Macronutrient diet selection in thirteen mouse strains

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Macronutrient diet selection in thirteen mouse strains. Am J Physiol Regulatory Integrative Comp Physiol 278: R797–R805, 2000.—The strain distribution for macronutrient diet selection was described in 13 mouse strains (AKR/J, NZB/B1NJ, C57BL/6J, C57BL/6ByJ, DBA/2J, SPRET/Ei, CD-1, SJL/J, SWR/J, 129/J, BALB/cByJ, CAST/Ei, and A/J) with the use of a self-selection protocol in which separate carbohydrate, fat, and protein diets were simultaneously available for 26–30 days. Relative to carbohydrate, nine strains consumed significantly more calories from the fat diet; two strains consumed more calories from carbohydrate than from fat (BALB/cByJ, CAST/Ei). Diet selection by SWR/J mice was variable over time, resulting in a lack of preference. One strain (A/J) failed to adapt to the diet paradigm due to inadequate protein intake. Comparisons of proportional fat intake across strains revealed that fat selection/consumption ranged from 26 to 83% of total energy, AKR/J, NZB/B1NJ, and C57BL/6J mice self-selected the highest proportion of dietary fat, whereas the CAST/Ei and BALB/cByJ strains chose the lowest. Finally, epididymal fat depot weight was correlated with fat consumption. There were significant positive correlations in AKR/J and C57BL/6J mice, which are highly sensitive to dietary fat consumption, in AKR/J mice. In the lean strains: SWR/J and CAST/Ei. We hypothesize that the SWR/J and CAST/Ei strains are highly sensitive to a negative feedback signal generated by increasing body fat, but the AKR/J and C57BL/6J mice are not. The variation in dietary fat selection across inbred strains provides a tool for dissecting the complex genetics of this trait.

There are few empirical studies of macronutrient consumption in humans largely because of the procedural difficulties inherent to studies employing direct measures of food intake (19). Thus evidence for variation in human macronutrient selection comes mainly from studies in which dietary intake was self-reported. For example, a wide range in macronutrient intakes was demonstrated by the results of a population survey in which 7-day weighed food records were used to classify a large sample of adults according to the percent contribution of fat to total caloric intake. Approximately 26% of the study population were classified as either low (<35% energy)-fat consumers (17). One recent report, however, provides direct evidence for variation in the preferred level of dietary fat intake (12). In a laboratory study employing a macronutrient self-selection paradigm, measures of fat intake ranged from 3 to 50% of energy in men and these results were consistent with subjects' reports of habitual fat intake (12).

At least 20% of the variance associated with fat and carbohydrate preference in humans is likely to be genetic, although a large portion of the variation in total energy and macronutrient intakes can be accounted for by environmental effects (26). Although evidence for a genetic basis for nutrient selection in humans is limited, the results of twin studies suggest that macronutrient intakes may have a heritable component (7, 28). For example, Rha et al. (30) demonstrated stronger heritability estimates for fat and carbohydrate consumption, but a much lower estimate for protein intake, in monozygotic compared with dizygotic twins when evaluated in a laboratory setting. In a recent review of literature, Reed et al. (28) concluded that the available evidence provides stronger support for a genetic basis for macronutrient intakes than for individual food preferences (28).

The possible physiological factors contributing to macronutrient diet selection are unknown, but are thought to include responses to both the orosensory and postdigestive effects of food, which may be genetically determined. For example, a study of subjects' appetite responses to a variety of food characteristics (weight, energy, nutrient composition, and taste) found differences between habitual high- and low fat consumers (4). High fat consumers ate a constant weight of food, but low fat consumers ate a constant level of energy; high fat consumers rated the high- and low-fat foods equally for taste, whereas low fat consumers showed a preference for high-carbohydrate foods (4). The contrasting responses in these two subject groups could be a function of intrinsic biological differences or of the adaptation to high or low fat consumption (4).

In animal models, key evidence for genetic influence on behavioral phenotypes is demonstrated by the existence of strain differences (6). Among inbred rat strains, differences in macronutrient diet selection have been reported, i.e., strains that self-select a low (SSB/P1) or high (Osborne-Mendel, Zucker obese) fat intake (3, 24). In outbred strains of rat, littermates exhibit similar patterns of diet selection (34, 43), providing further evidence of a genetic basis for this trait. Macronutrient selection in mice has been evaluated previously in only the ob/ob mouse, a single gene model of obesity (18, 31).
However, recently we observed contrasting patterns of macronutrient selection in two nonobese mouse strains: AKR/J mice self-selected a higher proportion of dietary fat intake, whereas the SWR/J mice consumed a higher proportion of carbohydrate (36). Additional studies showed that the difference in proportional fat intake between AKR/J and SWR/J strains generalized across several diet paradigms, indicating a robust model suitable for genetic analyses (35). As a foundation for future investigations of the genetic basis for dietary fat consumption, we now describe macronutrient diet selection in 13 mouse strains.

METHODS

Five-week-old male mice were purchased from the Jackson Laboratory (Bar Harbor, ME): AKR/J, AJ, BALB/cByJ, CAST/Ei, C57BL/6J, C57BL/6ByJ, DBA/2J, NZB/B1NJ, SJL/J, SPRET/Ei, SWR/J, and 129/J, or from Charles River Laboratories (Raleigh, NC): CD-1. Animals were individually housed and tested in stainless steel mouse cages 7 × 10 × 7 (width × depth × height, in.) with wire mesh floors. Polyvinylchloride nesting tubes (1.5-in. diameter) were provided to reduce time spent on the wire bottom. Mice were maintained on a 12:12-h light-dark photoperiod, with lights on at 0600, and at an ambient temperature of 24–26°C. Mice were fed standard matrix was assessed using the autoregressive type I structure. These analyses revealed the macronutrient diet “preference” of the strains when expressed as energy consumed (kcal). The proportional contribution of fat kilocalories to total energy was used for comparisons between strains, thus controlling for differences in body size and total food intake. Multiple comparisons across strains were adjusted using the Tukey-Kramer method.

RESULTS

Macronutrient diet preference by strain. Patterns of macronutrient diet selection in 12 strains for the entire length of the study (26–30 days) are illustrated in Fig. 1. The results of ANOVA by strain for caloric intake across macronutrient diets and time are listed in Table 2 and are based on data from day 12 through the end of the study, after a 10-day period of acclimation to the experimental diet paradigm. There were significant interactions between time and diet for all 12 strains (Table 2). Relative to carbohydrate intake, nine strains voluntarily consumed significantly more calories from the fat diet: AKR/J, NZB/B1NJ, C57BL/6J, C57BL/6ByJ, DBA/2J, SPRET/Ei, CD-1, SJL/J, and 129/J. Two strains consumed more calories from the carbohydrate diet than from fat: BALB/cByJ and CAST/Ei (Fig. 1; Table 2).

Table 1. Composition of macronutrient diets

<table>
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<tr>
<th>3-Choice Carbohydrate</th>
<th>Fat</th>
<th>Protein</th>
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<tr>
<td>Powdered sugar 29.06</td>
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<td>0.00</td>
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<td>0.77</td>
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<tr>
<td>AIN-76A mineral Mix 3.07</td>
<td>5.95</td>
<td>3.07</td>
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<tr>
<td>Choline chloride 0.18</td>
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<td>0.18</td>
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<tr>
<td>Cellulose (alphacel) 8.72</td>
<td>16.91</td>
<td>8.72</td>
</tr>
<tr>
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<th>Protein</th>
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</thead>
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<tr>
<td>Vegetable shortening 0.00</td>
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<td>AIN-76A mineral mix 3.20</td>
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<tr>
<td>Choline chloride 0.18</td>
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<tr>
<td>Cellulose (alphacel) 4.92</td>
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<tr>
<td>Energy density, kcal/g 3.61</td>
<td>5.96</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Composition of macronutrient diets

Ingredients expressed as percent by weight. Vitamin and mineral mixes contain 97 and 12% sucrose, respectively.
Diet selection by SWR/J mice was highly variable over time, resulting in a lack of preference. A/J mice failed to adapt to the three-choice macronutrient diet protocol in two separate experiments. In the first experiment, A/J consumed an inadequate amount of protein even after 3 wk. In a second experiment with another group of naive A/J mice, protein intake was coaxed (33) by presenting chow plus the protein diet for 4 days before starting the three-choice macronutrient diet protocol. Five days after initiation of the three-choice macronutrient diets, mice were in negative weight balance and consuming inadequate protein. The A/J mice then were switched to another diet paradigm consisting of a choice between a carbohydrate/protein and a fat/protein diet; the macronutrient sources used in these preparations were the same as those contained in the three-choice diet (Table 1). Food intake stabilized in the A/J mice 6 days after beginning the two-choice diet, and statistical analyses were performed on data from days 13 to 29 (Fig. 2). The proportion of energy consumed from the fat/protein diet by A/J mice was 0.55 ± 0.05. Although there was a significant diet × time interaction \[ F(8,238) = 3.15, P < 0.005 \], a post hoc test failed to show a reliable diet preference in A/J mice (P = 0.17).

Proportional fat intake across strains. With the three-choice macronutrient diet paradigm, the proportion of energy consumed from the fat diet differed across mouse strains [F(11,157) = 29.51, P < 0.0001], and the rank order is shown in Fig. 3. AKR/J mice self-selected a significantly higher proportion of energy from fat (0.83 ± 0.03) than any other strain tested (P < 0.01), with the exception of NZB/B1NJ (0.78 ± 0.04) and C57BL/6J mice (0.73 ± 0.03; P = not significant NS). In contrast, the CAST/Ei mice self-selected a significantly lower proportion of fat intake (0.25 ± 0.03) than all other strains (P < 0.0001), except for the BALB/cByJ mice (0.36 ± 0.03; P = NS).

Body weight, epididymal depot, and organ weights. As shown in Table 3, CD-1 mice at the beginning of the study weighed more (P < 0.0001) than all other age-matched strains, whereas CAST/Ei (P < 0.0001) and SPRET/Ei (P < 0.0001) weighed the least [F(11,157) = 74.44, P < 0.0001]. The final body weight of non-food deprived mice at the time of death was highest also in the CD-1 mice (P < 0.0001) compared with all strains [F(11,157) = 73.72, P < 0.0001], followed by AKR/J (P < 0.0001) and NZB/B1NJ (P < 0.05). At the end of the study, CAST/Ei mice weighed significantly less than the other strains surveyed (P < 0.0001). Analysis of epididymal depot weight/full body weight across strains indicated that AKR/J and SJ L/J mice developed the greatest adiposity in the macronutrient self-selection paradigm [F(11,157) = 24.25, P < 0.0001]. The mouse strains with the smallest epididymal fat depots at the end of the study were SWR/J, BALB/cByJ, and CAST/Ei. There were strain differences in spleen [F(11,157) = 74.34, P < 0.0001] and liver [F(11,158) = 63.02, P < 0.0001] weights (Table 3).

Correlation analysis of fat intake and epididymal fat depot size. A post hoc analysis of the relationship between absolute fat intake and epididymal depot weight (adjusted by initial body weight) revealed significant positive correlations in two mouse strains: AKR/J (r = 0.54, P < 0.05) and C57BL/6J (r = 0.58, P < 0.05; Fig. 4). Thus a higher consumption of fat calories was associated with a larger epididymal fat depot. In contrast, significant negative correlations were found in two of the leanest strains: SWR/J (r = -0.60, P < 0.05) and CAST/Ei (r = -0.61, P < 0.05), indicating that a greater consumption of fat was associated with a smaller epididymal fat depot. No other significant correlations were found in the remaining eight strains: C57BL/6ByJ (r = 0.363), SPRET/Ei (r = -0.321), DBA/2J (r = 0.167), SJ L/J (r = 0.184), CD-1 (r = 0.351), 129J (r = -0.144), NZB/B1NJ (r = -0.605), and BALB/cByJ (r = 0.089).

**Discussion**

This report contains the first evidence for variation in macronutrient diet self-selection across mouse strains. Three patterns of strain responses were identified. Nine strains consumed significantly more calories from fat, relative to carbohydrate intake: AKR/J, NZB/B1NJ, C57BL/6J, C57BL/6ByJ, DBA/2J, SPRET/Ei, CD-1, SJ L/J, and 129J. In contrast, two strains consumed significantly more calories from carbohydrate than from fat: BALB/cByJ and CAST/Ei. A lack of preference for fat or carbohydrate was displayed by SWR/J (3-choice diet) and A/J (2-choice diet) mice. When expressed as proportional fat intake, the data showed a significant range in this phenotype, i.e., 26–83% across mouse strains. Thus the results of this strain survey provide valuable phenotypic data for investigating the genetic basis of dietary fat versus carbohydrate preference.

Because the mice used in the current study were obtained from commercial suppliers, the observed strain differences may have been influenced by factors that were not under experimental control, e.g., effects of prenatal, postnatal, preweaning, nutritional, husbandry, and physical environments (6). For example, both premature weaning and small litter size result in elevated plasma cholesterol and insulin levels as well as increased adiposity in adult rats (13). It is possible that differences in diets fed to the mice in the production colonies may influence their diet selection behavior later in life. For the mouse strains used in present study, we obtained information about the animals' nutritional history and found that it varied little with regard to percent macronutrient composition (11). Prior to 5 wk of age when the mice were shipped to our facility, all the strains studied were maintained on one of three different commercial diets containing 9–14% fat, 64–66% carbohydrate, and 22–24% protein by energy (11).

We observed unique responses in some mouse strains to the protein and fat diets. First, there was no apparent explanation for the inability of the A/J mice in two separate experiments to adapt to the three-choice macronutrient diet paradigm; the mice consumed large amounts of fat but did not eat the protein diet. Two other reports of aberrant behavior in A/J mice were noted in the literature. In a dietary obesity study, A/J
mice failed to consume a synthetic low-fat diet, preferring instead to eat their own feces and cage bedding (25). Also, in a recent study of the genetics of several indexes of mouse behavior, A/J mice failed to complete the task of escaping from a water maze because of wall-hugging behavior (5). Collectively, these observations suggest that A/J mice may have a learning impairment such as that described previously for 129/Sv mice (6). Also, excess fat spillage occurred with some strains (NZB/B1NJ, SWR/J, and C57BL/6J), and this was remedied by placing food followers (see METHODS) on top of the fat diet. Apparently, this intervention had an effect on the animals’ macronutrient selection patterns, i.e., by decreasing fat intake and/or slightly enhancing carbohydrate intake (see Fig. 1, beginning on day 18).

The possible mechanisms underlying the observed strain differences in macronutrient diet selection in the present survey are not well understood. Animals given a choice of individual macronutrient diets may select a

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**Fig. 1.** Means ± SE food intake in kcal of 13 mouse strains self-selecting from among 3 macronutrient diets (carbohydrate, fat, protein) for a study period of 26–30 days. Diet presentation began on day 0, and food intake was measured at 48-h intervals. CHO, carbohydrate.
particular diet because of its flavor, i.e., the combination of taste, aroma, texture, and temperature cues, or because of its postingestive metabolic effects (32). Most studies of how diet preferences are formed have focused on the learned associations between the flavor of food and its postingestive consequences. It is also possible that differences in immediate responses to flavor cues, independent of the postingestive effects, are key in determining diet selection (32). However, little is known about the possible contribution of genetic taste differences to macronutrient intakes.

The evidence in inbred mouse strains for genetic taste traits such as sweetness, bitterness, and saltiness includes results from behavioral, electrophysiological, anatomic, and genetic studies (2, 15, 16, 21, 41). For example, phenotypic strain differences in sucrose intake and peripheral neural responsivity to sucrose (1, 22) led to the identification of two loci on chromosome 4 that accounted for over 50% of the genetic variability in sucrose intake (1, 23). In addition, at least three genetic loci are thought to influence differences in response to bitter tastants in standard inbred strains of mice (41).
We considered known taste phenotypes of strains used in the present study. Of those strains which preferentially consumed the carbohydrate diet, both CAST/Ei (B. K. Smith, unpublished observation) and SWR (16) mice avidly prefer sucrose solutions, whereas BALB/cByJ mice show only a weak preference for sucrose (16). Among the strains displaying a preference for dietary fat, both high (C57BL/6J, C57BL/6ByJ) and low (AKR/J, 129/J, DBA/2J) sucrose consumption has been reported (1, 16, 27; B. K. Smith and D. B. West, unpublished data). Thus there is no clear indication of an association between these phenotypes, i.e., consumption of a sucrose solution and the preferential intake of dietary fat or carbohydrate.

Results from recent clinical studies provide evidence that genetic variation in bitter taste function may contribute to the ability to detect dietary fat stimuli. The ability to perceive as bitter the taste of 6-n-propylthiouracil (PROP) is an inherited trait, and linkage studies have identified a genetic locus on human chromosome 5p15 (29). Specifically, PROP tasters could discriminate differences in the fat content of foods, but nontasters (of PROP) could not (37). In another study, the perceived bitterness of PROP was negatively correlated with liking of high-fat foods (9). These findings suggest that individuals' fat perception may be linked to genetic differences in bitter taste function. However, further investigation is needed, particularly in light of the evidence that PROP perception is also correlated with the perceived intensity of sweet-tasting compounds (14).

Dietary fat is a key environmental component influencing the development of obesity in animals (40) and in humans (8). For example, the C57BL/6J and AKR/J mouse strains are very sensitive to dietary obesity. When fed a moderately high-fat (30%) diet, C57BL/6J and AKR/J mice developed 15–18% and 23% body fat, respectively (20, 39). In the present study, these same two strains were also found to have a high voluntary fat intake, suggesting that the two traits may be genetically linked. Consistent with this notion, we found a significant positive association in both the AKR/J and C57BL/6J strains when we examined the relationship between epididymal depot weight and absolute fat intake. Surprisingly, this post hoc analysis also revealed a significant positive association with liking of high-fat foods. These findings suggest that individuals' fat perception may be linked to genetic differences in bitter taste function. However, further investigation is needed, particularly in light of the evidence that PROP perception is also correlated with the perceived intensity of sweet-tasting compounds (14).

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revealed significant negative correlations in two of the leanest strains, i.e., SWR/J and CAST/Ei, whose percent body fat remains unusually low (7–8%) when they are maintained on a medium high-fat diet (20, 39, 42). Thus in SWR/J and CAST/Ei mice, a higher consumption of fat calories was associated with a lower epididymal fat pad weight. One possible explanation for this set of contrasting observations is that the SWR/J and CAST/Ei strains are highly sensitive to a negative feedback signal generated by increasing body fat, whereas the AKR/J and C67BL/6J mice are insensitive. Leptin is a metabolic signal thought to provide feed-

### Table 3. Body weight, epididymal depot, and organ weights

<table>
<thead>
<tr>
<th>Strain</th>
<th>Number of Mice</th>
<th>Initial Body Wt</th>
<th>Final Body Wt</th>
<th>Epididymal Depot</th>
<th>Epididymal Depot/Initial Body Wt</th>
<th>Spleen</th>
<th>Liver</th>
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<tr>
<td>AKR/J</td>
<td>15</td>
<td>23.1 ± 0.5</td>
<td>35.3 ± 0.8</td>
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<td>NZB/B1NJ</td>
<td>6</td>
<td>20.9 ± 0.8</td>
<td>31.1 ± 1.2</td>
<td>0.763 ± 0.119</td>
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<td>C57BL/6J</td>
<td>13</td>
<td>18.8 ± 0.5</td>
<td>27.5 ± 0.8</td>
<td>0.803 ± 0.081</td>
<td>0.042 ± 0.004</td>
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<td>C57BL/6ByJ</td>
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<td>20.5 ± 0.5</td>
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<td>DBA/2J</td>
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<td>19.8 ± 0.5</td>
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<td>13.4 ± 0.6</td>
<td>17.7 ± 0.9</td>
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<td>0.050 ± 0.004</td>
<td>0.035 ± 0.003</td>
<td>0.980 ± 0.054</td>
</tr>
<tr>
<td>CD-1</td>
<td>14</td>
<td>30.8 ± 0.5</td>
<td>41.3 ± 0.8</td>
<td>1.750 ± 0.078</td>
<td>0.057 ± 0.004</td>
<td>0.103 ± 0.003</td>
<td>1.937 ± 0.045</td>
</tr>
<tr>
<td>SJ/L</td>
<td>14</td>
<td>20.6 ± 0.5</td>
<td>24.9 ± 0.8</td>
<td>1.374 ± 0.078</td>
<td>0.067 ± 0.004</td>
<td>0.093 ± 0.003</td>
<td>1.073 ± 0.045</td>
</tr>
<tr>
<td>SWR/J</td>
<td>14</td>
<td>18.4 ± 0.5</td>
<td>22.9 ± 0.8</td>
<td>0.373 ± 0.078</td>
<td>0.020 ± 0.004</td>
<td>0.101 ± 0.003</td>
<td>1.027 ± 0.045</td>
</tr>
<tr>
<td>129/J</td>
<td>14</td>
<td>19.3 ± 0.5</td>
<td>24.7 ± 0.8</td>
<td>0.845 ± 0.078</td>
<td>0.043 ± 0.004</td>
<td>0.060 ± 0.003</td>
<td>1.121 ± 0.045</td>
</tr>
<tr>
<td>BALB/cByJ</td>
<td>15</td>
<td>23.2 ± 0.5</td>
<td>27.8 ± 0.8</td>
<td>0.492 ± 0.075</td>
<td>0.021 ± 0.004</td>
<td>0.112 ± 0.003</td>
<td>1.677 ± 0.044</td>
</tr>
<tr>
<td>CAST/Ei</td>
<td>14</td>
<td>13.5 ± 0.5</td>
<td>15.6 ± 0.8</td>
<td>0.498 ± 0.081</td>
<td>0.037 ± 0.004</td>
<td>0.029 ± 0.003</td>
<td>0.546 ± 0.045</td>
</tr>
</tbody>
</table>

Data are presented as means ± SE in g. All mice were 7–8 wk old, except for SPRET/Ei whose ages ranged from 6.7 to 8.6 wk. Epididymal depot weights were sum of left and right depots. Values without common superscripted letters are significantly different at P < 0.05 by the Tukey-Kramer method.

Fig. 4. Correlation analysis of absolute fat intake in kcal and epididymal (epid) fat depot adjusted for initial (init) body weight (bwt) in mice self-selecting from 3 macronutrient diets for −4 wk (Pearson $r$, 2-tailed, *P < 0.05).
back from adipose tissue stores to sites involved in the regulation of energy homeostasis. In this regard, both C57BL/6j and AKR/J mice become resistant to the hypophagic effects of peripherally administered leptin after chronic consumption of a high-fat diet (38). Data regarding the response of leptin to high-fat feeding in SWR/J and CAST/Ei mice are not available.

In summary, we observed variation in self-selected fat consumption ranging from 26 to 83% of total energy among mouse strains in response to the macronutrient diet selection paradigm. The significant variation in proportional fat intake among inbred mouse strains indicates that this trait is amenable to genetic analysis and eventual identification of the genes involved. Furthermore, we found evidence that the deposition of epididymal fat is inversely correlated with dietary fat consumption in two lean, inbred strains.

Perspectives

Inbred strain distributions for a wide variety of behavioral traits have been reported (6). Phenotypic trait information can be referenced for planning targeted mutations and transgenic models and for designing genetic crosses used in the analysis of complex traits. Techniques for assessing behavioral phenotypes require careful development and refinement to allow precise and reliable measurement and to control the effects of environmental background (5). The ultimate goal is to identify gene(s) that account for the observed strain variation and to understand the function of these gene products at the molecular level.

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