again, differential genetic organization. Nonetheless, given the complexity of regulating glucose intake, the lack of correlation does not imply a lack of integration between such systems. Both will likely contribute to glucosensing in the mouse, although the relative contribution of each may vary with genotype. Further work is needed to provide a model for their integration.

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