Published in final edited form as:

Physiol Behav. 2010 April 19; 99(5): 679–683. doi:10.1016/j.physbeh.2010.02.001.

Comparison of C57BL/6 and DBA/2 mice in food motivation and satiety

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Abstract

Demand functions describe the relationship between the consumption of a commodity and its mean or unit price. In the first experiment, we analyzed food demand in two strains of mice (C57BL/6 and DBA/2) that differ on several behavioral dimensions, but have not been examined extensively for differences in feeding and meal patterns. Mice worked for food pellets in a continuous access closed economy in which total intake and meal patterns could be measured. A series of fixed (FUP), variable (VUP), and progressive (PUP) unit price schedules were imposed. Under all schedules, DBA/2 mice consumed significantly more food than C57BL/6, a difference that was not attributable to disparity in body weight or weight gain. The higher intake of DBA/2 mice was due predominantly to larger meal size compared with C57BL/6, with no strain difference in meal frequency. In a second experiment, strain differences in meal size were not found to correlate with anorectic sensitivity to cholecystikinin (CCK) administration, or with c-Fos expression induced by CCK in PVN, AP and NTS. Thus, DBA/2 mice were motivated to sustain a higher daily food intake and meal size than C57BL/6 under the range of demand costs employed in the present work, but this strain difference is unlikely to be due to CCK action or responsiveness.

Index terms

Demand function; strain differences; meal size; progressive unit price; CCK

1. Introduction

We have reported previously on the performance of several strains of mice under operant schedules of food access. Those strains include ob/ob and lean littermates [1] which are derived from C57BL/6 (B6) stock, melanocortin-4 receptor knockout mice and littermates from a 129/B6 background [2,3], and albino ICR-CD1 mice [4]. Under some of the schedules that we have reported, mice are required to pay an approach cost (analogous to travel) to gain access to the food as well as a consummatory or unit price for each food morsel once food is proximate. Under these conditions, like rats and other species studied [5], mice show great adaptability in their meal patterns as a function of approach cost. Usually, many small meals are taken at low approach costs and a few large meals are taken at high approach costs. In contrast, relatively large changes in consummatory or unit price, while changing the duration of meals, have only small effects on meal size and frequency [4].

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Collier [6] considered these changes to reflect the operation of an adaptive planning mechanism, but the gene(s) or parts of the brain involved are unknown. Much evidence suggests that both the hindbrain and the hypothalamus are importantly involved in regulation of meals and overall food intake [7,8]. It is reasonable to anticipate that higher level decisions about behavior will involve the cerebral cortex. In previous studies, we have examined genetically obese mice for feeding motivation [1,3], but those studies have shown little evidence for genetic differences in adaptive strategy. An alternative approach to this question is to compare strains of mice that differ most prominently along behavioral dimensions other than feeding. In this regard, B6 and DBA/2 (D2) strains have often been compared because they show differences in behavior, physiology, and brain anatomy [9-18]. B6 mice are used extensively in genetic and metabolic studies, and the first objective of this paper is to compare demand characteristics for food in B6 mice compared with another commonly-used strain (D2), and to analyze the meal patterns. In free feeding studies, D2 mice have been reported to eat slightly more and/or have a higher metabolic rate than B6 [10,14,19,20] but to our knowledge neither food intake parameters (meal size, frequency) nor demand functions have previously been established.

In this study, mice were compared under three different schedules of reinforcement for food that we have studied previously in outbred mice [4]. These are:

- Fixed ratio or fixed unit price (FUP) in which the price per food pellet is constant.
- Variable ratio or variable unit price (VUP) in which unit price varies around a specified mean
- Progressive ratio or progressive unit price (PUP) in which unit price of successive pellets within a meal increases

The results of this behavioral experiment indicated a strain difference in intake and meal size so a second experiment was conducted to examine whether these strains differed in their anorectic response to a satiety hormone, cholecystokinin (CCK). CCK is released in the gut during meals and is believed to restrain meal size by stimulating glutamatergic vagal afferent fibers that project to the nucleus of the solitary tract (NTS) [21-24]. To assess indirectly the cellular activation by CCK in the NTS and other brain regions, we additionally compared the induction of c-Fos by CCK in B6 and D2 mice.

2. Methods

2.1. Subjects and housing

Eight male B6 mice and eight male D2 mice (Jackson Laboratories; Bar Harbor, ME), initially 2-4 months of age and weighing about 20g, were used in each experiment. During the study periods in Experiment 1, mice lived in operant chambers for 23 h per day. They were weighed daily and kept in empty holding cages during a 1 h cleaning period. When not on study, and throughout Experiment 2, mice were housed in a standard polycarbonate cages with Purina 5001 Chow pellets and tap water available ad libitum, except as noted. A 12:12 light cycle was in effect (lights on 0700). During study periods of Experiment 1, mice obtained 20 mg complete nutritional pellets (Purina Test Diet 5TUM) when they completed a cost that was determined by the reinforcement schedule.

2.2. Operant behavior chambers

Sixteen operant behavior chambers (Med Associates, St. Albans, VT: 13×13×12 cm), with Plexiglas and alloy walls and stainless steel grill floor were used as the test enclosures. They were contained within ventilated, noise attenuating cabinets with the same 12:12 light cycle as the vivarium via a 7 w bulb in a night light fixture run from a 24 h timer. All chambers were

equipped with one nose poke operant device located approximately 2 cm above the floor and situated on one wall adjacent to a food receptacle. In a previous study [4] we found that mice consumed 5-10% more using a nose poke compared with a lever press operant, so we chose to use only the nose poke device in this study. Water was supplied from a sipper tube mounted on the wall opposite the food receptacle.

A record of total pellets obtained and number of responses were acquired by MED-PC IV computer software (Med Associates). Computer recordings allowed an analysis of the number of meals and the amount eaten at each meal. Data were accumulated in 15 min (for FUP and VUP) or 5 min (for PUP) time bins throughout each 23 h period.

2.3. Experiment 1: Demand functions for food

Eight mice of each strain were run through a series of consummatory cost schedules in which delivery of each pellet was contingent upon completion of a designated number of nose pokes. Prior to the study, to habituate mice to the operant chambers and to the novel pellets, a 1 h training period was applied with free food available in the food receptacle at no cost. For the next 1-2 days, a fixed unit price-1 (FUP1) schedule was in effect in which a food pellet was delivered after each nose poke. Mice were considered to have learned the contingency when they earned enough pellets over 23 h to maintain their body weights, typically within 2 days. No food deprivation was imposed prior to or at any time during the experimental phase.

After this initial training, mice were subjected to an incrementing series of FUPs (1,5,10,25,50). They next were tested with VUPs (10,20,50) in which the cost of any given pellet is varied by the computer program to be 10, 50,100,150 and 190% of the mean (viz: 1,5,10,15,19 for VUP10; 2, 10, 20, 30, 38 for VUP20; and 5, 25, 50, 75, 95 for VUP50) and with the constraint of equal probability of occurrence. The final phase of testing used PUPs in which the number of responses required for the next $(n+1)^{\text{th}}$ pellet in a series was calculated using the formula $R_{n+1} = R_n \times 1.25$ (PUP1.25), $R_{n+1} = R_n \times 1.5$ (PUP1.5), or $R_{n+1} = R_n \times 1.75$ (PUP1.75), where R_n = response requirement for the n^{th} pellet. The resulting number was rounded to the nearest integer. For example, the numbers of responses required for the 1st, 6th, 11th and 16th pellet at PUP 1.25 were 1, 4, 10, 28, respectively. At PUPs 1.5 and 1.75, the corresponding response numbers were 1, 8, 58, 441, and 2, 29, 471, 4417. Thus, the mean price per pellet within a run or meal escalated as the run became longer and the meal became larger. Further, during the PUP series, whenever 15 min elapsed without a response the ratio was reset to the initial value (R_1) of the schedule. This reset allowed the animals to quit eating when the unit price of a pellet became too high and be able to resume at low cost after a minimum 15 min delay.

The raw data showed the number of responses made and the number of pellets earned in each 15 min (FUP and VUP) or 5 min (PUP) time bin throughout the 23 h period (1380 min) each day. Non-responding (non-eating) episodes were defined as 15 min time bins with zero pellets received. This data stream was then separated into meals using a 15 min (eg for FUP, at least one zero separating nonzero bins) minimum criterion. On average, eating will have stopped in the middle of the interval preceding the zero entry and will have started in the middle of the interval following the zero entry, so that the "15 min" criterion on average in fact defines a minimum 30 min inter-meal interval but with a possible range from 15-45 min. After the numbers of meals per day were determined for each mouse, the mean meal size was derived by dividing the number of total pellets by the number of meals for each day. No systematic difference was noted across the 4 days of each schedule for either total intake or meal parameters. Thus, for each mouse, the mean number of meals, total pellets earned and meal sizes were averaged across the 4 days of each reinforcement schedule. These individual mean data were then treated using a repeated measures analysis of variance (ANOVA; SPSS) with the strain (B6 vs. D2) as a between-subject variable and the schedules as a within-subject

variable. For the analyses within each ratio schedule type (FUP, VUP, PUP), one-way ANOVAs were used.

2.4. Experiment 2: Effects of CCK

2.4.1. Behavioral procedure—Using 8 new mice from each strain, short term (30 min) intake was measured in two types of protocol that induce large meals in a short interval. The first protocol was a “dessert” test in which mice were adapted to receive a highly preferred food treat at the same time each day. The dietary treats were Fruit Crunchies (Bio-Serv; No. F05798; 52% carbohydrate, 20% protein, 6% fat by weight, with carbohydrate fraction ~75% mono- and disaccharides), 190-mg spherical pellets and available in grape, apple, and orange flavors [25]. During training, the mice received 10 pellets of mixed flavors in a 10 ml glass beaker, hung inside the cage from a metal stirrup. On the first day, the beaker was left in place for as long as needed for robust intake to occur. Thereafter, the time per day was tapered to 30 min. All mice readily consumed Crunchies. Test intakes were recorded as the number of Crunchies eaten; bedding was searched for half pellets, but these or smaller crumbs were typically minimal. Intakes were later transformed to weight using 190 mg as the average weight of each pellet. The second protocol, using the same mice, was a standard 18 h overnight food deprivation followed by access to a pre-weighed pellet of Purina 5001 chow. After 30 min, the pellet was removed and reweighed to determine the amount consumed.

On test days in both protocols mice were injected subcutaneously at about 1300 h with either the vehicle (saline, .02 ml/10 g body weight) or CCK (sulfated octapeptide, Sigma Chemical Co, St Louis MO; 6 µg/kg). This dose was chosen on the basis of our previous work [26]. The test food was presented 5 min after injection, and intake recorded after 30 min. Tests were conducted at 1 week intervals; half the mice of each strain received vehicle first while the other half received CCK. There was no effect of order. Absolute intakes were compared using ANOVA or t-tests, with $P < 0.05$ considered significant. Additionally, intakes after CCK were examined when expressed as % of the intake for each individual on the corresponding vehicle test.

2.4.2.C-Fos immunoreactivity—After completion of the feeding studies, the same mice now freely fed chow were used to study induction of c-Fos immunoreactivity by CCK. On the test day, and about 2 h before the time of day that the intake tests were conducted, chow pellets were removed from the home cages. After 2 h, mice received intraperitoneal injection of CCK (6 µg/kg) and were returned to their home cages for 1 h without food. At the end of this time, mice were anesthetized (Sleepaway, 1 ml/kg; Fort Dodge), and perfused transcardially with heparinized saline followed by paraformaldehyde. Brains were removed, stored in paraformaldehyde overnight, and then sliced by vibratome into coronal 75 µm sections at the levels of the paraventricular nucleus (PVN) of the hypothalamus and the area postrema (AP) and adjacent nucleus of the tractus solitarius (NTS). Sections were then incubated with primary (c-Fos 4 polyclonal; Santa Cruz) and secondary (biotinylated goat anti-rabbit IgG, Zymed) antibodies, and the reaction product visualized using ABC (Vector Labs), as we have described in detail elsewhere [27]. Sections were mounted on slides and c-Fos positive cells in regions of interest were examined under a microscope and counted manually by two observers. To ensure a blind procedure, identifying numbers were obscured on the slides during this phase. The counts from the two observers showed <5% variation and were averaged, then compared using t-tests.

3. Results

3.1. Experiment 1: Demand functions for food

At the time of these studies, D2 mice were about 17% heavier than B6 mice. B6 mice weighed a mean ($\pm$ SE) of 26.7 ± 0.5 g during the FUP and VUP schedules and D2 mice weighed 31.1 ± 0.6 g ($P < 0.01$). During the PUP phase, the corresponding weights were 28.7 ± 0.1 g and 33.4 ± 0.3 g ($P < 0.01$).

The mean food intakes for B6 and D2 strains at each schedule are shown in the top row of Figure 1. D2 mice ate significantly more pellets per day than B6 on each series of schedules, and pairwise comparisons at each unit price were highly significant ($P_s < 0.01$). For all FUP and VUP consummatory costs, mice of the D2 strain emitted correspondingly more consummatory responses (nose pokes) per day compared to B6 (Figure 1, second row). This was also true for the PUP schedules; again, all the pairwise comparisons were highly significant ($P_s < 0.01$).

With the exception of PUP1.75, the numbers of meals taken per day were identical in the two strains (Figure 1, third row). The higher food intake of the D2 mice thus was accounted for predominantly by increases in meal size (Figure 1, bottom row; all $P_s < 0.01$). No interactions between strain and schedule type were found.

The numbers of responses emitted per day under PUP were less than with most other schedules (Figure 1) and the mean price per pellet was correspondingly lower. Since food spillage was very small, the mean price per pellet consumed during the FUP and VUP series, computed as nose pokes per pellet consumed over 23 h periods, was within 5% of the actual ratio value. By contrast, in the PUP series, mice emitted relatively few nose pokes for a relatively large number of pellets. The mean prices (nose pokes per pellet) on the PUP 1.25, 1.5 and 1.75 schedules, respectively, were 3.6, 6.1 and 8.8 for B6 mice and 4.5, 12.5 and 16.5 for D2 mice.

3.2. Experiment 2: Effects of CCK

The results are shown in Figure 2. CCK injections reduced food intake relative to vehicle in both strains and in both protocols (all $P_s < 0.05$). In the dessert protocol, B6 mice consumed ~25% more Crunchies after the vehicle injections than D2 ($P < 0.05$). However, the anorectic effect of CCK, measured as % suppression from vehicle, did not differ between strains (46 vs 51%).

The chow intake in the food deprivation protocol was higher in B6 than D2, but not significantly so, after the vehicle injection. However, the anorectic effect of CCK was significantly greater in B6 than D2 (86 vs 54% suppression, $P < 0.01$). For B6 mice, the % suppression in the deprivation-chow protocol was significantly greater than in the Crunchies protocol ($P < 0.05$).

The effect of CCK on Fos-ir in PVN, AP and NTS was not significantly different between strains. This dose of CCK induced very strong Fos in the PVN, AP and NTS of both strains, so much so that accurate counting was not possible, but no strain differences were obvious. However, while examining the sections, an unexpected neuroanatomical difference between the strains was noted insofar as the lateral cerebral ventricles were markedly larger in B6 than D2. To quantify this, we selected a section as close as possible to Figure 32 (bregma -0.1 mm) in the Paxinos and Franklin atlas [28] and measured the distance between the two most dorsolateral corners of the left and right lateral ventricles (distance A) and the width at the narrowest part of the dorsolateral septum (distance B). The difference between A and B is an index of ventricular size/width at this level. For B6 mice ($n=7$), A was $2.87 \pm .05$ mm (Mean $\pm$ SE), B was $1.03 \pm .02$ mm, and the difference $1.84 \pm .05$ mm. For D2 mice ($n=7$), corresponding values were $2.52 \pm .03$ ($P < 0.001$), $1.15 \pm .05$ ($P < 0.05$), and $1.37 \pm .07$ mm ($P < .001$).

4. Discussion

The major finding in the first experiment is that the overall food intake and meal sizes of male D2 mice are higher than in B6 mice. To our knowledge, this is the first detailed report of spontaneous food intake and meal structure in D2 mice. Bachmanov et al [29] and Lewis et al [19] reported that total food intake of male D2 mice was 5-10% higher than in B6 mice of the same body weight. In contrast, Lewis et al [20] found that basal food intake of D2 mice was almost 50% higher than in B6 despite weighing slightly less. Lewis et al did not explain this difference between their studies [19,20] but given that D2 mice may have 30% higher basal metabolic rate and a core temperature 0.7°C higher than B6 [14], it is possible that only small differences in ambient temperature could modulate the magnitude of the strain difference. In the present study, D2 mice ate approximately 50% more than B6 (Figure 1); a difference of only 10-16% can be accounted for by their higher body weight, depending on whether a 2/3 power or linear relation with body weight is assumed. Further, despite higher food intake, D2 mice did not gain weight faster than the B6 mice, also suggesting higher metabolic rate.

It has been reported that there is a difference in baseline locomotion between the two strains; under food restriction both D2 and B6 mice decreased in body temperature but only D2 displayed increased locomotion [15]. Both B6 and to a lesser extent D2 mice are considered to be obesity prone when fed a calorically dense diet [30-32] and the findings summarized above suggest that B6 mice are energetically thrifty.

While the B6 mice in the present study consumed less than the D2, it is noteworthy that they also consumed some 20-30% less than young adult male albino CD-1 mice obtaining food by nose poke in our previous study [4]. Further, in a previous study using young adult female B6 mice and a combined approach cost and consummatory lever press cost protocol [1], the average daily intake was 200-250 pellets, somewhat higher than in the males of the present study. The reasons for these differences are not clear, but suggest that the intakes of the D2 mice in the present study are not exceptionally high but instead that those of the B6 mice are lower than in some other strains we have studied.

The food intake of both strains increased in switching from FUP to VUP and VUP to PUP schedules (Figure 1). This is most likely a function of the successive nature of these phases, with animals becoming more experienced with a variety of costs. Intake declined within each ratio type as unit price increased, and rebounded on the easiest schedule of the next type. Body weight did not increase markedly between phases so it cannot account fully for the greater food intake in the VUP or PUP series.

Following the studies described in this paper, the same mice were studied briefly using a concurrent schedule of approach (procurement) and unit (consummatory) costs. In this study, both lever and nose poke manipulanda were present and active. For all mice, nose poke was the procurement response and lever press was the consummatory response. Mice were then tested in a series of FUP costs (5, 10, 25, 50) at an approach cost of 5. Each schedule was applied for one day only, to examine the rapidity with which adjustments could be made to increased price in a complex environment. Initially, the D2 mice had higher food intake than the B6, but by the highest ratio the D2 mice consumed less than the B6. This suggests either that combination costs may reveal more subtle aspects to the strain difference and/or that D2 mice are less able to readjust to sudden increases in cost; systematic studies will be needed to verify this possibility. This would potentially be consistent with observations that the brain is heavier and the neocortex is 7% larger in B6 compared to D2 [9,33]. In the brains that we examined, the dimensions of the brains of B6 mice were very close to those in Figure 32 of Paxinos and Franklin [32] which also used B6 mice. Relative to this, D2 mice had a wider dorsal septum, smaller distance between the lateral edges of the lateral ventricles, and a smaller

ventricular space. This suggests that subcortical structures such as septum and striatum may be slightly larger in D2 mice than B6, although more systematic studies would be needed to verify this possibility. Thus, several aspects of cerebral architecture may differ between B6 and D2 mice, and underlie their behavioral phenotypes [10-18].

The reason for the difference in food intake and/or metabolism between B6 and D2 mice remains unclear, although some neurochemical differences have been reported. For example, D2 mice have higher levels or turnover of enkephalin in some brain regions than B6 [34-36]. It was reported that mice genetically lacking enkephalin had decreased motivation to press a lever for food reinforcement compared with wild type controls [16]. Thus, lower responding in order to receive food in B6 mice in the present study is consistent with this interpretation. However, PUP schedules are widely believed to be sensitive indicators of motivation [3], so the fact that B6 mice did not show a greater relative impairment on the PUP schedules compared with FUP or VUP may suggest that their motivation is normal and instead that mechanisms of satiation (ending a meal) differ between the two strains.

Experiment 2 was designed to make a preliminary assessment of satiation in B6 compared with D2 mice. CCK is released in the gut during meals and is believed to restrain meal size by stimulating glutamatergic vagal afferent fibers that project to the nucleus of the tractus solitarius (NTS), and/or by direct action in the area postrema (AP) [7,21-23]. Exogenous administration of CCK-8 reduces meal size by engaging either or both of these mechanisms. However, in two different protocols, using either moderately sweet Crunchies or bland chow as the food, vehicle-treated B6 mice consumed more than D2 mice, the opposite result from the ad lib meal patterns. The effect of CCK did not differ between strains in the dessert protocol but in the deprivation protocol B6 mice were more sensitive to exogenous CCK than D2. The discrepancy between a larger meal of chow after vehicle and a greater suppression of intake with CCK in B6 relative to D2 argues that factors other than CCK are driving normal satiation in mice. Since c-Fos induced in AP or NTS by this dose of CCK was not found to differ between strains, it is possible that B6 mice release less endogenous CCK per unit of food consumed.

In a studies related to alcohol intake, it was reported that alcohol-preferring B6 mice had a higher content of POMC mRNA in the arcuate nucleus, and a higher density of δ opioid receptors in the ventral tegmental area and nucleus accumbens compared with alcohol-avoiding D2 [34,35]. However, dynorphin levels were higher in nucleus accumbens of D2 mice [36]. These opioids have also been implicated in feeding [7] so it is plausible that the higher dynorphin levels in the nucleus accumbens of D2 strain could contribute higher food intake in D2 mice. Further, increased POMC content in B6 mice could present an inhibitory signal (α -MSH) for eating, resulting in reduced food intake in this strain. Further studies will be needed, for example manipulating opioid synaptic activity, to determine whether these neurochemical differences contribute to differences in food intake or choice between strains.

Acknowledgments

This work was supported in part by NIH grant DK064712.

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Figure 1.

Mean ($\pm$ SE; $N_s=8$) performance of C57BL/6 (B6, closed circles) and DBA/2 (D2, open circles) working for food according to various fixed unit price (FUP) ratios (left panels), variable unit prices (VUP, middle panels) and progressive unit prices (PUP, right panels). Note that the FUP and VUP abscissae are scaled logarithmically. The top row shows the food demand in pellets consumed per day. The second row shows the number of nose pokes emitted in obtaining that food (logarithmic ordinate). The third row shows the mean meals per day, and the fourth row the corresponding mean meal size. All differences between B6 and D2 were significant ($P_s<0.05$) except for the meals per day.

Figure 2.

Mean ($\pm$ SE; $N=8$) 30 min intakes of food in groups of B6 and D2 mice following injection of either vehicle or CCK-8 ($6\mu\text{g/kg}$). The left panel shows intakes of Crunchies treat by non-deprived mice and the right panel shows intakes of chow after 18 h food deprivation. In all cases, intakes after CCK were significantly lower than after the corresponding vehicle injection ($P<0.01$). The intake of Crunchies was lower in D2 than B6 mice both after vehicle ($P<0.01$) and CCK ($P<0.05$), but both the absolute and fractional suppression by CCK did not differ between strains. The intake of chow did not differ between strains after vehicle but was lower in B6 than D2 after CCK ($P<0.05$). The fractional suppression by CCK was thus greater in B6 than D2 ($P<0.01$).