ELSEVIER

Physiology & Behavior 88 (2006) 516–522

PHYSIOLOGY & BEHAVIOR

Genetic variance contributes to ingestive processes: A survey of mercaptoacetate-induced feeding in eleven inbred and one outbred mouse strains

Sarah R. Lewis [a,b], Cheryl Dym [a,b], Miriam Ginzberg [b], Benjamin Kest [a,c], Richard J. Bodnar [a,b,*]

[a] *Neuropsychology Doctoral Sub-Program and Departments of Psychology, City University of New York, USA*
[b] *Queens College, City University of New York, USA*
[c] *College of Staten Island, City University of New York, USA*

Received 22 December 2005; received in revised form 19 April 2006; accepted 1 May 2006

Abstract

The feeding response following administration of the free fatty acid oxidation inhibitor, mercaptoacetate (MA) is conceptualized as an experimental model of lipoprivation, which may contribute to the understanding of inter-individual differences in the modulation of this homeostatic response. Although variation in the intake of food, water and glucoprivation as well as intake of several nutrients is known to be associated with genetic variation, it is not known whether MA-induced feeding is similarly dependent upon genotype. The present study therefore examined MA-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 MA doses (5, 35, 70, 100 mg/kg) and test times (1–4 h). MA produced significant dose-dependent and strain-dependent increases in food intake with strong responses noted in DBA/2J, outbred CD-1 and AKR/J mice. More limited dose-specific increases in food intake following MA occurred in C3H/HeJ, BALB/cJ, CBA/J, SJL/J, SWR/J and C57BL/6J mice. In contrast, MA failed to significantly increase food intake in A/J, C57BL/10J and 129P/3J mice. MA-induced food intake correlated significantly across strains only following the two highest doses, and intake following only the highest MA dose correlated significantly across strains with intake following only a moderate glucoprivic dose of 2-deoxy-D-glucose. Thus, these inter-strain differences suggest that lipoprivic (e.g., MA intake) and glucoprivic (e.g., 2-deoxy-D-glucose intake) responsivity operate via only partially overlapping genetic mechanisms of action. The demonstration of genotype-dependent variability in this lipoprivic response may provide the basis for the subsequent identification of trait-relevant genes.

Keywords: Genetics; Lipoprivation

1. Introduction

The free fatty acid oxidation inhibitor, mercaptoacetate (MA: [8]) significantly increases food intake following systemic administration [19,33]. This lipoprivic ingestive response has been compared with increases in food intake [12,40,41] following systemic administration of the anti-metabolic glucose analogue, 2-deoxy-D-glucose (2DG: [48]) to determine if they share similar circuitry [16]. Both MA and 2DG administration elicit c-fos responses in the nucleus of the solitary tract, lateral parabrachial nucleus, central nucleus of the amygdala and the dorsal motor nucleus of the vagus [27], and elevate sympathoadrenal plasma levels of epinephrine and norepinephrine [34]. However, MA-induced and 2DG-induced feeding show different sensitivities to vagotomy [32], capsaicin treatment [31], brain lesions [13,24,28], peripheral responses [30], interoceptive sensory signals [10], and macronutrient selection [29,35,36,38].

Within a given species, substantial inter-individual variability in ingestive responses has been demonstrated, and is often associated with genetic variance (e.g., see review: [26]). In the mouse, for example, strain differences have been reported for the

* Corresponding author. Department of Psychology, Queens College, CUNY, 65-30 Kissena Blvd., Flushing, NY 11367, USA. Tel.: +1 718 997 3543; fax: +1 718 997 3257.
E-mail address: Richard.Bodnar@qc.cuny.edu (R.J. Bodnar).

0031-9384/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.physbeh.2006.05.003

intake of salts (e.g., [2,6,7,9,44]), bitter tastants (e.g., [6,11,44]), fats (e.g., [5,43]), saccharin (e.g., [11,14,23,26,44]), sucrose (e.g., [4,11,18,21,23,25]) and food and water [3]. Our laboratory [21] found differences in the threshold, magnitude and kilocalories in sucrose (0.0001–20%) intake among 11 inbred and one outbred strains in two-bottle 24-h preference tests such that A/J, C57BL/6J, C57BL/10J, CD-1 and SWR/J strains consumed the greatest amounts (11.6–22 ml) and percentages of kilocalories (44–56%) of sucrose. Correspondingly, AKR/J, CBA/J, C3H/HeJ and DBA/2J strains consumed lesser amounts (6.9–7.9 ml) and percentages of kilocalories (20–30%) of sucrose. We [22] subsequently used a similar strategy in assessing strain differences in the magnitude of intake across four 2DG doses (200–800 mg/kg) and test times (1–4 h). Orderly strain-specific and dose-dependent increases in 2DG-induced feeding were observed in outbred and inbred mouse strains with the greatest effects noted for CD-1 and DBA/2J mice. Whereas BALB/cJ, SJL/J, 129P3/J, CBA/J and AKR/J) mice displayed moderate levels of 2DG-induced feeding, 2DG elicited limited increases (C57BL/6J and C3H/HeJ mice), no changes (C57BL/10J mice), and actual reductions (SWR/J mice) in intake in other mouse strains. Further, rat strains differentially susceptible to dietary obesity show similar responses to 2DG-induced feeding, but MA is more effective in eliciting feeding in diet-susceptible relative to diet-resistant strains [37].

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 [17], which can then be used to map chromosomal regions and potentially genes that contribute to complex traits. This general mapping approach has been applied to differences in the intake of fat, carbohydrate, bitter tastants, saccharin, sucrose, and total kilocalorie intake [11,43]. Thus, identification of QTLs associated with variability in ingestive behaviors like lipoprivation is an important first step in the genetic dissection of obesity, and 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 response variability is associated with genetic variability.

To begin to provide for the genetic analyses of MA-induced feeding, the present study surveyed the same 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 used in our previous studies [21,22] for feeding responses across a wide range of previously determined effective systemic MA doses (5, 35, 70, 100 mg/kg) and test times (1–4 h). The order of MA doses was controlled by exposing half of the mice of each strain to an ascending dose order and the remainder to a descending dose order.

2. Methods

2.1. Subjects

Outbred (CD-1, Charles River Laboratories, Wilmington, MA; $n=10$) 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 1 week in group (5 per cage) housing. Then, each animal was housed individually in plastic cages (30×20×15 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 (Purina 5015 Mouse Diet, 5.3 kcal/g) and water available ad libitum.

2.2. MA 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 chow 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 4 days of baseline data collection in which pre-weighed food pellets were placed on the grid floor, and cumulative 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 MA (Sigma Chemical Company, St. Louis, MO: 5, 35, 70 and 100 mg/kg, ip) at 4–6 h into the light cycle. MA was dissolved fresh in distilled water at concentrations of 0.5, 3.5, 7 and 10 mg/ml and injected intraperitoneally in a 10 ml/kg volume. The interval between each injection was minimally 72 h, and maximally after 1 week. Half of the mice of each strain were tested in an ascending MA dose order, and the remaining half were tested in a descending order.

2.3. Statistics

Alterations in cumulative MA-induced feeding relative to vehicle 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 MA 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 food intake following vehicle treatment across the 4 h time course (Vehicle Intake, Table 1), Tukey comparisons ($P<0.05$) were performed in the presence of significant effects only relative to corresponding vehicle values within strains. A subsequent separate three-way randomized-block analysis of variance was performed on MA difference scores in which each intake value at effective time points (2 and 4 h) following vehicle in each animal in each strain was subtracted from each corresponding MA dose value with the 12 strains as the between-subject variable, the four MA dose conditions as a within-subject variable, and the two later (2–4 h) intake times as a second within-subject variable. Additionally, percent change of food intake after 4 h following each of the MA doses relative to corresponding vehicle values was calculated for each animal. A separate two-way randomized-block analysis of variance was performed on

Table 1
Food intake difference scores (g, ±S.E.M., minus vehicle values) relative to vehicle baseline intake, and percentage change over vehicle baseline intake 4 h following MA in 12 mouse strains

MA dose/strain	Vehicle intake (4 h)	Measures	5 mg/kg	35 mg/kg	70 mg/kg	100 mg/kg
A/J	0.59 (0.09)	Diff. Score % Veh	−0.11 (0.07) 15% ↓	0.00 (0.14) 29%	+0.04 (0.04) 19% ↑	−0.01 (0.10) 0%
AKR/J	0.80 (0.06)	Diff. Score % Veh	+0.02 (0.11) 1% ↓	+0.30[a] (0.12) 28%↑	+0.38[a] (0.19) 57% ↑	+0.04 (0.17) 16% ↑
BALB/cJ	0.73 (0.11)	Diff. Score % Veh	−0.13 (0.16) 22% ↓	+0.17 (0.12) 19% ↑	+0.02 (0.10) 2% ↑	+0.07 (0.11) 6% ↑
C57BL/6J	0.40 (0.05)	Diff. Score % Veh	−0.13 (0.09) 24% ↓	+0.12 (0.10) 42% ↑	+0.00 (0.07) 0%	+0.22[a] (0.11) 66% ↑
C57BL/10J	0.66 (0.09)	Diff. Score % Veh	+0.29 (0.18) 44% ↑	+0.22 (0.13) 39% ↑	+0.10 (0.07) 32% ↑	+0.08 (0.13) 22% ↑
CBA/J	0.58 (0.05)	Diff. Score % Veh	+0.05 (0.12) 24% ↑	+0.14 (0.09) 31% ↑	+0.03 (0.08) 7% ↑	−0.07 (0.07) 11% ↓
CD-1	1.01 (0.13)	Diff. Score % Veh	+0.08 (0.13) 3% ↑	+0.16 (0.22) 30% ↑	+0.59[a] (0.16) 63% ↑	+0.65[a] (0.21) 60% ↑
C3H/HeJ	0.42 (0.07)	Diff. Score % Veh	+0.37[a] (0.17) 80% ↑	−0.17 (0.10) 39% ↓	−0.14 (0.07) 35% ↓	−0.06 (0.10) 2% ↑
DBA/2J	0.84 (0.11)	Diff. Score % Veh	+0.17 (0.14) 37% ↑	+0.47[a] (0.06) 63% ↑	+0.33[a] (0.10) 55% ↑	+0.61[a] (0.18) 103% ↑
SJL/J	0.78 (0.06)	Diff. Score % Veh	+0.04 (0.06) 8% ↑	+0.18 (0.09) 22% ↑	+0.11 (0.12) 21% ↑	+0.08 (0.10) 10% ↑
SWR/J	0.69 (0.08)	Diff. Score % Veh	−0.07 (0.06) 17% ↓	+0.06 (0.07) 9% ↑	+0.21 (0.09) 39% ↑	−0.14 (0.11) 11% ↓
129P3/J	0.58 (0.15)	Diff. Score % Veh	+0.11 (0.17) 164% ↑	+0.06 (0.17) 173% ↑	+0.25 (0.15) 222% ↑	+0.16 (0.14) 183% ↑

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

these values with the 12 strains as the between-subject variable and the four MA dose conditions as the within-subject variable.

Narrow-sense trait heritability was determined by comparing the between-strain variance to the total variance. Since animals are isogenic (i.e., genetically identical) within individual inbred strains, between-strain variance provides a measure of additive genetic ('allelic') variation (VA), whereas within-strain variance ('error variance') represents environmental variability (VE). An estimate of narrow-sense heritability (h^2) for each trait was obtained using the formula: $h^2 = VA/(VA+VE)$ [15]. Since animals in strains were initially chosen randomly, these values are likely accurate estimates of the true trait heritabilities [17].

All correlations of strain means were calculated using Pearson product-moment correlation coefficients (r) subject to Bonferroni correction for multiple comparisons. To assess whether observed differences in vehicle intake were due to enduring strain-specific effects, correlations of strain means at 1, 2 and 4 h following vehicle treatment in the present study were compared with corresponding vehicle values collected in our previous study evaluating 2DG [22]. Correlations of strain means were also performed among the 4 h difference scores for the four doses of MA-induced intake. Subsequent correlations assessed whether inter-strain differences were observed between lipoprivic responses 4 h following each MA dose in the 12 tested mouse strains with previously determined [22] food intake difference scores elicited by four doses (200–800 mg/kg) of the glucoprivic stimulus, 2DG.

3. Results

Significant differences in cumulative food intake were observed among strains ($F(11,99)=16.74$, $p<0.0001$), among the injection conditions ($F(4,36)=7.30$, $p<0.002$), across test times ($F(2,18)=803.47$, $p<0.0001$), and for the interactions between strains and times ($F(22,198)=8.52$, $p<0.0001$) and among strains, conditions and times ($F(88,792)=2.04$, $p<0.0001$), but not between strains and conditions ($F(44,336)=3.01$, $p>0.07$) or conditions and times ($F(8,72)=2.05$, $p>0.053$). Significant differences in short-term vehicle cumulative intake were observed across strains ($F(11,99)=5.76$, $p<0.0001$), across test times ($F(2,18)=490.63$, $p<0.0001$) and for the interaction between strains and times ($F(22,198)=2.75$, $p<0.0001$). Table 1 summarizes the strain-specific differences in cumulative vehicle intake with CD-1 mice consuming the greatest amount (~1 g/4 h) followed by DBA/2J, AKR/J, SJL/J and BALB/cJ mice (~0.7–0.8 g/4 h), C57BL/10J and SWR/J mice (~0.6 g/4 h), A/J, CBA/J and 129P3/J (~0.5 g/4 h) and finally C57BL/6J and C3H/HeJ mice (~0.4 g/4 h). Correlations of strain means for vehicle intakes in the present and our previous glucoprivation study [22] revealed that significant relationships among strains failed to be observed for vehicle intakes after 1 ($r=0.32$), 2 ($r=0.21$) or 4 ($r=0.38$) h in the two studies. This suggests that short-term differences in light cycle intake among strains are probably due to simple inter-animal variability rather than systematic strain-specific effects.

Significant differences in the difference scores for cumulative MA-induced intake were observed among strains ($F(11,99)=3.03$, $p<0.0016$), among MA doses ($F(3,27)=3.39$, $p<0.032$), across the two test times ($F(1,9)=5.31$, $p<0.047$), and for the interactions between strains and times ($F(11,99)=3.38$, $p<0.0005$) and among strains, doses and times ($F(33,297)=1.51$, $p<0.041$), but not between strains and doses ($F(33,297)=2.64$, $p>0.14$) and doses and times ($F(3,27)=1.09$, $p>0.41$). There were clear strain differences in the magnitude and pattern of MA-induced intake relative to corresponding vehicle conditions. MA produced significant dose-dependent increases in cumulative food intake following each of the three highest (35 (4 h), 70 (4 h), 100 (2–4 h) mg/kg) doses in DBA/2J mice (Fig. 1I), following each of the two highest (70–100 mg/kg, 4 h) doses in CD-1 mice (Fig. 1G), and following each of the two middle (35 (4 h)–70 (1–4 h) mg/kg) doses in AKR/J mice (Fig. 1B). MA produced significant dose-specific increases in food intake following only the lowest (5 mg/kg) dose in C3H/HeJ (1–4 h) mice (Fig. 1H), following only the lower middle (35 mg/kg) dose in BALB/cJ (2 h) and CBA/J (1–2 h) mice (Fig. 1C and F), following only the high middle (70 mg/kg) dose in SJL/J (2 h) and SWR/J (1–2 h) mice (Fig. 1J and K), and following only the highest (100 mg/kg) dose in C57BL/6J (4 h) mice (Fig. 1D). In contrast, MA failed to significantly increase food intake in A/J, C57BL/10J and 129P/3J mice (Fig. 1A, E, and L). Table 1 also summarizes the food intake difference scores 4 h following each MA dose in the 12 tested mouse strains, allowing for inter-strain

comparisons across MA doses. Thus, DBA/2J mice displayed significantly greater magnitudes of MA-induced feeding following the 100 mg/kg dose than all other inbred strains, following the 70 mg/kg dose than A/J, BALB/cJ, CBA/J, C57BL/6J and C3H/HeJ mice, and following the 35 mg/kg dose than A/J, BALB/cJ, CBA/J, C57BL/6J, C3H/HeJ, CD-1, SJL/J, SWR/J and 129P/3J mice. CD-1 mice displayed significantly greater magnitudes of MA-induced feeding following the 100 mg/kg dose than all other inbred (except DBA/2J) strains and following the 70 mg/kg dose than A/J, BALB/cJ, CBA/J, C57BL/6J, C57BL/10J, C3H/HeJ, SJL/J, SWR/J and 129P/3J mice. AKR/J mice displayed significantly greater magnitudes of MA-induced feeding following the 70 mg/kg dose than all other inbred (except C3H/HeJ and DBA/2J) strains and following the 35 mg/kg dose than A/J and C3H/HeJ mice. C57BL/6J mice displayed significantly greater magnitudes of MA-induced feeding following the 100 mg/kg dose

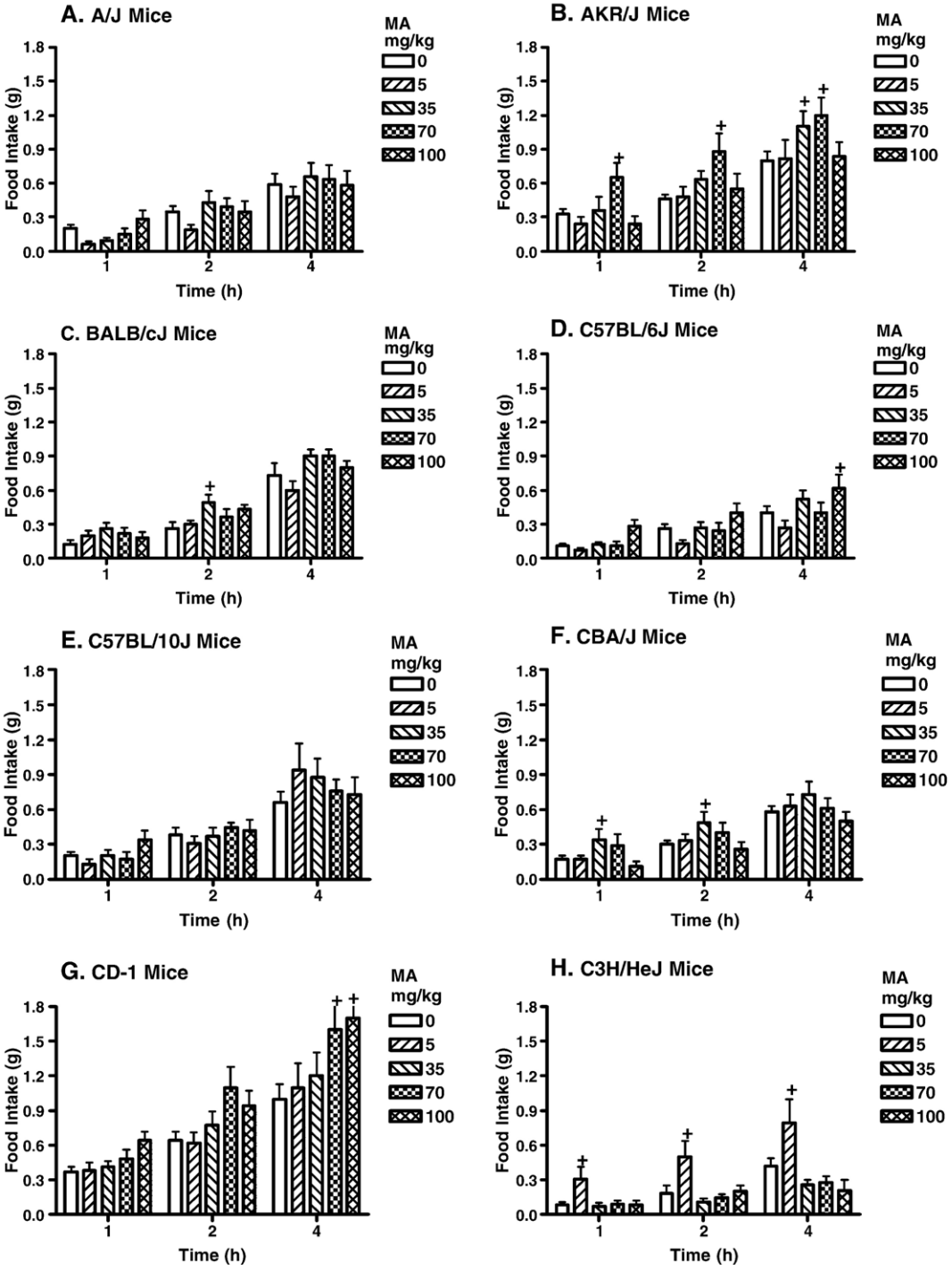

Fig. 1. Cumulative food intake (g, ±S.E.M.) following four doses of mercaptoacetate (MA) in 12 mouse strains over 4 h. Ordinates are identical to facilitate interstrain comparisons. The crosses (+) denote significant alterations in food intake relative to the corresponding vehicle value obtained within each strain (Tukey comparisons, $P<0.05$).

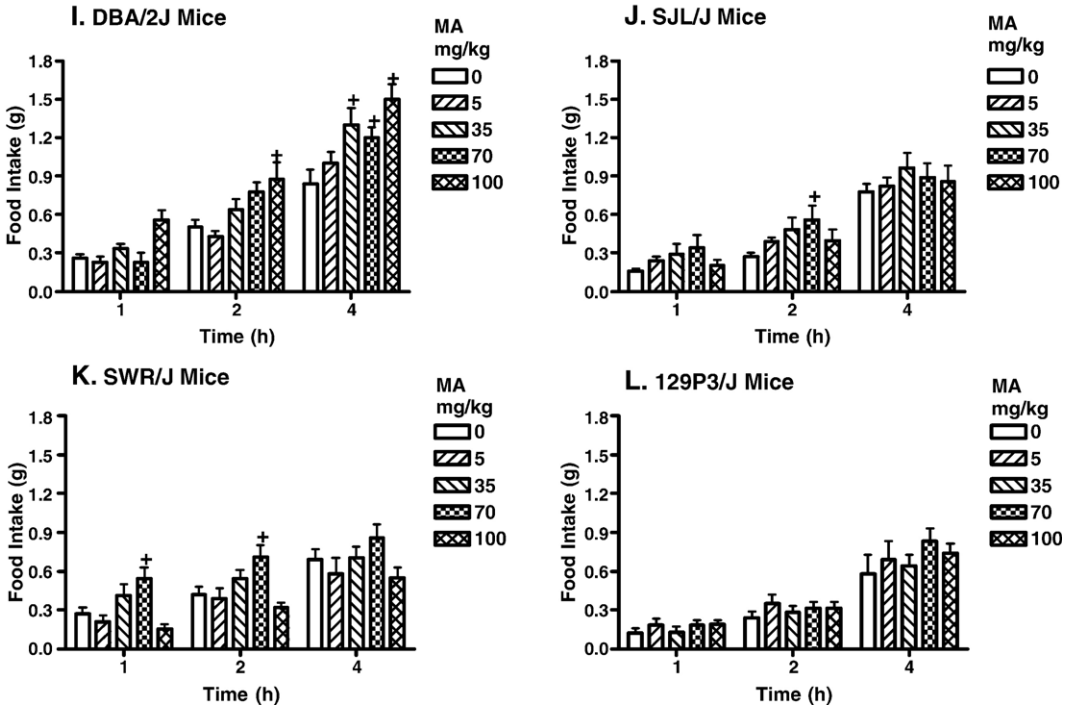

Fig. 1 (*continued*).

than C3H/HeJ, CBA/J and SWR/J mice. Significantly greater magnitudes of MA-induced feeding following the 70 mg/kg dose were observed in SJL/J mice relative to C3H/HeJ and C57BL/6J mice, and in SWR/J mice relative to A/J, C3H/HeJ and C57BL/6J mice. Significantly greater magnitudes of MA-induced feeding following the 35 mg/kg dose were observed in BALB/cJ and CBA/J mice relative to C3H/HeJ mice. Finally, significantly greater magnitudes of MA-induced feeding following the 5 mg/kg dose were observed in C3H/HeJ mice relative all other strains except 129P/3J mice.

Evaluation of percent change of intake following MA doses relative to vehicle values revealed significant differences among strains ($F(11,99)=2.62$, $p<0.027$), for the interaction between strains and doses ($F(33,297)=2.68$, $p<0.0001$), but not among doses ($F(3,27)=1.63$, $p>0.2$). Table 1 also summarizes the percent change in food intake 4 h following MA doses for all strains. Given that individual 129P/3J mice ate very little (0.1–0.2 g/4 h) under vehicle treatment, some of the MA effects were therefore very pronounced, and this strain showed significantly greater increases relative to all other strains. DBA/2J mice displayed significantly greater increases in the percent change of intake 4 h following the 100 mg/kg dose relative to C3H/HeJ, BALB/cJ, SWR/J, A/J, SJL/J and CBA/J mice. Finally, C3H/HeJ mice displayed significantly greater increases in the percent change of intake 4 h following the 5 mg/kg dose relative to BALB/cJ, C57BL/6J, SWR/J and A/J strains.

Narrow-sense heritability estimates were obtained for 4 h cumulative food intake following only the highest MA dose (100 mg/kg), where more robust genetic effects are to be expected, and they were compared to 4 h cumulative intake following vehicle. The obtained h^2 values were moderately high for both MA (0.37) and vehicle (0.43) values. These values are consistent with calculated heritability estimates obtained in our previous study [22] investigating strain differences in 2DG-induced feeding: 2DG (800 mg/kg at 4 h): $h^2=0.51$; vehicle: $h^2=0.44$. In addition, Table 2 compares food intake difference scores 4 h following each MA dose in the 12 tested mouse strains as well as with previously determined [22] food intake difference scores elicited by the glucoprivic stimulus, 2DG. In analyzing possible relationships among intakes elicited by the MA doses themselves, Bonferroni-corrected pairwise correlations revealed significant effects only between intakes following the two highest (70 and 100 mg/kg) MA doses across all strains. Further, in analyzing possible relationships among intakes elicited by the wide range of four MA doses used in the present study and the wide range of four 2DG doses used previously [22], the pairwise correlations revealed significant effects only between intakes following the highest (100 mg/kg) MA dose and a moderate (400 mg/kg) 2DG dose.

Table 2
Pearson product–moment correlation coefficients for the strain means of difference scores for food intake after 4 h across the 11 inbred and one outbred mouse strains subtracted from corresponding vehicle values after the four MA doses, and as compared with previously derived and published four 2-deoxy-D-glucose (2DG) doses[a]

MA (mg/kg)	5	35	70	2DG[a] (mg/kg)	200	400	600	800
MA 5	–				+0.21	−0.14	+0.03	−0.01
MA 35	−0.07	–			+0.18	+0.18	+0.45	−0.09
MA 70	−0.30	+0.55	–		+0.10	+0.19	+0.34	+0.02
MA 100	+0.13	+0.55	+0.68*		+0.57	+0.66*	+0.55	+0.14

Significant correlation (*$p<0.05$) after Bonferroni corrections.
[a] Data derived from [22].

4. Discussion

First, to our knowledge, this is the first demonstration that outbred CD-1 mice significantly and dose-dependently increase their food intake following the free fatty acid oxidation inhibitor, MA in the same manner as observed for outbred rats [19,33]. As with different rat strains [37], strain-specific effects for MA-induced feeding were observed that varied as functions of post-injection test time and MA dose. Any dose-dependent effect of MA is important given the fact that the ingestive responses elicited by only the two highest MA doses significantly correlated with each other across strains. Moreover, moderately high heritability estimates were observed for intake following the largest MA dose (h^2=0.37) and vehicle (h^2=0.43). To this end, orderly and significant dose-dependent increases in food intake were observed following the three highest (35–100 mg/kg) MA doses in inbred DBA/2J mice and the two highest (70–100 mg/kg) doses in outbred CD-1 mice. Dose-specific increases in intake were observed following the two middle (35–70 mg/kg) MA doses in AKR/J mice, only the 5 mg/kg MA dose in C3H/HeJ mice, only the 35 mg/kg MA dose in BALB/cJ and CBA/J mice, only the 70 mg/kg dose in SJL/J and SWR/J mice, and only the 100 mg/kg dose in C57BL/6J mice. In contrast, MA failed to significantly increase food intake at any dose in this wide range in A/J, C57BL/10J and 129P/3J mice. The demonstration of genotype-dependent variability in this lipoprivic response may provide the basis for the subsequent identification of trait-relevant genes.

The intake of dietary fat also systematically varies as a function of genetic predisposition among a host of other variables (see review: [47]) and has led to the identification of dietary resistance and susceptibility phenotypes in inbred and outbred strains of mice (e.g., [42,45,46]). Thus, moderate intake of high-fat diets of shortening, lard or powder promoted weight gain and obesity in AKR/J mice, yet large intake of a high-fat diet was not accompanied by weight gain in SWR/J mice. Notably, AKR/J mice showed significantly increases in food intake following 35 and 70 mg/kg MA doses, and SWR/J mice displayed MA-induced feeding only following the 70 mg/kg dose. Indeed, whereas AKR/J and C57BL/6J mice self-selected the highest proportion of fat in macronutrient diet selection with ependymal fat correlating with fat consumption, SWR/J strains consumed a great deal of fat that was inversely correlated with ependymal fat [39]. Although AKR/J and C57BL/6J mice responded similarly in this latter study, the C57BL/6J strain displayed a very muted feeding response following MA in the present study. Moreover, whereas the diet-sensitive AKR/J and DBA/2J strains consumed greater amounts of fat, displayed more adiposity and displayed elevated levels of leptin and insulin, the C57BL/6J strain showed an equal preference between protein and fat, and displayed normal insulin and leptin levels [1] Interestingly, both DBA/2J and AKR/J strains displayed greater feeding sensitivity to MA relative to C57BL/6J mice. In contrast, obesity-resistant SWR/J and A/J mice consume more fat than carbohydrate, but fail to gain weight, potentially because of lower insulin levels, increased capacity of skeletal muscle to metabolize fat, enhanced paraventricular galanin, and reduced arcuate NPY [20]. Of importance was the inability of A/J mice to increase food intake at any time point following any of the MA doses. Thus, there appears to be no overall clear picture in which strain differences fully explain lipoprivic responses on the one hand, and predict fat intake on the other hand.

Functional comparisons between lipoprivic feeding induced by MA and glucoprivic feeding induced by 2DG have been examined previously. One similarity between these ingestive responses is that each elicit c-fos responses in the nucleus of the solitary tract, lateral parabrachial nucleus, central nucleus of the amygdala and the dorsal motor nucleus of the vagus [27]. Sympathoadrenal plasma levels of epinephrine and norepinephrine are also elevated by 2DG and MA respectively [34]. However, there are differences in sensitivity to different physiological manipulations with MA-induced feeding reduced to a far greater degree than 2DG-induced feeding by vagotomy [32], destruction of visceral sensory neurons with capsaicin [31], lesions placed in the lateral parabrachial nucleus [13] or the central nucleus of the amygdala [28] or administration of the beta-2-adrenoceptor agonist, salbutamol [24]. 2DG, but not MA, increases c-fos responses in the adrenal medulla and sympathetic preganglionic spinal cord neurons [30] and elicits interoceptive sensory signals similar to that of food deprivation [10]. Whereas 2DG stimulates intake of all three macronutrients, MA reliably stimulates protein, but not fat intake, and stimulates carbohydrate intake only when carbohydrate palatability is enhanced [29,38]. A wider range of intravenous nutrients reduces feeding induced by MA (glucose, lipid, fructose) relative to 2DG (glucose) [35], and intraventricular glucose reduces feeding responses following 2DG, but not MA [36]. Finally, rat strains differentially susceptible to dietary obesity show similar responses to 2DG-induced feeding, but MA is more effective in eliciting feeding in diet-susceptible relative to diet-resistant strains [37]. In analyzing possible relationships among intakes elicited by the wide dose ranges of MA and 2DG, the present study only found significant correlations between intakes across strains following the highest (100 mg/kg) MA dose and a moderate (400 mg/kg) 2DG dose, and not for any other pair. Thus, the differences among diverse genotypic mouse strains in their ingestive responses to lipoprivation induced by MA) and glucoprivation induced by 2DG support the notion that they employ different neural circuitry and indeed provide evidence that the two responses operate via only partially overlapping genetic mechanisms of action.

Acknowledgements

This research was supported in part by a CUNY Collaborative Grant (80209-03-09) to BK and RJB. CD is a CUNY Chancellor's Fellow. We thank the two anonymous reviewers for their helpful and constructive comments.

References

[1] Alexander J, Chang GQ, Dourmashkin JT, Leibowitz SF. Distinct phenotypes of obesity-prone AKR/J, DBA/2J and C57BL/6J mice compared to control strains. Int J Obesity 2006;30:50–9.

[2] Bachmanov AA, Beauchamp GK, Tordoff MG. Voluntary consumption of NaCl, KCl, $CaCl_2$, and NH_4Cl solutions by 28 mouse strains. Behav Genet 2002;32:445–57.

[3] Bachmanov AA, Reed DR, Beauchamp GK, Tordoff MG. Food intake, water intake, and drinking spout side preference of 28 mouse strains. Behav Genet 2002;32:435–43.
[4] Bachmanov AA, Reed DR, Ninomiya Y, Inoue M, Tordoff MG, Price RA, et al. Sucrose consumption in mice: major influence of two genetic loci affecting peripheral sensory responses. Mamm Genome 1997;8:545–8.
[5] Bachmanov AA, Reed DR, Tordoff MG, Price RA, Beauchamp GK. Nutrient preference and diet-induced adiposity in C57BL/6J and 129P3/J mice. Physiol Behav 2001;72:603–13.
[6] Bachmanov AA, Schlager G, Tordoff MG, Beauchamp GK. Consumption of electrolytes and quinine by mouse strains with different blood pressures. Physiol Behav 1998;64:323–30.
[7] Bachmanov AA, Tordoff MG, Beauchamp GK. Voluntary sodium chloride consumption by mice: differences among five inbred strains. Behav Genet 1998;28:117–24.
[8] Bauche F, Sabourault D, Giudicelli Y, Nordmann J, Nordmann R. 2-mercaptoacetate administration depresses the beta-oxidation pathway through an inhibition of long-chain acyl-CoA dehydrogenase activity. Biochem J 1981;196:803–9.
[9] Beauchamp GK, Fisher AS. Strain differences in consumption of saline solutions by mice. Physiol Behav 1993;54:179–84.
[10] Benoit SC, Davidson TL. Interoceptive sensory signals produced by 24-hr food deprivation, pharmacological glucoprivation, and lipoprivation. Behav Neurosci 1996;110:168–81.
[11] Blizard DA, Kotlus B, Frank ME. Quantitative trait loci associated with short-term intake of sucrose, saccharin and quinine solutions in laboratory mice. Chem Senses 1999;24:373–85.
[12] Booth DA. Modulation of the feeding response to peripheral insulin, 2-deoxy-D-glucose or 3-*O*-methoxyglucose injection. Physiol Behav 1972;8:1069–76.
[13] Calingasan NY, Ritter S. Lateral parabrachial sub-nucleus lesions abolish feeding induced by mercaptoacetate but not by 2-deoxy-D-glucose. Am J Physiol 1993;265:R1168–78.
[14] Capeless CG, Whitney G. The genetic basis of preference for sweet substances among inbred strains of mice: preference ratio phenotypes and the alleles of the Sac and dpa loci. Chem Senses 1995;20:291–8.
[15] Falconer DS, Mackay TFC. Introduction to quantitative genetics. Fourth Edition. Essex, UK: Longman; 1996.
[16] Friedman MI, Tordoff MG. Fatty acid oxidation and glucose utilization interact to control food intake in rats. Am J Physiol 1986;251:R840–5.
[17] Hegmann JP, Possidente B. Estimating genetic correlations from inbred strains. Behav Genet 1981;11:103–14.
[18] Inoue M, Reed DR, Li X, Tordoff MG, Beauchamp GK, Bachmanov AA. Allelic variation of the TasIr3 taste receptor gene selectively affects behavioral and neural taste responses to sweeteners in the F_2 hybrids between C57Bl/6J and 129P3/J mice. J Neurosci 2004;24:2296–303.
[19] Langhans W, Scharrer E. Evidence for a vagally mediated satiety signal derived from hepatic fatty acid oxidation. J Auton Nerv Syst 1987;18:13–8.
[20] Leibowitz SF, Alexander J, Dourmashkin JT, Hill JO, Gayles EC, Chang G-Q. Phenotypic profile of SWR/J and A/J mice compared to control strains: possible mechanisms underlying resistance to obesity on a high-fat diet. Brain Res 2005;1047:137–47.
[21] Lewis SR, Ahmed S, Dym C, Khaimova E, Kest B, Bodnar RJ. Inbred mouse strain survey of sucrose intake. Physiol Behav 2005;85:546–56.
[22] Lewis SR, Khaimova E, Israel Y, Singh A, Kandov Y, Kest B, et al. Genetic variance contributes to ingestive processes: a survey of 2-deoxy-D-glucose-induced feeding in eleven inbred mouse strains. Physiol Behav 2006;87:595–601.
[23] Lush IE. The genetics of tasting in mice. VI. Saccharin, acesulfame, dulcin and sucrose. Genet Res 1989;53:95–9.
[24] Nisoli E, Garosi V, Blundell JE, Carruba MO. Salbutamol antagonizes insulin- and sodium mercaptoacetate-induced but not 2-deoxy-D-glucose-induced hyperphagia. Pharmacol Biochem Behav 1996;54:409–13.
[25] Pothion S, Bizot J-C, Trovero F, Belzung C. Strain differences in sucrose preference and in the consequences of unpredictable chronic mild stress. Behav Brain Res 2004;155:135–46.
[26] Reed DR, Li S, Li X, Huang L, Tordoff MG, Starling-Roney R, et al. Polymorphisms in the taste receptor gene (Tas1r3) region are associated with saccharin preference in 30 mouse strains. J Neurosci 2004;24:938–46.
[27] Ritter S, Dinh TT. 2-Mercaptoacetate and 2-deoxy-D-glucose induce fos-like immunoreactivity in rat brain. Brain Res 1994;641:111–20.
[28] Ritter S, Hutton R. Mercaptoacetate-induced feeding is impaired by central nucleus of the amygdala lesions. Physiol Behav 1995;58:1215–20.
[29] Ritter S, Ritter JB, Cromer L. 2-Deoxy-D-glucose and mercaptoacetate induce different patterns of macronutrient ingestion. Physiol Behav 1999;66:709–15.
[30] Ritter S, Scheurink A, Singer LK. 2-Deoxy-D-glucose but not 2-mercaptoacetate increases Fos-like immunoreactivity in adrenal medulla and sympathetic preganglionic neurons. Obes Res 1995;3:729S–34S.
[31] Ritter S, Taylor JS. Capsaicin abolishes lipoprivic but not glucoprivic feeding in rats. Am J Physiol 1989;256:R1232–9.
[32] Ritter S, Taylor JS. Vagal sensory neurons are required for lipoprivic but not glucoprivic feeding in rats. Am J Physiol 1990;258:R1395–401.
[33] Scharrer E, Langhans W. Control of food intake by fatty acid oxidation. Am J Physiol 1986;250:R1003–6.
[34] Scheurink A, Ritter S. Sympathoadrenal responses to glucoprivation and lipoprivation in rats. Physiol Behav 1993;53:995–1000.
[35] Singer LK, Ritter S. Differential effects of infused nutrients on 2-deoxy-D-glucose- and 2-mercaptoacetate-induced feeding. Physiol Behav 1994;56:193–6.
[36] Singer LK, Ritter S. Intraventricular glucose blocks feeding induced by 2-deoxy-D-glucose but not mercaptoacetate. Physiol Behav 1996;59:921–3.
[37] Singer LK, York DA, Bray GA. Feeding responses to mercaptoacetate in Osborne–Mendel and S5B/PL rats. Obes Res 1997;5:587–94.
[38] Singer LK, York DA, Bray GA. Macronutrient selection following 2-deoxy-D-glucose and mercaptoacetate administration in rats. Physiol Behav 1998;65:115–21.
[39] Smith BK, Andrews PK, West DB. Macronutrient diet selection in thirteen mouse strains. Am J Physiol 2000;278:R797–805.
[40] Smith GP, Epstein AN. Increased feeding response to decreased glucose utilization in the rat and monkey. Am J Physiol 1969;217:R1083–7.
[41] Smith GP, Root AW. Effect of feeding on hormonal responses to 2-deoxy-D-glucose in conscious monkeys. Endocrinology 1969;85:963–6.
[42] Smith-Richards BK, Andrews PK, York DA, West DB. Divergence in proportional fat intake in AKR/J and SWR/J mice endures across diet paradigms. Am J Physiol 1999;277:R776–85.
[43] Smith-Richards BK, Belton BN, Poole AC, Mancuso JJ, Churchill GA, Li R, et al. QTL analysis of self-selected macronutrient diet intake: fat, carbohydrate and total kilocalories. Physiol Genomics 2002;11:205–17.
[44] Tordoff MG, Pilchak DM, Williams JA, McDaniel AH, Bachmanov AA. The maintenance diets of C57BL/6J and 129/J mice influence their taste solution preferences: implications for large-scale phenotyping projects. J Nutr 2002;132:2288–97.
[45] West DB, Boozer CN, Moody DL, Atkinson RL. Obesity induced by a high-fat diet in nine strains of inbred mice. Am J Physiol 1992;262:R1025–32.
[46] West DB, Waguespack J, McCollister S. Dietary obesity in the mouse: interaction of strain with diet composition. Am J Physiol 1995;268:R658–65.
[47] West DB, York B. Dietary fat, genetic predisposition, and obesity: lessons from animal models. Am J Clin Nutr 1998;67:505S–12S.
[48] Wick AN, Drury DR, Nakada HI, Wolfe JB. Localization of the primary metabolic block produced by 2-deoxy-D-glucose. J Biol Chem 1957;224:963–9.