

Genetic variance contributes to ingestive processes: A survey of eleven inbred mouse strains for fat (Intralipid) intake

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Abstract

Genetic variation across inbred and outbred mouse strains have been observed for intake of sweet solutions, salts, bitter tastants and a high-fat diet. Our laboratory recently reported marked strain differences in the amounts and/or percentages of kilocalories of sucrose consumed among 11 inbred and one outbred mouse strains exposed to a wide range of nine sucrose concentrations (0.0001–5%) in two-bottle 24-h preference tests. To assess whether differences in fat intake were similarly associated with genetic variation, the present study examined intake of chow, water and an emulsified fat source (Intralipid) across nine different concentrations (0.00001–5%) in the same 11 inbred and 1 outbred mouse strains using two-bottle 24-h preference tests, which controlled for Intralipid concentration presentation effects, Intralipid and water bottle positions, and measurement of kilocalorie intake consumed as Intralipid or chow. Strains displayed differential increases in Intralipid intake relative to corresponding water with significant effects observed at the seven (BALB/cJ: 0.001% threshold sensitivity), four (AKR/J, C57BL/6J, DBA/2J, SWR/J: 0.5% threshold sensitivity), three (CD-1, C57BL/10J, SJL/J: 1% threshold sensitivity) and two (A/J, CBA/J, C3H/HeJ, 129P3/J: 2% threshold sensitivity) highest concentrations. In assessing the percentage of kilocalories consumed as Intralipid, SWR/J mice consumed significantly more at the three highest concentrations to a greater degree than BALB/cJ, C57BL/6J, CD-1, C3H/HeJ, DBA/J and 129P3/J strains which in turn consumed more than A/J, AKR/J, CBA/J, C57BL/10J and SJL/J mice. Relatively strong ($h^2=0.73-0.79$) heritability estimates were obtained for weight-adjusted Intralipid intake at those concentrations (0.001–1%) that displayed the largest strain-specific effects in sensitivity to Intralipid. The identification of strains with diverging abilities to regulate kilocalorie intake when presented with high Intralipid concentrations may lead to the successful mapping of genes related to hedonics and obesity.

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1. Introduction

Systematic analyses of rodent strain differences are important sources regarding the genetic control of all aspects of ingestive behavior (see review: [32]). These studies indicate widespread strain-dependent (i.e., genetic) variance in food, water and mineral intake as well as spout side preference [2,3]. Particular orosensory stimuli such as salts (e.g., [2,6–8,39]), bitter tastants

(e.g., [6,9,11,14,16,25,39]), saccharin (e.g., [9,10,13,20,26–29,33,39]), and sucrose (e.g., [4,9,20,23,26,30,31,38]) are also subject to intake differences among strains. In addition, these studies help to identify strains with divergent sensitivities for subsequent QTL analyses to localize chromosomal regions, and ultimately genes, critically involved in such differences [17].

Differences in dietary fat intake are also associated with genetic variation (see review: [45]) and have led to identification of dietary resistance and susceptibility in inbred and outbred strains of rats (e.g., [22,34]) and mice (e.g., [41,43]). The latter studies identified particular strains in which moderate intake of a high-fat diet promoted weight gain and obesity (e.g., AKR/J mice), and other strains in which large intake of the high-fat diet

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was not accompanied by weight gain (e.g., SWR/J). Moreover, such weight effects were largely due to variation in the dietary fat content, but this variable weakly correlated with total energy intake. These particular strains displayed similar effects whether the fat source was shortening, lard or granular, and whether the high- and low-fat diets were isocaloric [36]. Indeed, whereas AKR/J and C57BL/6J mice self-selected the highest proportion of fat in macronutrient diet selection with epididymal fat correlated with fat consumption, SWR/J and CAST/Ei strains consumed fat that was inversely correlated with epididymal fat [35]. Moreover, whereas the diet-sensitive AKR/J and DBA/2J strains consumed more 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]. 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 [21]. Our laboratory [24] found genetic variance in the sensitivity and magnitude of feeding responses of mouse strains exposed to the free fatty acid oxidation inhibitor, mercaptoacetate. Thus, inbred DBA/J and outbred CD-1 mice were the most sensitive to mercaptoacetate-induced feeding, whereas mercaptoacetate failed to significantly increase food intake in A/J, C57BL/10J and 129P3/J mice. A series of genetic loci were mapped to explain some of these genetic variations for fat and obesity (e.g., [5,12,37,40,42,44]). Because the above studies used solid fat sources (e.g., shortening, lard, granular), it is therefore relatively difficult to systematically manipulate the amount of fat in the diet over a wide concentration range in short-term intake tests to determine if differences in sensitivity may account for some of the observed genetic variance.

Our laboratory [23] recently reported on a number of factors potentially involved in murine genetic variance in sucrose intake among 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, thereby allowing for the valid estimation of genetic correlations [16]. Intake across a range of nine different sucrose concentrations (0.0001–20%) was compared with water intake in two-bottle 24-h preference tests which importantly controlled for order effects by exposing half of the mice to an ascending concentration order and the remainder to a descending concentration order [15]. Bottle positions of the sucrose and water bottles were also systematically switched across animals and across strains, another demonstrably important variable [3]. Additionally, chow intake was measured in order to determine strain differences in kilocalorie intake as a function of sucrose relative to chow. A/J, C57BL/6J, CD-1 and SWR/J strains consumed the greatest (11.6–22 ml) amount of sucrose, whereas the A/J, C57BL/10J, SJL/J and SWR/J strains consumed the greatest (44–56%) percentages of kilocalories as sucrose. The AKR/J, CBA/J, C3H/HeJ and DBA/2J strains consumed the least (6.9–7.9 ml) amount of sucrose and displayed lower (20–30%) percentages of kilocalories consumed as sucrose. Whereas A/J, C57BL/6J,

C57BL/10J, CD-1, SWR/J and SJL/J strains all displayed the most pronounced compensatory decreases in chow intake as the percentage of kilocalories consumed as sucrose increased, the AKR/J, C3H/HeJ and DBA/2J strains failed to significantly alter chow intake even at high sucrose concentrations. Therefore, in this study, the use of liquid sucrose solutions at a wide range of different concentrations allowed for analyses of concentration-dependent differences in sensitivities as a function of murine strain.

Typical difficulties in using different liquefied fat sources presented at different concentrations are their inability to stay in solution over a time course (e.g., 24 h) that is reasonable to study murine intake. Intralipid (Baxter Healthcare Corporation, Deerfield, Illinois) is an emulsified fat solution (20%) made almost exclusively from soybean oil (20 g in 100 ml) and is used clinically for delivery of a fat source to patients. Therefore, the use of Intralipid insures that the fat is equally distributed in solution across a wide range of concentrations, and indeed, Intralipid solutions are readily consumed in a manner similar to sucrose and other palatable solutions (e.g., [18,19]). Therefore, analysis of Intralipid intake across concentrations (0.00001–5%) can potentially parallel our previous use [23] of different sucrose concentrations (0.0001–20%) and can be compared to water intake in two-bottle 24-h preference tests for the study of genetic variance in fat intake. Given that a number of strains evaluated in our previous study [23] display high levels of fat intake with weight gain (e.g., AKR/J, C57BL/6J, DBA/2J: [1,36,41,43]), high levels of fat intake without weight gain (e.g., A/J, SWR/J: [21,35]), and lower levels of fat intake (BALB/cJ, C3H/HeJ SJL/J, 129/J: 1,35) in prior studies, the present study examined these same strains for Intralipid intake across a wide range of concentrations in two-bottle 24 h preference tests using all of the dependent measures assessed previously [23] for sucrose.

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, C57BL/6J, C57BL/10J, DBA/2J, SJL/J, SWR/J, 129P3/J (Jackson Laboratories, Bar Harbor, ME; $n=9-10$ each) male mice (12 weeks of age) were initially acclimated to the Queens College vivarium for their 13th week in group (5 per cage) housing and were maintained on a 12-h light/12-h dark cycle (lights off at 2000 h) at a constant temperature of 22 °C with *ad libitum* access to food and water. Given the large (120 animals across the 12 strains) number of animals involved, it was not possible to test all of them contemporaneously. Therefore, the mice were tested in three sequences of 40 animals each with subgroups ($n=5$) of the inbred strains tested in at least two of the sequences, and subgroups of the outbred strain tested in each of the three sequences. Analyses of their data did not reveal any sequence-specific effects. Each animal was housed individually in plastic cages (30×20×15 cm) during the ensuing 14th week to acclimate them to isolated housing. Animals were then tested

over an approximate 2-week period (weeks 15–17) in the following paradigm.

2.2. Intralipid intake procedure

All procedures were approved by the Queens College Institutional Animal Care and Use Committee. Initially, each animal was provided with a pre-weighed ration (~20 g) of Purina Mouse chow (5.3 kcal/g) and two calibrated and pre-weighed (100 ml capacity, +0.1 g = +0.1 ml; Lab Products, Seaford, DE) sipper tubes each filled with water (~40 ml each). Each animal of each strain was assessed for chow and water intakes from each individual bottle every 24 h over 4 days. Whereas chow spillage was measured and adjustments of intake were made accordingly, there was no systematic measurement of fluid spillage during the experimental protocol, although there was not any malfunction of a sipper tube (resulting in large spillage). To assess whether Intralipid at the lowest (0.00001%) and highest (5%) concentrations as well as water were subject to spillage, we placed these tubes on empty cages and assessed changes in weight of the tubes. This procedure resulted in minimal changes in fluid (<0.1 g) regardless of whether the two Intralipid concentrations or water were measured. It should be noted that this procedure does not control for strain-specific spillage. Body weights of the animals were measured every 3 days throughout the paradigm and the mean body weight was chosen for each animal of each strain for further analysis. The position of the two water bottles were switched across animals and across strains every 24 h according to a left (L)–right (R)–R–L and R–L–L–R position, respectively, to minimize potential bottle position preference effects [3]. Following baseline, every mouse of each strain received chow, one bottle of water and one bottle of Intralipid each day. Nine Intralipid concentrations were diluted from the original 20% concentration and used for testing in these two-bottle preference tests: 0.00001%, 0.0001%, 0.001%, 0.01%, 0.1%, 0.5%, 1.0%, 2.0% and 5.0%. Half of the mice of each strain were tested in an ascending Intralipid concentration order, and the remaining half were tested in a descending order, with Intralipid bottle position systematically controlled [15]. Chow, Intralipid and water intakes (± 0.1 g) were measured daily for each concentration of Intralipid.

2.3. Statistics

One-way analyses of variance were performed to assess whether any pre-existing differences in body weight and in total baseline water intake and chow intakes were observed across strains. To assess sampling of the two water bottles under baseline conditions, a two-way randomized block analysis of variance was also performed with strains as the between-subject variable and water intake from the two bottles as a repeated measure. In assessing alterations in Intralipid relative to water intake, a three-way randomized block analysis of variance was performed with the 12 strains as the between-subject variable, the 10 (baseline and nine Intralipid concentrations) conditions as a within-subject variable, and the intake from the Intralipid

and water bottles as a second within-subject variable. The threshold for or sensitivity to Intralipid for each mouse strain was operationally defined as that lowest concentration which Intralipid intake significantly differed from water. Further, to assess order effects upon Intralipid intake, another set of three-way randomized-block analyses of variance systematically compared within each strain those mice that received an ascending order of Intralipid concentrations with those that received a descending order. Two-way randomized-block analyses of variance were also systematically performed across strains and across Intralipid concentrations to assess changes in the percentage of Intralipid consumed, the total amount of chow intake, and the percentage of kilocalories consumed as Intralipid. Because there were significant differences in body weight across strains (Table 1), two further analyses were performed to adjust intake while accounting for weight and lean body mass. Corresponding to previous analyses performed in our laboratory [23] and elsewhere (e.g., [3]), a two-way randomized block analysis of variance was performed with the 12 strains as the between-subject variable and the 10 conditions as a within-subject variable for transformed Intralipid intake per 30 g of body weight. Given that energy requirements and lean body mass are often normalized to the .75 power, another two-way randomized block analysis of variance was performed with the 12 strains as the between-subject variable and the 10 conditions as a within-subject variable for transformed Intralipid intake normalized to the .75 power. Tukey comparisons ($P < 0.05$) were performed in the presence of significant effects relative to corresponding baseline values within strains.

To assess the consistency of genetic variance across the different Intralipid concentrations for Intralipid intake per se and for the percentage of kilocalories consumed as Intralipid in the 12 tested mouse strains, Pearson product–moment correlation coefficients (r) subject to Bonferroni correction for multiple comparisons were calculated for both measures, examining those Intralipid concentrations (0.5%, 1%, 2% and 5%) producing sizable intake. Correlations were also performed for data from baseline water and chow intakes as well as body weight and compared with previous studies from our [23] and other [3] laboratories. Further, narrow-sense trait heritability was

Table 1
Baseline water (ml, \pm S.E.M.) and chow (g, \pm S.E.M.) intake and body weight (g, \pm S.E.M.) in 12 mouse strains

Strain	Water (ml)	Chow (g)	Body weight (g)
A/J	4.6 (0.2)	3.8 (0.2)	19.6 (0.5)
AKR/J	8.6 (0.2)*	4.1 (0.1)	26.6 (1.0)*
BALB/cJ	7.4 (0.2)	6.7 (0.2)**	23.5 (0.2)
C57BL/6J	4.8 (0.4)	3.6 (0.2)	27.8 (0.8)*
C57BL/10J	6.9 (0.5)	4.8 (0.2)*	22.7 (0.3)
CBA/J	6.7 (0.2)	4.0 (0.2)	22.6 (0.5)
CD-1	9.3 (0.8)*	4.1 (0.4)	37.0 (1.0)**
C3H/HeJ	5.5 (0.2)	4.4 (0.2)	18.5 (1.1)
DBA/2J	6.5 (0.2)	5.3 (0.2)*	23.7 (0.2)
SJL/J	6.6 (0.1)	3.6 (0.2)	21.1 (0.3)
SWR/J	9.2 (0.3)*	3.9 (0.1)	18.3 (0.6)
129P3/J	5.9 (0.4)	5.0 (0.4)*	22.6 (0.4)

* Significantly greater relative to all other unmarked strains in column.

** Significantly greater than * strains in column.

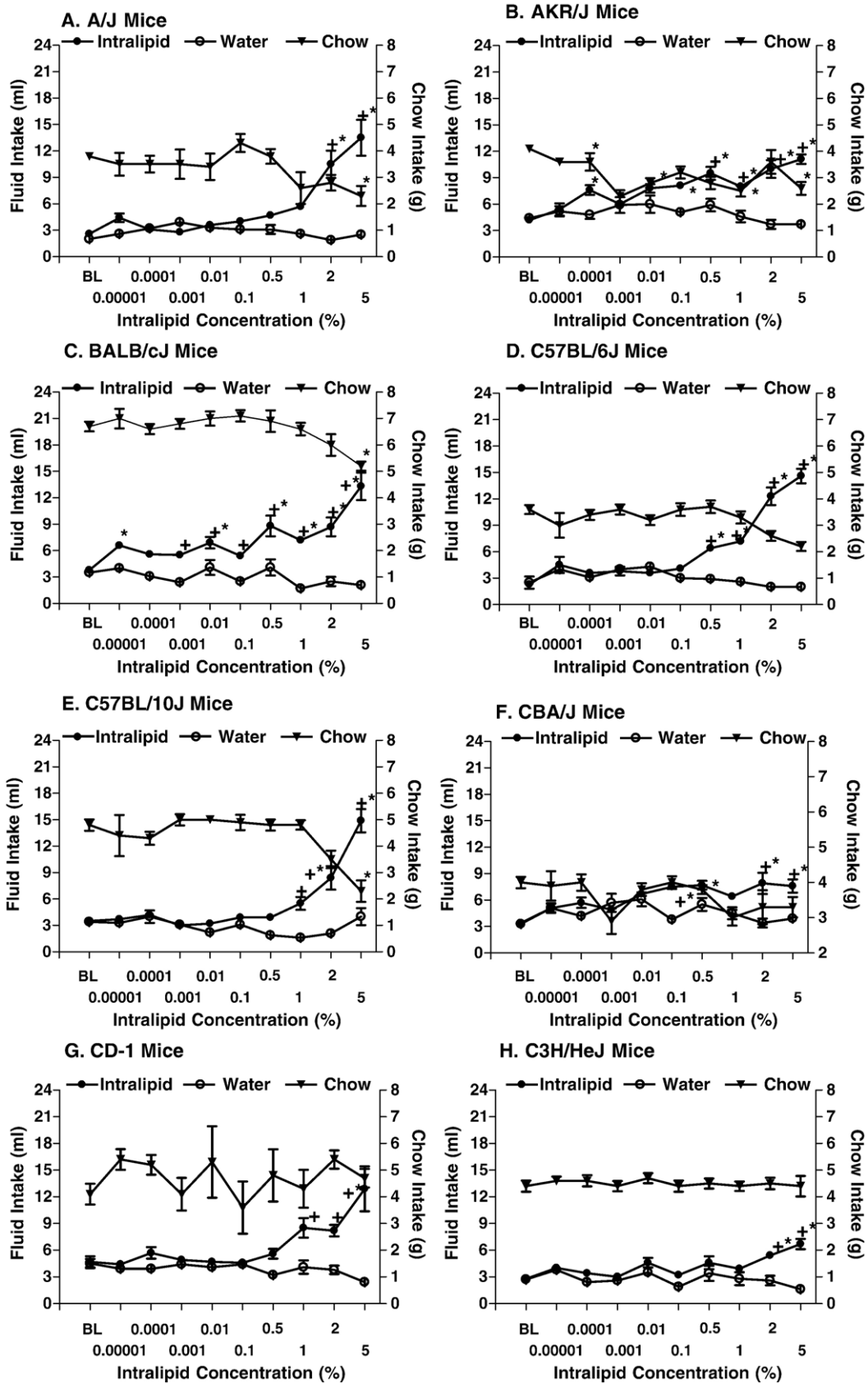


Fig. 1. Alterations in intralipid (left ordinate, mean±S.E.M.), water (left ordinate, mean±S.E.M.) and chow (right ordinate, mean±S.E.M.) intake across baseline and nine different intralipid concentrations in one outbred (CD-1) and eleven inbred (A/J, AKR/J, BALB/cJ, C57BL/6J, C57BL/10J, CBA/J, C3H/HeJ, DBA/2J, SJL/J, SWR/J, 129P3/J) strains of mice. In this and all subsequent figures, the asterisks (*) denote a significant difference in intake relative to corresponding baseline conditions, and the crosses (+) denote a significant difference in sucrose intake relative to corresponding water intake at that concentration (Tukey comparisons, $P<0.05$).

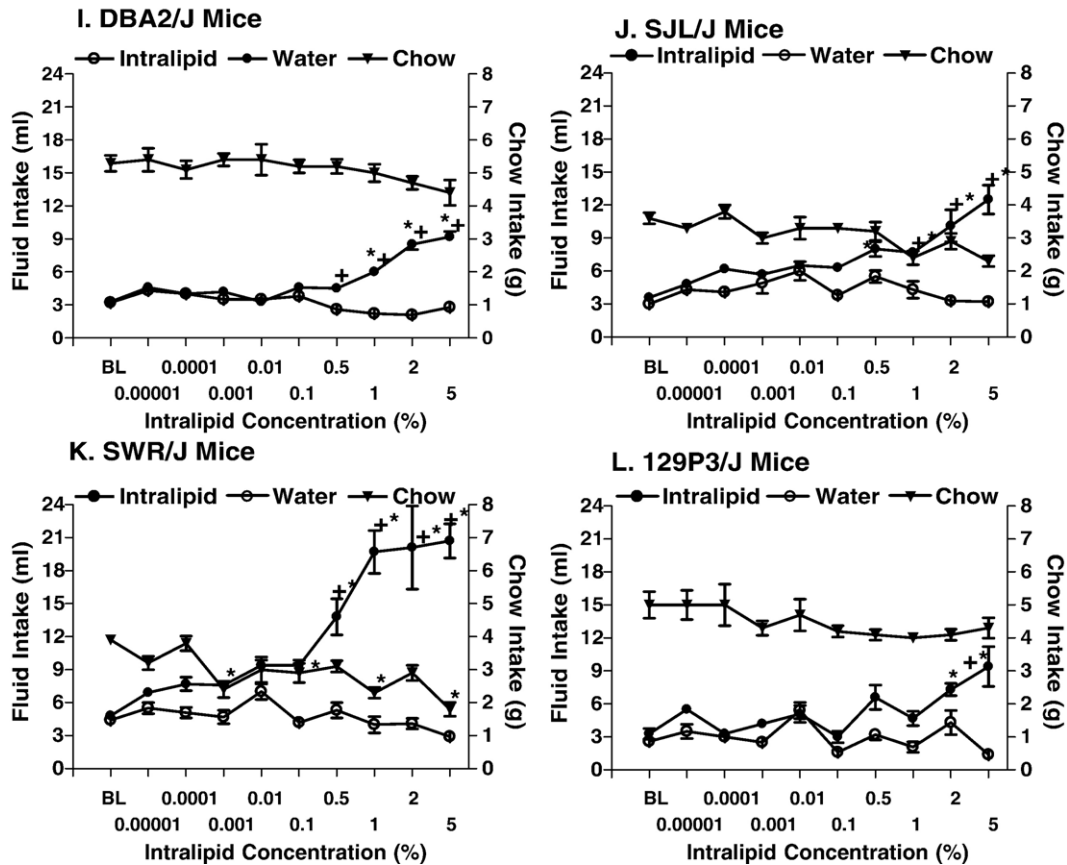


Fig. 1 (continued).

determined by comparing the between-strain variance to the total variance for each concentration of Intralipid in terms of intake itself and intake adjusted for body weight. Because 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: $h^2 = VA / (VA + VE)$ as performed previously [24]. Since animals in strains were initially chosen randomly (by the supplier), these values are likely accurate estimates of the true trait heritabilities.

3. Results

3.1. Baseline values in water and chow intake

Significant differences were observed among mouse strains in total baseline water ($F(11,106)=19.66$, $p<0.0001$) and chow ($F(11,105)=15.71$, $p<0.0001$) intakes. As summarized in Table 1, baseline water intake was greatest in CD-1, SWR/J and AKR/J strains, with significantly less water intake observed in all other strains. Baseline chow intake was greatest in the BALB/cJ strain relative to all other strains with DBA/2J, 129P3/J and C57BL/10J mice consuming significantly greater amounts of chow relative to the remaining strains as well (Table 1). Significant differences were observed among mouse

strains in body weight ($F(11,106)=58.67$, $p<0.0001$). Body weight was significantly greater in CD-1 mice relative to the 11 inbred strains; C57BL/6J and AKR/J in turn weighed significantly more than the remaining nine inbred strains (Table 1). Interestingly, the strain-specific effects upon baseline water intake displayed strong positive correlations with previous studies performed in our ($r=.647$ [23]) and other ($r=.666$ [3]) laboratories; a similar significant pattern of effects ($r=0.77$) was observed for strain-specific body weights in the present and our previous [23] study. In contrast, baseline chow intake in the present study failed to display strain-specific correlations with either our previous [23] or other [3] studies. Analysis of two-bottle baseline water intake revealed significant differences across strains ($F(11,99)=21.28$, $p<0.0001$), for intake for the two fluids ($F(1,9)=7.24$, $p<0.25$), but not for the interaction between strains and fluid choice ($F(11,99)=0.45$, n.s.). Importantly, individual comparisons revealed that all 12 strains displayed similar patterns of sampling of their two water bottles during baseline (BL) testing (Fig. 1), indicating that preferences described for intake of different concentrations of Intralipid were not due to some underlying intra-strain preference for intake from one water bottle relative to the other.

3.2. Intralipid and water intake

In analyzing Intralipid and water intake across strains and Intralipid concentrations, significant differences in intake were

observed among strains ($F(11,99)=46.17$, $p<0.0001$), across concentrations ($F(9,81)=37.03$, $p<0.0001$), between the two fluids ($F(1,9)=303.06$, $p<0.0001$), and for the interactions between strains and concentrations ($F(99,891)=6.84$, $p<0.028$), strains and fluids ($F(11,99)=16.41$, $p<0.0001$), concentrations and fluids ($F(9,81)=145.76$, $p<0.0001$) and among strains, concentrations and fluids ($F(99,891)=4.62$, $p<0.0001$). Significant differences in chow intake were observed among strains ($F(11,110)=43.62$, $p<0.0001$), across concentrations ($F(9,90)=28.70$, $p<0.0001$) and for the interaction between strains and concentrations ($F(99,990)=2.80$, $p<0.0001$). First, it is important to note that systematic analyses of intrastrain differences in Intralipid intake at a given concentration were performed as a function of whether the nine Intralipid concentrations were presented in ascending or descending order. This factor failed to produce significant effects in outbred CD-1 mice and the CBA/J, C3H/HeJ, C57BL/6J, DBA/2J and 129P3/J inbred strains. However, significant order effects were observed for the BALB/cJ (main effect: $F(1,4)=12.18$, $p<0.025$) inbred strain in which mice exposed to the descending order consumed significantly more Intralipid at the 0.1% concentration and less Intralipid at the 0.5%, 2% and 5% concentrations. Significant order effects were observed for the A/J (main effect: $F(1,4)=43.06$, $p<0.003$), AKR/J (main

effect: $F(1,4)=16.62$, $p<0.015$), C57BL/10J (order by concentration interaction: $F(9,36)=9.18$, $p<0.039$), SJL/J (main effect: $F(1,4)=17.52$, $p<0.014$) and SWR/J (order by concentration interaction: $F(9,36)=13.12$, $p<0.022$) inbred strains in which mice exposed to the descending order consumed significantly more Intralipid at the 0.0001% (AKR/J), 0.5% (SJL/J, SWR/J), 1% (AKR/J), 2% (A/J, C57BL/10J, SJL/J, SWR/J) and 5% (A/J) concentrations, thereby indicating the importance of controlling for order effects in concentration presentation [15,23].

Analysis of the sensitivity to low Intralipid concentrations among strains revealed that BALB/cJ mice significantly increased their Intralipid intake relative to their corresponding water intake at all concentrations from 0.001% to 5% (Fig. 1C), thereby displaying the greatest sensitivity (0.001% threshold). Intralipid intake was significantly increased relative to corresponding water intake between concentrations of 0.5–5% in AKR/J, C57BL/6J, DBA/2J and SWR/J inbred strains (Fig. 1B, D, I, and K: 0.5% threshold), of 1–5% in outbred CD-1 and inbred C57BL/10J and SJL/J strains (Fig. 1E, G, and J: 1% threshold), and of 2–5% in A/J, CBA/J, C3H/HeJ and 129P3/J inbred strains (Fig. 1A, F, H, and L: 2% threshold), thereby indicating systematic strain-specific sensitivities to lower Intralipid concentrations.

Table 2

Alterations in Intralipid intake (mean), each corrected for 30 g of body weight, across baseline and nine different sucrose concentrations in one outbred (CD-1) and eleven inbred (A/J, AKR/J, BALB/cJ, C3H/HeJ, C57BL/6J, C57BL/10J, CBA/J, DBA/2J, SJL/J, SWR/J, 129P3/J) strains of mice

Strain	Water*	.00001%	.0001%	.001%	.01%	0.1%	0.5%	1.0%	2.0%	5.0%
A/J	3.97	6.55	4.51	3.98	4.76	5.19	5.92	7.03	12.43+L	15.62+D
AKR/J	4.80	5.95	8.36N	6.55	8.51G	8.54H	9.76+J	8.24	10.28+Q	10.93+
BALB/cJ	4.87	8.28Q	6.93	6.74	8.50G	6.55	10.44+E	8.46	10.04+	15.17+F
C57BL/6J	2.54	4.72	3.65	3.80	3.57	3.96	6.02	6.64	11.25+L	12.89+M
C57BL/10J	4.60	4.89	5.46	3.95	4.23	4.96	4.90	6.59	9.22+	13.99+I
CBA/J	4.57	6.58	7.21	6.11	7.62	8.55H	8.61Q	7.22	8.78+	8.39
CD-1	3.91	3.64	4.55	3.89	3.74	3.68	4.27	6.49	5.95	9.59+
C3H/HeJ	4.74	6.30	5.13	4.36	6.19	4.21	5.79	4.82	6.53	8.02
DBA/2J	4.18	5.78	5.08	5.26	4.15	5.69	5.58	7.16	9.68+	9.54+
SJL/J	5.13	6.71	8.46N	7.68	8.73G	7.81O	9.95+P	9.53+R	12.44+L	14.72+K
SWR/J	7.92	11.02C	11.95B	11.19B	14.02+A	13.05+A	18.81+A	26.49+A	26.63+A	25.89+A
129P3/J	4.47	7.18	4.11	5.11	6.24	3.65	7.59	5.46	8.47	11.01+

*Baseline water intake from designated "Intralipid" bottle.

+ Significant increase in Intralipid intake from corresponding baseline value ($p<0.05$).

A: Significantly greater weight-adjusted Intralipid intake than all other eleven strains ($p<0.05$).

B: Significantly greater weight-adjusted Intralipid intake than A/J, AKR/J, C57BL/6J, C57BL/10J, CBA/J, CD-1, C3H/HeJ, DBA/2J and 129P3/J strains ($p<0.05$).

C: Significantly greater than A/J, AKR/J, C57BL/6J, C57BL/10J, CD-1, DBA/2J and SJL/J strains ($p<0.05$).

D: Significantly greater than AKR/J, CBA/J, CD-1, C3H/HeJ, DBA/2J and 129P3/J strains ($p<0.05$).

E: Significantly greater than A/J, C57BL/10J, CD-1, C3H/HeJ and DBA/2J strains ($p<0.05$).

F: Significantly greater than AKR/J, CBA/J, CD-1, C3H/HeJ and DBA/2J strains ($p<0.05$).

G: Significantly greater than C57BL/6J, C57BL/10J, CD-1 and DBA/2J strains ($p<0.05$).

H: Significantly greater than C57BL/6J, CD-1, C3H/HeJ and 129P3/J strains ($p<0.05$).

I: Significantly greater than CBA/J, CD-1, C3H/HeJ and DBA/2J strains ($p<0.05$).

J: Significantly greater than C57BL/10J, CD-1 and DBA/2J strains ($p<0.05$).

K: Significantly greater than CD-1, C3H/HeJ and DBA/2J strains ($p<0.05$).

L: Significantly greater than CD-1 and C3H/HeJ strains ($p<0.05$).

M: Significantly greater than CBA/J and C3H/HeJ strains ($p<0.05$).

N: Significantly greater than C57BL/6J and 129P3/J strains ($p<0.05$).

O: Significantly greater than CD-1 and 129P3/J strains ($p<0.05$).

P: Significantly greater than CD-1 and DBA/2J strains ($p<0.05$).

Q: Significantly greater than the CD-1 strain ($p<0.05$).

R: Significantly greater than the C3H/HeJ strain ($p<0.05$).

To control for the possibility that the magnitude of Intralipid intake might vary as a function of the significant body weight differences (Table 1), one additional analysis of variance examined Intralipid intake per 30 g of body weight, and revealed significant differences among strains ($F(11,99)=47.36$, $p<0.0001$), among Intralipid concentrations ($F(9,81)=83.71$, $p<0.0001$) and for the interaction between strains and concentrations ($F(99,891)=6.40$, $p<0.0001$). As summarized in Table 2, weight-adjusted Intralipid intake was significantly greater than corresponding water intake following the six highest concentrations in SWR/J mice, the four highest concentrations in SJL/J mice, three high concentrations in AKR/J and BALB/cJ mice, the two highest concentrations in A/J, C57BL/6J, C57BL/10J and DBA/2J mice, and only at one of the highest concentration in CBA/J, CD-1 and 129P3/J mice. When adjusting for weight, the C3H/HeJ strain failed to display significant differences in Intralipid relative to water intake across concentrations. Rather profound strain-specific differences in Intralipid intake were observed in the following six strains. SWR/J mice displayed significantly greater weight-adjusted Intralipid intake from the 0.01% through 5% concentrations relative to the 11 other tested strains, from the 0.0001–0.001% concentrations relative to nine other tested strains, and at the 0.00001% concentration relative to seven other tested strains. A/J mice displayed significantly greater weight-adjusted Intralipid intake at the 5% concentration relative to six other tested strains, and at the 2% concentration relative to two other tested strains. BALB/cJ mice displayed significantly greater weight-adjusted Intralipid intake at the 0.5% and 5% concentrations relative to five other tested strains, at the 0.01% concentration relative to four other tested strains, and at the 0.00001% concentration relative to the outbred CD-1 strain. AKR/J mice displayed significantly greater weight-adjusted Intralipid intake at the 0.01% and 0.05% concentrations relative to four other tested strains, at the 0.5% concentration relative to three other tested strains, at the 0.0001% concentration relative to two other tested strains, and at the 2% concentration relative to the outbred CD-1 strain. SJL/J mice displayed significantly greater weight-adjusted Intralipid intake at the 0.01% concentration relative to four other tested strains, at the 0.5% concentration relative to

three other tested strains, at the 5% concentration relative to three other tested strains, at the 0.0001, 0.1%, 0.5% and 2% concentrations relative to two other tested strains, and at the 1% concentration relative to the C3H-HeJ strain. The other seven strains displayed more modest differences in Intralipid intake across concentrations relative to each other (Table 2).

A second control for the possibility that the magnitude of Intralipid intake might vary as a function of the significant body weight differences (Table 1) evaluated transformed Intralipid intake normalized to the 0.75 power, and revealed significant differences among strains ($F(11,99)=49.97$, $p<0.0001$), among Intralipid concentrations ($F(9,81)=94.82$, $p<0.0001$) and for the interaction between strains and concentrations ($F(99,891)=6.02$, $p<0.0001$). Table 3 summarizes these transformed data, and when systematically compared with Intralipid intake per se (Fig. 1) or Intralipid intake adjusted per 30 g of body weight (Table 2), it is quite apparent that the pattern of results is consistent across the three analyses, suggesting that the weight differences did not account for the genetic variation in Intralipid intake.

Significant differences in the percentage of fluid intake consumed as Intralipid were observed among strains ($F(11,99)=5.36$, $p<0.0001$), across concentrations ($F(9,81)=73.34$, $p<0.0001$), and for the interaction between strains and concentrations ($F(99,891)=2.20$, $p<0.0001$). There was a great deal of congruence between sensitivity to Intralipid as measured by intake per se and the percentage of fluid intake consumed as Intralipid. Thus, the percentage of fluid intake consumed as Intralipid was significantly greater in BALB/cJ mice at the seven highest concentrations (Fig. 2C), in SWR/J mice at the five highest concentrations (Fig. 2K), in C57BL/6J (Fig. 2D), C57BL/10J (Fig. 2E) and DBA/2J (Fig. 2I) mice at the four highest concentrations, and in A/J (Fig. 2A), AKR/J (Fig. 2B), and SJL/J (Fig. 2J) mice at the two highest concentrations. However, the percentage of Intralipid intake was significantly greater only at the highest concentration in outbred CD-1 (Fig. 2G), C3H/HeJ (Fig. 2H), and 129P3/J (Fig. 2L) mice, but failed to differ at any concentration in CBA/J mice (Fig. 2F). This latter group displayed significantly lower percentages of fluid intake consumed as Intralipid at the highest 5%

Table 3
Alterations in Intralipid intake, normalized by weight to the 3/4 as an indicator of lean body mass, across baseline and nine different sucrose concentrations in one outbred (CD-1) and eleven inbred (A/J, AKR/J, BALB/cJ, C3H/HeJ, C57BL/6J, C57BL/10J, CBA/J, DBA/2J, SJL/J, SWR/J, 129P3/J) strains of mice

Strain	Water ^a	.00001%	.0001%	.001%	.01%	0.1%	0.5%	1.0%	2.0%	5.0%
A/J	0.22	0.32	0.24	0.22	0.25	0.27	0.30	0.34	0.51 ^b	0.60 ^b
AKR/J	0.25	0.29	0.38 ^b	0.32	0.39 ^b	0.39 ^b	0.43 ^b	0.38 ^b	0.44 ^b	0.47 ^b
BALB/cJ	0.25	0.38 ^b	0.33	0.33	0.39 ^b	0.32	0.45 ^b	0.39 ^b	0.44 ^b	0.59 ^b
C57BL/6J	0.16	0.25	0.20	0.21	0.20	0.22	0.30 ^b	0.32 ^b	0.48 ^b	0.53 ^b
C57BL/10J	0.24	0.25	0.28	0.22	0.23	0.26	0.26	0.32	0.41 ^b	0.56 ^b
CBA/J	0.24	0.32	0.34	0.30	0.36	0.39 ^b	0.39 ^b	0.34	0.39 ^b	0.38 ^b
CD-1	0.21	0.20	0.24	0.22	0.21	0.20	0.23	0.31	0.30	0.41 ^b
C3H/HeJ	0.25	0.31	0.26	0.23	0.30	0.22	0.28	0.25	0.32	0.37
DBA/2J	0.23	0.29	0.26	0.27	0.23	0.29	0.28	0.34	0.43 ^b	0.42 ^b
SJL/J	0.27	0.32	0.39	0.36	0.40 ^b	0.36	0.43 ^b	0.42 ^b	0.51 ^b	0.58 ^b
SWR/J	0.37	0.47	0.50 ^b	0.48	0.56 ^b	0.53 ^b	0.70 ^b	0.90 ^b	0.89 ^b	0.89 ^b
129P3/J	0.24	0.34	0.22	0.26	0.30	0.20	0.35	0.27	0.39 ^b	0.46 ^b

^a Baseline water intake from designated "Intralipid" bottle.

^b Indicates a significant change from baseline (water).

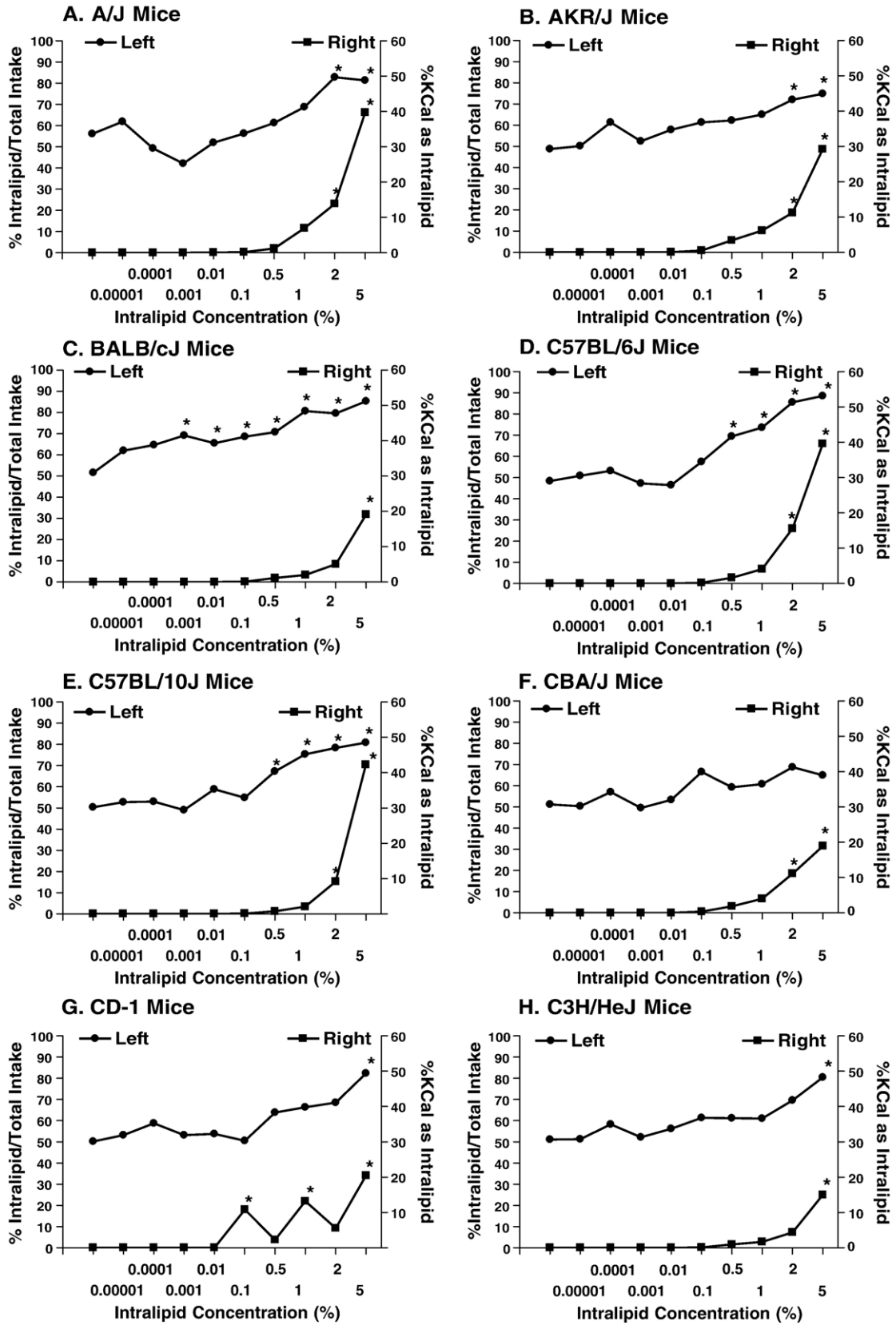


Fig. 2. Alterations in the percentage of intralipid over total intake (left ordinate, mean±S.E.M.) and the percentage of kilocalories consumed as intralipid (right ordinate, mean±S.E.M.) across the nine different intralipid concentrations in one outbred (CD-1) and eleven inbred (A/J, AKR/J, BALB/cJ, C57BL/6J, C57BL/6J, CBA/J, C3H/HeJ, DBA/2J, SJL/J, SWR/J, 129P3/J) strains of mice.

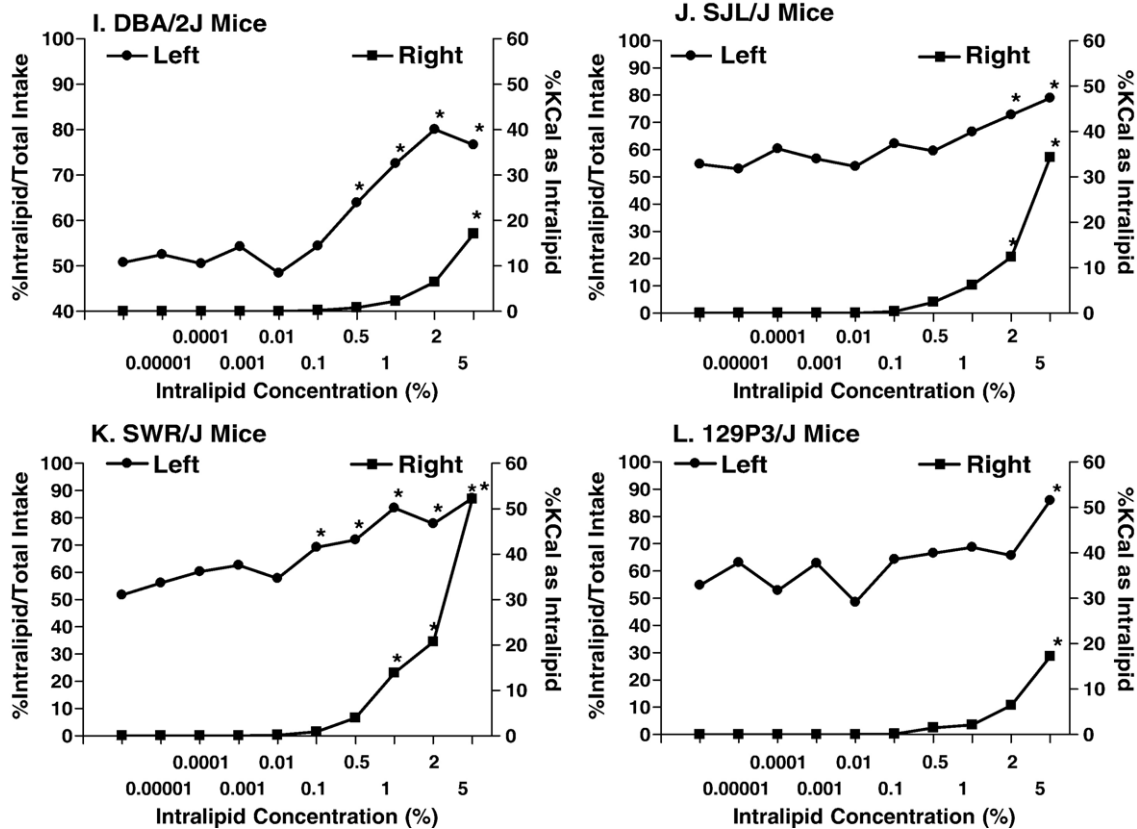


Fig. 2 (continued).

concentration relative to BALB/cJ, C57BL/6J, CD-1, SWR/J and 129P3/J strains.

3.3. Kilocalorie intake as Intralipid and chow

Significant differences in the percentage of kilocalorie intake consumed as Intralipid were observed among strains ($F(11,99)=9.57, p<0.0001$), across concentrations ($F(9,81)=326.73, p<0.0001$) and for the interaction between strains and concentrations ($F(99,891)=5.58, p<0.0001$). SWR/J mice displayed significantly greater percentages of kilocalorie intake as Intralipid for the three highest concentrations (Fig. 2K) that were also in turn significantly greater percentages than BALB/cJ, C57BL/6J, CD-1, C3H/HeJ, DBA/J and 129P3/J strains. Strains that displayed significantly greater percentages of kilocalorie intake consumed as Intralipid at the two highest concentrations included A/J (Fig. 2A), AKR/J (Fig. 2B), C57BL/6J (Fig. 2D), CBA/J (Fig. 2F), and SJL/J (Fig. 2J) mice. A/J and AKR/J mice displayed significantly higher percentages than BALBc/J, CD-1, C3H/HeJ, DBA/2J and 129P3/J mice at the highest concentrations, with A/J mice displaying significantly higher percentages than AKR/J mice at the highest concentrations. In turn, C57BL/6J and SJL/J mice displayed significantly higher percentages at the highest concentration than BALB/cJ, C3H/HeJ and DBA/2J mice. The other six strains displayed significantly greater percentages of kilocalorie intake consumed as Intralipid at only the highest concentration (Fig. 2C, E, G–I, and L).

3.4. Chow intake and compensatory changes by intralipid intake

Significant differences in chow intake were observed among strains ($F(11,110)=43.62, p<0.0001$), across concentrations ($F(9,90)=28.70, p<0.0001$) and for the interaction between strains and concentrations ($F(99,990)=2.80, p<0.0001$). Chow intake showed significant decreases at the highest Intralipid concentration in A/J (Fig. 1A), AKR/J (Fig. 1B), BALB/cJ (Fig. 1C), C57BL/10J (Fig. 1E) and SWR/J (Fig. 1K) strains; the

Table 4
Pearson product–moment correlation coefficients between Intralipid concentrations for Intralipid intake (A) and for the percentage of kilocalories consumed as Intralipid in the 12 tested mouse strains

Intralipid concentration	0.5%	1.0%	2.0%
<i>A. Intralipid intake (ml)</i>			
0.5%	–		
1.0%	.84 ^a	–	
2.0%	.75 ^a	.92 ^a	–
5.0%	.53	.76 ^a	.86 ^a
<i>B. Percent kilocalories consumed as intralipid</i>			
0.5%	–		
1.0%	.75 ^a	–	
2.0%	.62	.51	–
5.0%	.43	.46	.87 ^a

^a Significant correlation after Bonferroni corrections ($p<0.01$).

Table 5

Narrow-sense heritability estimates (h^2) for each Intralipid concentration in terms of Intralipid intake itself and Intralipid intake adjusted for body weight

Concentration measure	0.00001%	0.0001%	0.001%	0.01%	0.1%	0.5%	1%	2%	5%
Intralipid intake	0.32	0.59	0.64	0.70	0.77	0.58	0.76	0.41	0.45
Intralipid intake 30 g BW	0.51	0.62	0.73	0.78	0.79	0.64	0.79	0.47	0.55

remaining seven strains failed to show significant compensatory decreases in chow intake at the highest Intralipid concentration. Although significant differences in the total amount of kilocalories were observed among strains ($F(11,99)=34.95$, $p<0.0001$), across concentrations ($F(9,81)=5.72$, $p<0.0001$) and for the interaction between concentrations and strains ($F(99,891)=2.06$, $p<0.0001$), only CD-1 mice displayed significant increases in total kilocalorie intake at the two highest Intralipid concentrations with AKR/J and SWR/J mice displaying transient decreases in kilocalorie intake at the 0.001% Intralipid concentration.

3.5. Correlational and heritability data

Table 4 displays the pairwise correlation coefficients between those Intralipid concentrations (0.5–5%) at which the greatest number of strains displayed significant increases in consumption, using measures of intake per se and the percentage of kilocalories consumed as Intralipid. Stronger and significant correlations were observed among the 0.5%, 1%, 2% and 5% concentrations between Intralipid intakes (0.5% and 1%; 0.5% and 2%; 1% and 2%; 1% and 5%; 2% and 5%) relative to the percentage of kilocalories consumed as Intralipid (0.5% and 1%; 2% and 5%). Table 5 summarizes the narrow-sense heritability estimates for each Intralipid concentration in terms of Intralipid intake itself and Intralipid intake adjusted for body weight. Relatively strong ($h^2=0.73$ – 0.79) heritability estimates were obtained for weight-adjusted Intralipid intake at those concentrations (0.001–1%) that displayed the largest strain-specific effects in sensitivity to Intralipid; corresponding smaller estimates ($h^2=0.64$ – 0.77) were obtained for Intralipid intake itself at this concentration range. Heritability estimates dropped at both those low concentrations (0.00001–0.0001%: $h^2=0.32$ – 0.62) that failed to show significant differences in Intralipid intake relative to water in any strain, and at those high concentrations (2–5%: $h^2=0.41$ – 0.55) at which virtually all strains were consuming Intralipid more than water.

4. Discussion

First, it was clear that Intralipid intake relative to water intake was significantly increased in all strains in 24 h, two-bottle preference tests. Second, as expected, we observed dramatic strain differences for Intralipid intake. The most striking increases in Intralipid preferences were observed in BALB/cJ mice across a range of concentrations (0.001–5%), and to progressively lesser degrees in AKR/J, C57BL/6J, DBA/2J and SWR/J inbred strains (0.5–5%), in outbred CD-1 and inbred C57BL/10J and SJL/J strains (1–5%), and to the least degree in A/J, CBA/J, C3H/HeJ and 129P3/J inbred strains (2–5%).

Congruent sensitivity data were observed for the percentage of fluid intake consumed as Intralipid with significant increases noted in BALB/cJ mice at the seven highest concentrations, in SWR/J mice at the five highest concentrations, in C57BL/6J, C57BL/10J and DBA/2J mice at the four highest concentrations, and in A/J, AKR/J and SJL/J mice at the two highest concentrations. However, the percentage of fluid intake consumed as Intralipid was only significantly greater at the highest concentration in outbred CD-1, C3H/HeJ and 129P3/J mice, but failed to differ at any concentration in CBA/J mice. In contrast to the observation of limited order effects noted for CBA/J mice in testing ascending and descending concentrations of sucrose [23], a number of strains displayed clear order effects for consumption of Intralipid, an important variable identified in previous work [15]. Thus, although Intralipid order effects were not important in outbred CD-1 mice and the CBA/J, C3H/HeJ, C57BL/6J, DBA/2J and 129P3/J inbred strains, Intralipid intake was higher in BALB/cJ mice exposed to the descending order at the 0.1% concentration, but lower at the 0.5%, 2% and 5% concentrations. Further, exposure to descending Intralipid concentrations produced greater intake at the 0.00001% (AKR/J), 0.5% (SJL/J, SWR/J), 1% (AKR/J), 2% (A/J, C57BL/10J, SJL/J, SWR/J) and 5% (A/J) concentrations. Such data reinforce the need for this important control in multi-strain analyses of intake across concentrations. Although Intralipid and water bottle positions were also controlled given the previous [3] relevance of this variable, the bottle positions were switched every 24 h as in our previous work [23]. However, this testing procedure does differ from presentation of solutions for two consecutive days (“the 48 h test”), allowing for switching the sides of the solution presentations at each and every concentration. This is a potential limitation, but although our 1-day test procedure may have added some noise to the data, we do not believe that this invalidates the results.

Third, strain differences were noted in the total amount of Intralipid intake consumed, as well as Intralipid intake adjusted for body weight, and Intralipid intake normalized to the 0.75 power to estimate changes in lean body mass. Thus, SWR/J mice (20.7 ml actual; 25.9 ml adjusted ml) consumed by far the most among inbred strains, followed by A/J, BALB/cJ, C57BL/10J and C57BL/6J mice (13.3–14.9 ml actual; 12.9–15.6 ml adjusted), followed then in turn by SJL/J, AKR/J and 129P3/J mice (9.4–12.5 ml actual; 10.9–14.7 ml adjusted), and finally by DBA/2J, C3H/HeJ and CBA/J mice (6.7–9.2 ml actual; 8–9.5 ml adjusted). This differential Intralipid consumption across strains remained consistent across the highly effective 0.5%, 1%, 2% and 5% Intralipid concentrations given the highly significant correlations for intake for the 0.5% and 1% ($r=0.84$), the 0.5% and 2% ($r=0.75$), the 1% and 2% ($r=0.92$), the 1% and 5% ($r=0.76$) and the 2% and 5% ($r=0.86$) concentrations.

Moreover, relatively strong ($h^2=0.73-0.79$) heritability estimates were obtained for weight-adjusted Intralipid intake at those concentrations (0.001–1%) that displayed the largest strain-specific effects in sensitivity to Intralipid; an identical pattern of results was observed for Intralipid intake itself. Therefore, the close correspondence between actual and the two different weight-adjusted Intralipid intakes suggests that initial differences in body weight among mouse strains were not an integral factor in the short-term (24 h) Intralipid preference across a range of concentrations in two-bottle choice tests. The previous parallel analysis of sucrose intake [23] revealed that SWR/J mice displayed the most pronounced actual and weight-adjusted intake followed by A/J, C57BL/6J, C57BL/10J and SJL/J mice, followed in turn by BALB/cJ and 129P3/J mice, and finally by AKR/J, C3H/HeJ, CBA/J and DBA/2J mice, a pattern of effects that is highly similar to that observed for Intralipid intake in the present study.

It should be noted that a number of previous studies have employed the percentage of the palatable solution consumed as a function of total fluid intake as a measure of preference (e.g., [10,13,26,30]). However, this did not appear to be a reliable predictor of effects in the present study as it was previously for sucrose intake [23]. Indeed, some strains displaying very high (~90%) fluid preferences as Intralipid showed markedly different amounts of Intralipid intake at the identical concentration: SWR/J (20.7 ml), C57BL/6J (14.9 ml) and 129P3/J (9.4 ml). Moreover, CD-1 (14 ml) and C3H/HeJ (7 ml) strains displaying great differences in actual Intralipid intake both showed moderately high (~80%) fluid preferences as Intralipid. This further underlines the need to survey genetic models of food intake across a greater range of palatable solution concentrations.

Fourth, the systematic measurement of chow, water and Intralipid intake allowed us to assess and detect strain differences in kilocalorie intake consumed as Intralipid. Hence, SWR/J mice displayed significant increases in Intralipid kilocalorie intake at the three highest concentrations, A/J, AKR/J, C57BL/6J, CBA/J and SJL/J mice displaying significant effects at the two highest concentrations, and the other six strains displaying significant effects at only the highest concentration. It should be noted that a more limited range of significant correlations among the percentage of kilocalories consumed as Intralipid was observed between the 0.5% and 1% ($r=0.75$) and the 2% and 5% ($r=0.87$) concentrations. Again, this pattern for Intralipid kilocalorie consumption is strikingly similar to that observed for sucrose [23] with C57BL/10J, SJL/J, SWR/J and A/J mice displaying 45–60% of kilocalories consumed as sucrose, C57BL/6J displaying a 37% sucrose kilocalorie consumption, and the other five inbred strains consuming less than 30% of their kilocalories as sucrose.

Finally, compensatory decreases in chow intake were noted only at the highest Intralipid concentration and only in A/J, AKR/J, BALB/cJ, C57BL/10J and SWR/J strains. This compares with the compensatory decreases in chow intake as sucrose intake increased noted for A/J, C57BL/6J, C57BL/10J, SJL/J and SWR/J inbred strains [23]. That C57BL/10J but not C57BL/6J mice displayed this compensatory decrease in chow intake following Intralipid represents a relatively rare differen-

tiation between these two strains in behavioral assays. This short-term and rapid (within 24 h) compensation to chow in the presence of Intralipid, like sucrose, suggests that such strains may be displaying sensitivity to energy intake and/or a greater ability to both adapt and respond. Divergent responders may be a model for studying and identifying genetic substrates associated with this ability to regulate kilocalorie intake across a variety of energy sources.

These short-term differences in sensitivity to and consumption of different Intralipid solutions across inbred mouse strains reveal some interesting similarities and differences when compared with studies using solid fat sources, macronutrient selection of different diets, or comparison of low-fat, high-carbohydrate with high-fat, low-carbohydrate diets (e.g., [41,43]). Thus, SWR/J mice consumed by far the greatest overall and weight-adjusted amounts of Intralipid, and among the greatest amounts of kilocalories consumed as Intralipid. This strain also displayed the largest intake of a variety of other high fat diets [35,36,41,43], indicating clear similarities for this effect. Yet in prior paradigms which lasted from a week to a month, these animals failed to gain weight despite increased fat intake, potentially because as indicated in the present study, they adjust their intake of other food sources. Other factors are clearly at work given that their fat intake was inversely correlated with epididymal fat [35], and since SWR/J mice, like Intralipid-preferring A/J mice, displayed lower insulin levels, increased capacity of skeletal muscle to metabolize fat, enhanced paraventricular galanin and reduced arcuate NPY [21]. Similarities between Intralipid intake and other forms of fat intake [1,35] were also observed in C57BL/6J mice. This strain also avidly consumed Intralipid in the present study and showed equal preferences between protein and fat while displaying normal insulin and leptin levels [1]. Further, in self-selection studies, C57BL/6J mice consumed some of the highest proportions of fat that correlated with epididymal fat stores [35].

Some other strains failed to display similar patterns of fat intake when comparing Intralipid to other fat sources. Thus, AKR/J mice, a strain that consumed appreciably less Intralipid than the strains described above, have been shown to consume moderate intake of high-fat diets that are accompanied by weight gain [36,41,43], high proportions of fat in self-selection studies that correlated with epididymal fat [35] and, along with the less-sensitive Intralipid DBA/2J strain, consumed more fat, displayed more adiposity, and had elevated levels of leptin and insulin [1]. Some of the discrepancies may be due to methodological factors related to the goals of the individual studies. Hence, many of the previously cited studies used solid forms of fat (e.g., shortening, lard or granular fat) at specific concentrations in the diet over longer periods of time to assess differences between small numbers of strains. The present study used an experimental approach allowing for the evaluation of a larger number of strains across a wide range of fat concentrations to assess sensitivity to fat solutions. Since many liquefied fat sources fail to stay in solution when presented at different concentrations over a time course (e.g., 24 h) reasonable to study murine intake, our laboratory chose an emulsified soybean oil solution (Intralipid) capable of equal distribution of fat in solution across a wide range of concentrations. Thus, the texture

and other sensory cues presented by Intralipid as compared to the other solid fat sources may be reasons for the differences in strain responsivity to specific aspects of fat intake, and not fat intake per se. However, all of these studies taken together do provide converging information about the potential genetics of fat intake with the differences in some strains indicating a role for environmental factors interacting with genetic predisposition.

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References

- 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 Obes* 2006;30:50–9.
- Bachmanov AA, Beauchamp GK, Tordoff MG. Voluntary consumption of NaCl, KCl, CaCl₂, and NH₄Cl solutions by 28 mouse strains. *Behav Genet* 2002;32:445–57.
- 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.
- 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.
- Bachmanov AA, Reed DR, Tordoff MG, Price RA, Beauchamp GK. Nutrient preference and diet-induced adiposity in C57BL/6JByJ and 129P3/J/J mice. *Physiol Behav* 2001;72:603–13.
- 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.
- Bachmanov AA, Tordoff MG, Beauchamp GK. Voluntary sodium chloride consumption by mice: differences among five inbred strains. *Behav Genet* 1998;28:117–24.
- Beauchamp GK, Fisher AS. Strain differences in consumption of saline solutions by mice. *Physiol Behav* 1993;54:179–84.
- 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.
- 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.
- Capeless CG, Whitney G, Azen EA. Chromosome mapping of Soa, a gene influencing gustatory sensitivity to sucrose octaacetate in mice. *Behav Genet* 1992;22:655–63.
- Fisler JS, Warden CH, Pace MJ, Lusis AJ. BSB: a new mouse model of multigenic obesity. *Obes Res* 1993;1:271–80.
- Fuller JL. Single-locus control of saccharin preference in mice. *J Hered* 1974;65:33–6.
- Harder DB, Capeless CG, Maggio JC, Boughter JD, Gannon KS, Whitney G, et al. Intermediate sucrose octa-acetate sensitivity suggests a third allele at mouse bitter taste loci Soa and Soa-Rua identity. *Chem Senses* 1992;17:391–401.
- Harder DB, Maggio JC, Whitney G. Assessing gustatory detection capabilities using preference procedures. *Chem Senses* 1989;14:547–64.
- Harder DB, Whitney G. A common polygenic basis for quinine and PROP avoidance in mice. *Chem Senses* 1998;23:327–32.
- Hegmann JP, Possidente B. Estimating genetic correlations from inbred strains. *Behav Genet* 1981;11:103–14.
- Higgs S, Cooper SJ. Evidence for early opioid modulation of licking responses to sucrose and Intralipid: a microstructural analysis in the rat. *Psychopharmacology* 1998;139:342–55.
- Higgs S, Cooper SJ. Effects of benzodiazepine receptor ligands on the ingestion of sucrose, Intralipid and maltodextrin: an investigation using a microstructural analysis of licking behavior in a brief contact test. *Behav Neurosci* 1998;112:447–57.
- Inoue M, Reed DR, Li X, Tordoff MG, Beauchamp GK, Bachmanov AA. Allelic variation of the Tas1r3 taste receptor gene selectively affects behavioral and neural taste responses to sweeteners in the F₂ hybrids between C57BL/6JByJ and 129P3/J/J mice. *J Neurosci* 2004;24:2296–303.
- 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.
- Levin BE, Sullivan AC. Glucose-induced norepinephrine levels and obesity resistance. *Am J Physiol* 1987;253:R475–81.
- 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.
- Lewis SR, Dym C, Ginzberg M, Kest B, Bodnar RJ. Genetic variance contributes to ingestive processes: a survey of mercaptoacetate-induced feeding in eleven inbred and one outbred mouse strains. *Physiol Behav* 2005;88:516–22.
- Lush IE. The genetics of tasting in mice. III. Quinine. *Genet Res* 1984;44:151–60.
- Lush IE. The genetics of tasting in mice. VI. Saccharin, acesulfame, dulcin and sucrose. *Genet Res* 1989;53:95–9.
- Lush IE, Hornigold N, King P, Stoye JP. The genetics of tasting in mice. VII. Glycine revisited, and the chromosomal location of Sac and Soa. *Genet Res Camb* 1995;66:167–74.
- Nachman M. The inheritance of saccharin preference. *J Comp Physiol Psychol* 1959;52:451–7.
- Pelz WE, Whitney G, Smith JC. Genetic influences on saccharin preference in mice. *Physiol Behav* 1973;10:263–5.
- 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.
- Ramirez I, Fuller JL. Genetic influence on water and sweetened water consumption in mice. *Physiol Behav* 1976;16:163–8.
- Reed DR, Bachmanov AA, Beauchamp GK, Tordoff MG, Price RA. Heritable variation in food preferences and their contribution to obesity. *Behav Genet* 1997;27:373–87.
- 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.
- Schemmel R, Mickelson O, Gill JL. Dietary obesity in rats: body weight and body fat accretion in seven strains of rat. *J Nutr* 1970;100:1041–8.
- Smith BK, Andrews PK, West DB. Macronutrient diet selection in thirteen mouse strains. *Am J Physiol* 2000;278:R797–805.
- 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.
- 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.
- Stockton MD, Whitney G. Effects of genotype, sugar and concentration on sugar preference of laboratory mice (*Mus musculus*). *J Comp Physiol Psychol* 1974;86:62–8.
- Tordoff MG, Pilchak DM, Williams JA, McDaniel AH, Bachmanov AA. The maintenance diets of C57BL/6J and 129/JX1/SvJ mice influence their taste solution preferences: implications for large-scale phenotyping projects. *J Nutr* 2002;132:2288–97.
- Warden CH, Fisler JS, Shoemaker SM, Wen PZ, Svenson KL, Pace MJ, et al. Identification of four chromosomal loci determining obesity in a multifactorial mouse model. *J Clin Invest* 1995;95:1545–52.
- 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.
- West DB, Goudey-Lefevre J, York B, Truett GE. Dietary obesity linked to genetic loci on chromosomes 9 and 15 in a polygenic mouse model. *J Clin Invest* 1994;94:1410–6.

- [43] West DB, Waguespack J, McCollister S. Dietary obesity in the mouse: interaction of strain with diet composition. *Am J Physiol* 1995;268:R658–65.
- [44] West DB, Waguespack J, York B, Goudey-Lefevre J, Price GA. Genetics of dietary obesity in AKR/J×SWR/J mice: segregation of the trait and identification of a linked locus on chromosome 4. *Mamm Genome* 1994;5:546–52.
- [45] West DB, York B. Dietary fat, genetic predisposition, and obesity: lessons from animal models. *Am J Clin Nutr* 1998;67:505S–12S.