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ORIGINAL ARTICLE

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The hedonic overdrive model best explains high-fat diet-induced obesity in C57BL/6 mice

Lin Gao[1,2,3] | Sumei Hu[1,2] | Dengbao Yang[2] | Lu Wang[2] | Jacques Togo[2] | Yingga Wu[2] | Baoguo Li[2] | Min Li[1,2] | Guanlin Wang[2] | Xueying Zhang[1,2] | Li Li[2] | Yanchao Xu[2] | Moshen Mazidi[2] | Elspeth Couper[4] | Andrew Whittington-Davies[4] | Chaoqun Niu[1,2] | John R. Speakman[1,2,4,5]

[1]Shenzhen Key Laboratory of Metabolic Health, Center for Energy Metabolism and Reproduction, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China

[2]State Key Laboratory of Molecular Developmental Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing, China

[3]University of Chinese Academy of Sciences, Beijing, China

[4]Institute of Biological and Environmental Sciences, University of Aberdeen, Aberdeen, UK

[5]Institute of Public Health Sciences, China Medical University, Shenyang, China

Correspondence
John R. Speakman
Email: j.speakman@abdn.ac.uk

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Abstract

Objective: High-fat diets cause obesity in male mice; however, the underlying mechanisms remain controversial. Here, three contrasting ideas were assessed: hedonic overdrive, reverse causality, and passive overconsumption models.

Methods: A total of 12 groups of 20 individually housed 12-week-old C57BL/6 male mice were exposed to 12 high-fat diets with varying fat content from 40% to 80% (by calories), protein content from 5% to 30%, and carbohydrate content from 8.4% to 40%. Body weight and food intake were monitored for 30 days after 7 days at baseline on a standard low-fat diet.

Results: After exposure to the diets, energy intake increased first, and body weight followed later. Intake then declined. The peak energy intake was dependent on both dietary protein and carbohydrate, but not the dietary fat and energy density, whereas the rate of decrease in intake was only related to dietary protein. On high-fat diets, the weight of food intake declined, but despite this average reduction of 14.4 g in food intake, they consumed, on average, 357 kJ more energy than at baseline.

Conclusions: The hedonic overdrive model fit the data best. The other two models were not supported.

Lin Gao, Sumei Hu, and Dengbao Yang contributed equally.

INTRODUCTION

When exposed to a diet containing >40% fat by calories, the males of many strains of mice deposit large amounts of body fat [1–4]. The effects in females are smaller [5–7]. The underlying mechanism generating the obesity effect in males is not well understood. There are at least three contrasting ideas. The first is that the high-fat diets stimulate the hedonic system in the brain, and this overrides the normal homeostatic mechanisms that link together energy expenditure and intake [8, 9]. This has been called hedonic eating [10, 11], excessive hedonic drive [12], or hedonic overdrive [1]. The consequence is that the mice overconsume calories beyond their needs, and the result is then an accumulation of body fat because this excess energy needs to be stored somewhere. This idea is an integral part of the energy balance model of obesity [13]. An alternative idea has been proposed in the context of the carbohydrate-insulin model [14–16] and has been called "reverse causality" [16]. Although originally specified as a reason why dietary carbohydrates might lead to obesity, in the present paper, we are concerned with the obesogenic nature of dietary fat, and a similar process might be envisaged. That is, when the animals consume fat, it gets taken up and locked away into the adipose tissue, making it unavailable for utilization to fuel metabolism. The animal then finds itself with insufficient fuel available to support metabolism, and this leads simultaneously to reduce metabolic rate and elevate intake in a runaway process in which greater amounts of body fat drive greater intake, leading to greater accumulation [14, 16, 17].

The contrasting predictions of these two different mechanisms, in relation to the day-to-day changes in intake and body weight change, are illustrated in Figure 1A. The hedonic overdrive model predicts that, upon exposure to the high-fat diet, there would be an immediate increase in calorie intake relative to baseline, and, over time, this would lead to an increase in body weight. In contrast, reverse causality posits that the parameter to change first would be body weight, and, after that increase, there would be a secondary increase in food intake.

If the pattern matches that predicted by the hedonic overdrive model, then this might be due to stimulation of the hedonic system in the brain [18], but it could also reflect a third potential explanation. This is called the passive overconsumption model [19–22]. By this model, the animals overconsume calories, driving them into positive energy balance and weight gain, but they do so because the primary mechanism by which food intake is regulated is by its weight [19, 21, 23–25]. Because high-fat foods have a greater energy density [26], if an animal simply continued to eat the same weight of food after being swapped from a low-fat to a high-fat diet, then it would get fat by passively overconsuming calories. Consequently, reducing the energy density might be a way to reduce intake and control body weight [27]. These two alternatives might be distinguished, as illustrated in Figure 1B, in which the daily weight of food is plotted against the change in body weight. Under the hedonic overdrive, not only would calories be overconsumed, but also the weight of the food, dependent on its composition, whereas, under passive overconsumption, the weight consumed would remain constant as the animal gained weight, independent of its composition.

Study Importance

What is already known?

- When male mice are fed high-fat diets (>40% by energy), they get fat. The reasons for this effect remain uncertain because, generally, studies have not performed measurements frequently enough or used a sufficient range of different diets to test among alternative ideas.

What does this study add?

- We measured food intake and body weight daily for 12 groups of individually housed 12-week-old male C57BL/6 mice exposed to 12 different diets (n per group = 20, total n = 240). We tested among three different ideas for why male mice get fat on these high-fat diets: hedonic overdrive, reverse causality, and passive overconsumption. The data were not completely consistent with any single model, but the hedonic overdrive model provided the best fit.

How might these results change the direction of research or the focus of clinical practice?

- If these data also pertain in humans, they suggest that people overeat because hedonic qualities of high-fat diets override any homeostatic intake regulation. Therefore, reducing the rewarding qualities of high-fat foods may be a potential way to curb their intake.

Early work comparing "cafeteria diets" to purified high-fat or high-carbohydrate diets has found that rats exposed to a cafeteria diet exhibited accelerated weight and adipose gain, often attributed to hedonic properties of the foods [28]. However, such studies have two main issues. First, the details of exactly what the animals ate are often lacking; therefore, the intake may have increased because of passive overconsumption. Second, they may be predisposed to support the hedonic overdrive model because they would likely choose to eat only foods that they like. In contrast, rodents may get fat, even when eating foods that they do not choose to, because of passive overconsumption and, potentially, reverse causality. To separate these different hypothetical responses, it is necessary to utilize a range of different macronutrient formulations. This is because, if a single level of fat was used in the high-fat diet, the hedonic stimulus of that food might, by chance, generate the same pattern as that produced by passive overconsumption and thereby would not allow us to separate the responses. Using a range of fatness levels then allows us to make variable exact quantitative predictions based on passive overconsumption against which the actual intake can be tested. Deviations from these predictions would then support the hedonic overdrive model.

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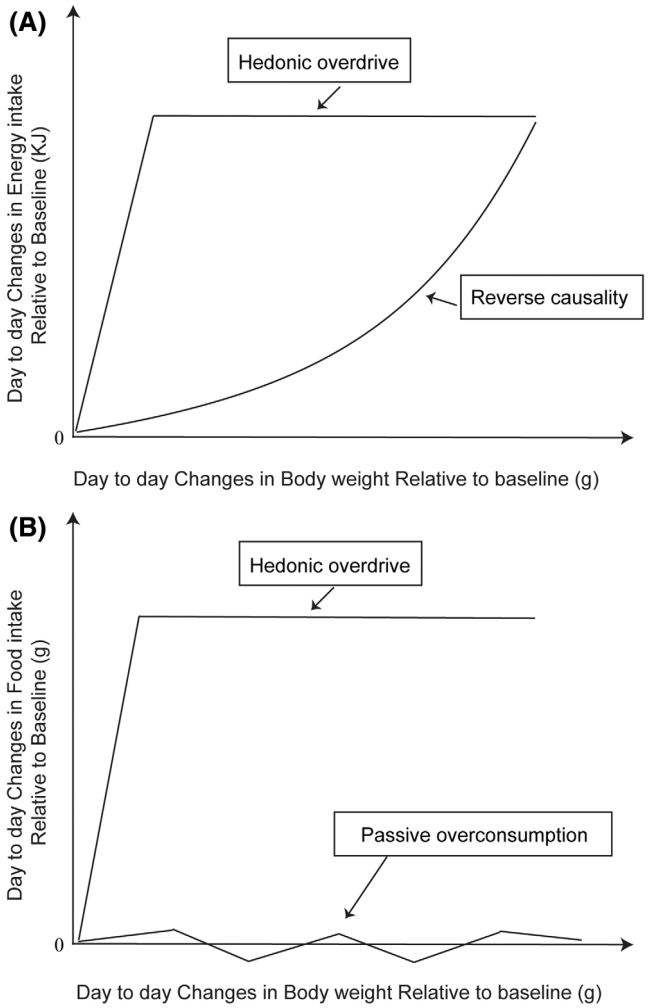

FIGURE 1 Different models of why male mice get fat on high-fat diets. (A) The hedonic overdrive model and the reverse causality model. (B) The hedonic overdrive and passive overconsumption models.

In this paper, we quantified the day-to-day food intake by both weight and energy and the day-to-day changes in body weight of 240 male C57BL/6 mice for 7 days prior to and 30 days after exposure to 12 different diets varying in their fat content (by energy), from 40% to 80% (20 mice per diet). From our previous studies, we established that there was a strong relationship between body weight and body fatness in C57BL/6 mice ($r^2 = 0.7618$; $p < 0.0001$; Figure S1), and, therefore, we used body weight as a surrogate measure for body fatness because we considered that measuring fatness daily by EchoMRI would impose stress that would potentially impact body weight. We did not study females because female mice of this strain put on relatively little weight when fed high-fat diets [5–7, 29, 30]. These data form part of a larger project, aspects of which have already been published [1, 7], but the data analysis performed here is new. We used the patterns observed in relation to the predictive framework established in Figure 1 to test among the different models.

METHODS

Ethics statement

All procedures were reviewed and approved by the Institutional Review Board, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences. The approval numbers were AP2014011 and AP2016039.

Mice

Eight-week-old male C57BL/6 mice were purchased from Charles River Laboratories and acclimated to the animal house for 3 weeks. Following that, there was a baseline period of 7 days during which all the mice were fed with a standard low-fat diet that contained 10% fat, 20% protein, and 70% carbohydrate by energy (D12450B, Research Diets, Inc.). Mice were individually housed, allowing us to accurately quantify their intake while also avoiding the issues of social stress in group-housed male mice [31–35]. After 7 days at baseline, the mice were exposed to 12 different diets that varied in their fat, protein, and carbohydrate contents for 30 days. The 12 diets analyzed here all had more than 40% fat by calories, which, in male mice, results in elevated body weight and fatness [1]. They had shredded paper, allowing them to make nests [36], as well as other items for enrichment. Room temperature was controlled at 22 to 24°C, and we used a 12:12 light:dark cycle in specific pathogen-free facility conditions. The mice were provided with ad-libitum access to food and water. They were also monitored for health status every day.

Experimental diets

The first six diets were fixed at 60% fat by energy, protein content ranged from 5% to 30%, and carbohydrate content varied reciprocally from 10% to 35% by energy (D14071601, D14071602, D14071603, D14071604, D14071605, and D14071606). In the remaining six diets, we fixed the level of protein at 10% or 25% by energy (three diets at each level), and the fat content of diets was varied. When the protein level was fixed at 10%, the fat contents were 50%, 70%, and 80% (D14071616, D14071617, and D14071618). When the protein level was fixed at 25%, the fat contents were 41.7%, 58.3%, and 66.6% (D14071622, D14071623, and D14071624). The carbohydrates included corn starch and maltodextrin, which are high glycemic index carbohydrates for mice [37]. Casein was used as the protein source in all diets. Sucrose and cellulose were fixed at 5% level by energy, and standard vitamins and mineral mix were also added to all diets [1]. A mix of cocoa butter, menhaden oil, sunflower oil, palm oil, and coconut oil was used as the fat source, and it was designed to generate a 47.5:36.8:15.8 proportion of saturated, monounsaturated, and polyunsaturated fats and a 14.7:1 proportion of n-6 and n-3 fatty acids, which aimed to match the Standard American Diet. The proportions of different fatty acids were

constant across different fat levels. In these diets, the sucrose, cellulose, and vitamin and mineral contents were the same as the diets of fixed 60% fat. The full details of all diets are shown in Table S1. For replication, all of these diets can be ordered direct from Research Diets, Inc. (https://researchdiets.com/) using the diet codes provided.

Food intake and body weight measurement

Body weight and food intake were measured daily over the 1-week baseline period and after switching to the experimental diets for 30 days. Food intake was measured from the weight of food that went missing from the food hopper each day. Mice occasionally pulled pellets of food through the hopper bars or ground their food; therefore, a thorough search of the cage was made to return any uneaten food to the hopper before weighing. No other procedures (such as glucose tolerance tests) were performed during these 30 days.

Statistical analysis

Statistics were performed using IBM SPSS 22, GraphPad Prism software version 9.0, and Microsoft Excel. All values are expressed as mean ± SD. Repeated-measures general linear modeling (GLM) was used to analyze body weight, food intake, and energy intake over time. After exposure to the diets, intake rose to a peak and then declined. Regression analysis was used to analyze the relationship between changes in body weight and changes in energy intake. Stepwise regression was used to explore the dietary factors influencing the intercept and gradients of the regressions linking body weight and intake changes. Differences were considered significant if $p < 0.05$. Significance levels were adjusted for multiple testing where appropriate using the Bonferroni adjustment.

RESULTS

Day-to-day changes in body weight and energy intake relative to baseline

After 30 days of dietary exposure, the body weights of all the mice were significantly higher than the body weights during baseline. The mice gained between 7% and 34% of their initial body weight over time among all groups (Table S2; Figure S2A–D). The energy intake of the mice fed with the 12 different diets were higher than when they were fed the baseline diets (Table S2; Figure S3A–D). The energy intake of mice reached a peak (after 2–10 days of high-fat diet exposure) when they consumed 24% to 63% more energy than at baseline. The time taken to reach the peak was not significantly related to the height of the peak (Figure S4). After the peak, there was a significant decrease, but energy intake always remained above the baseline level (Table S2; Figure S3A–D).

To test between the hedonic overdrive and reverse causality ideas, we first calculated the mean difference between daily body weight and baseline body weight, as well as the mean difference between energy intake and baseline food intake each day averaged across the 20 mice exposed to each of the 12 different diets. Then, we plotted the daily difference in body weight to baseline (grams) against the daily difference in energy intake to baseline (kilojoules, Figure 1). The energy intake increased rapidly over the first few days in all 12 diets to a maximum after 2 to 10 days with minimal change in weight, and the body weight increased gradually only after the energy intake had increased to this maximum (Figure 2A–L).

We performed regression analysis on the changes in body weight and energy intake after the maximum, which occurred on days 2 through 10. This showed that there was a significant negative relationship between changes in body weight and energy intake for 10 of the 12 diets. The nonsignificant relationships were for 25% and 30% protein groups under 60% fat (regression data, Table 1). We used the intercept of the fitted regressions to estimate the predicted energy intake at zero body weight change, i.e., the fitted intercept value (Table 1), and called this the zero weight change (ZWC) intake. This value is the predicted energy intake independent of any change in body weight. We explored how this ZWC intake was influenced by the dietary macronutrient content (respectively, fat, protein, and carbohydrate content of diets). There was a significant negative relationship between the ZWC intake and dietary protein content ($F = 9.03$, $p < 0.05$; $r^2 = 0.47$) and a positive association with carbohydrate content ($F = 19.01$, $p < 0.01$; $r^2 = 0.66$) of the diets. That is, intake rose higher when protein level was lower but was higher as carbohydrate increased. There was no significant relationship with the dietary fat content ($F = 1.008$, $p > 0.05$; $r^2 = 0.09$; Figure 3A–C). Using stepwise regression, the ZWC intake was only dependent on dietary carbohydrate ($r^2 = 0.66$ for carbohydrate: $t = 4.36$, $p = 0.001$). The ZWC intake was also not significantly related to the energy density of diets ($F = 0.68$, $p > 0.05$; $r^2 = 0.0636$; Figure 4A).

We also explored the relationship between the diet composition and the gradients of the fitted regressions (Table 1). This showed the gradient of decline in intake as weight increased was significantly associated with increasing protein content of diets ($F = 5.590$, $p < 0.05$; $r^2 = 0.359$), but not carbohydrate ($F = 0.392$, $p > 0.05$; $r^2 = 0.0377$) or fat contents ($F = 1.090$, $p > 0.05$; $r^2 = 0.098$; Figure 3D–F). This was reflected in the stepwise regression analysis in which only protein entered as a significant factor ($r^2 = 0.359$ for protein: $t = 2.36$, $p = 0.04$). Because the ZWC intake and the rate of decline were inversely related with each other (Figure 4B: $r^2 = 0.43$), this meant that, by days 25 through 30, when the mice had gained about 7 g of weight, the excess intake relative to baseline was far less variable among diets than the ZWC intake. We used the regression equations to predict the energy intake after the mice had gained 7 g of body weight. The choice of 7 g was arbitrary and only provided a reference point to compare across different diets. This was significantly associated with dietary fat content ($F = 11.08$, $p < 0.01$; $r^2 = 0.528$), carbohydrate content ($F = 23.48$, $p < 0.05$; $r^2 = 0.701$), and energy density ($F = 13.3$, $p < 0.01$; $r^2 = 0.571$), but not protein content ($F = 0.66$, $p > 0.05$; $r^2 = 0.062$; Figure 5A–D). Stepwise regression indicated that the only macronutrient significantly related to the predicted energy intake after 7 g of weight gain was carbohydrate content, which was positively related to the predicted intake ($r^2 = 0.701$ for carbohydrate: $t = 4.846$, $p = 0.001$). Therefore, mice

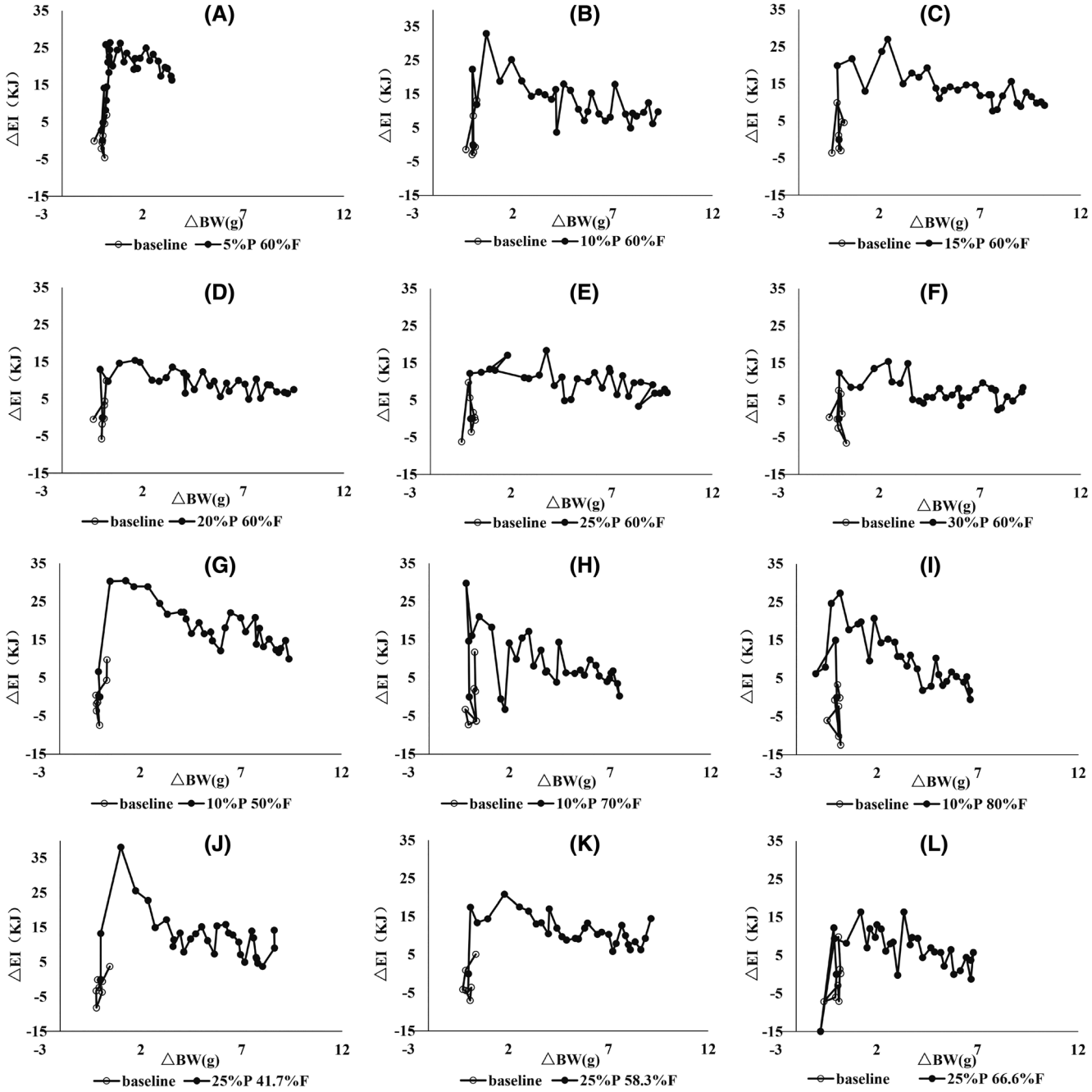

FIGURE 2 Trends of day-to-day changes in energy intake (△EI; kilojoules) against changes in body weight (△BW; grams), both calculated as difference to baseline, for 12 groups of mice fed with diets varying in fat content from 40% to 80%. Each point is the average of 20 mice on a given day and diet.

with higher carbohydrate levels in the diet were consuming more calories at this point.

Day-to-day changes in weight of food intake relative to baseline

All of the food intakes of the mice by weight, rather than energy, were lower than the weight of intake at baseline, except for the diet containing 5% protein and 60% fat (Figure S5A–D). Repeated-measures GLM analysis showed that, for this diet, the food intake of mice increased over time. For the diets with 10% protein and 50% fat and those with 25% protein with 41.7% fat, the food intake of mice was increased for 2 days after switching diets and declined after that. For the remaining nine diets, the mice reduced their food intake over time after switching diets. This was significant for seven of the diets, but, for the 10% protein and 60% fat diets and the 10% protein and 80% fat diets, the decreasing trend was not significant after Bonferroni correction (Figure 6A–L).

TABLE 1 Regression analysis among changes of energy intake and changes of body weight after changes of energy intake reached a maximum.

	r^2	*F*	*df*	*p* value	Equation
5%P 60%F	0.40	11.89	1, 18	0.0029	Y = −1.64*X + 24.4
10%P 60%F	0.42	18.43	1, 25	0.0002	Y = −1.45*X + 20.5
15%P 60%F	0.49	22.12	1, 23	<0.0001	Y = −0.98*X + 19.5
20%P 60%F	0.39	15.13	1, 24	0.0007	Y = −0.70*X + 13.1
25%P 60%F	0.04	0.7413	1, 19	0.4	Y = −0.30*X + 10.9
30%P 60%F	0.08	1.931	1, 23	0.178	Y = −0.38*X + 9.0
10%P 50%F	0.66	48.64	1, 25	<0.0001	Y = −1.81*X + 29.2
10%P 70%F	0.26	9.189	1, 26	0.0055	Y = −1.33*X + 14.1
10%P 80%F	0.77	76.12	1, 23	<0.0001	Y = −2.86*X + 20.5
25%P 41.7%F	0.40	17.34	1, 26	0.0003	Y = −1.62*X + 21.1
25%P 58.3%F	0.37	13.92	1, 24	0.001	Y = −0.98*X + 16.9
25%P 66.6%F	0.40	15.37	1, 23	0.0007	Y = −1.57*X + 13.1

Abbreviations: F, fat; P, protein.

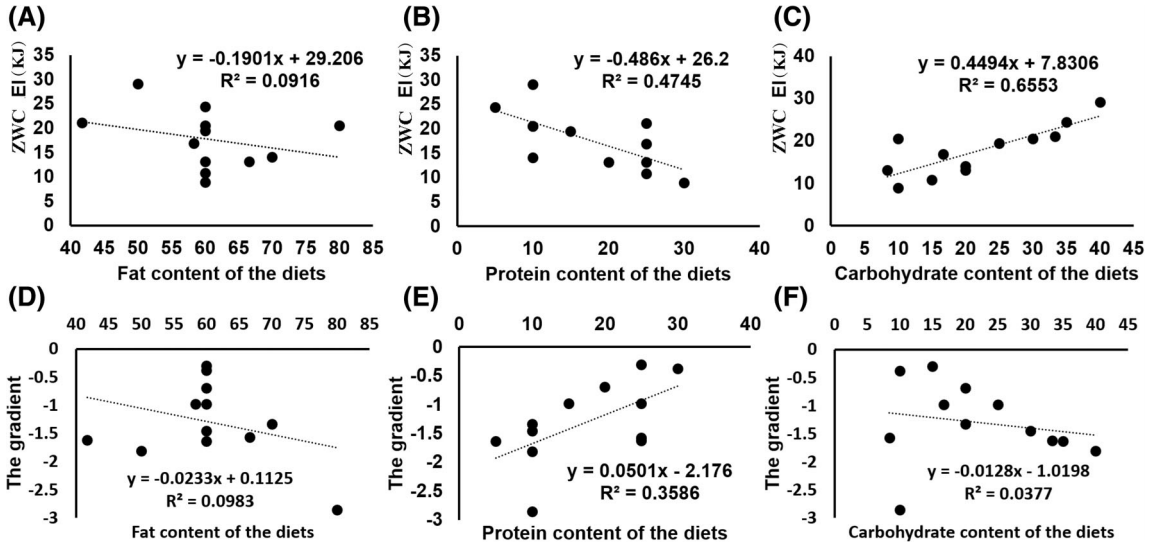

FIGURE 3 Relationships between dietary macronutrient content (percent) and the zero weight change (ZWC) energy intake (EI; kilojoules) or the gradient of the change in body weight relative to baseline in male C57BL/6 mice.

DISCUSSION

We evaluated three ideas regarding why male mice get fat when fed diets that contain >40% fat. We used 12 different diets and followed the changes in food intake and body weight daily for 30 days. The first comparison was between the reverse causality model (fat drives intake) and the hedonic overdrive model (intake drives fatness), as illustrated in Figure 1A. The data presented here clearly supported the hedonic overdrive model better than reverse causality. Within a day of the diet being switched to a high-fat alternative, the energy intake increased above the baseline levels (Figure 2). This increased for a few days until reaching a peak at days 2 through 10. At this point, there was generally less than 1 g of change in body weight. Therefore, the pattern of change in this initial phase clearly matched the pattern predicted by the hedonic overdrive model compared with that by reverse causality (Figure 1A). The weight increase followed rather than being simultaneous to or preceding the increase in energy intake. Although the reverse causality idea was formulated in the context of the carbohydrate-insulin model [15], mice do not get fat when fed high levels of carbohydrates in their diet [1, 7, 38]; therefore, it is not possible to test that mechanism with respect to carbohydrates. Mice (particularly males) do get fat when fed high-fat diets, and reverse causality remains a plausible mechanism in this situation. This study, however, indicates that it is unimportant in this context. That does not mean that reverse causality is unimportant in other contexts such as obesity driven by excess carbohydrate consumption in other species such as humans, as has been claimed elsewhere [14–16].

The energy intake at ZWC from the fitted regressions was heavily dependent on the protein and carbohydrate contents of the diet but less so on the universally high fat content. The relationship to

carbohydrate content was consistent with the idea that mixing together carbohydrates and high fat provides the greatest stimulus for intake [39–41]. Therefore, the highest ZWC intake occurred with both high fat and high carbohydrates. The hedonic overdrive model suggests that intake should remain high after it has increased (Figure 1A). This was not observed for the majority of diets. After the energy intake increased for a few days, it then started to decline. The decline was significant in 10 of 12 diets. Moreover, once the intake peaked, the rate at which it declined as the animals increased in weight was more dependent on the protein content of the diet compared with the fat and carbohydrate contents, and, in a stepwise multiple regression, only protein content was significant. The decline was steepest when the protein content was lower. This response to protein is the opposite from that anticipated by the protein leverage hypothesis, which would predict greater stimulation of intake at lower protein levels [42]. The reason for this effect is unclear.

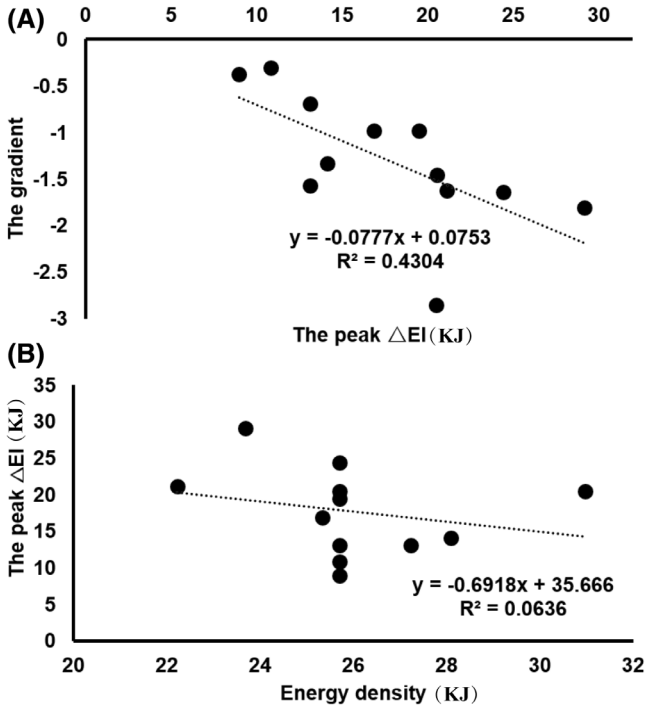

FIGURE 4 Relationship between (A) the gradient of body weight change and the zero weight change (ZWC) energy intake (EI; kilojoules) and (B) the energy density of diets (kilojoules) and the ZWC EI (kilojoules).

Predicted intake when the mice had gained 7 g of body weight was significantly related to both fat and carbohydrate contents of the diet, but not protein. Fat and carbohydrate contents were reciprocally related. Increasing fat above 40% had a negative effect on intake, whereas increasing carbohydrates from 8% to 40% had a positive effect. Increasing levels of carbohydrate content, in the context of a high-fat diet, thereby promoted continued elevated intake, even after the mice had gained 7 g of body weight (about 30% of their starting weight). It is important to note that this stimulatory impact of increasing carbohydrates in the diet only happens in the context of a diet containing >40% fat by calories [1]. These observations are also consistent with the hedonic overdrive model that a mix of about 30% to 40% carbohydrate and 40% to 50% fat (by calories) stimulates intake the most [41]. Similar work points to this combination as being stimulatory in humans [43].

We then compared the hedonic overdrive idea with the passive overconsumption model. When the diets were switched, the mice continued to eat roughly the same weight of food for a few days

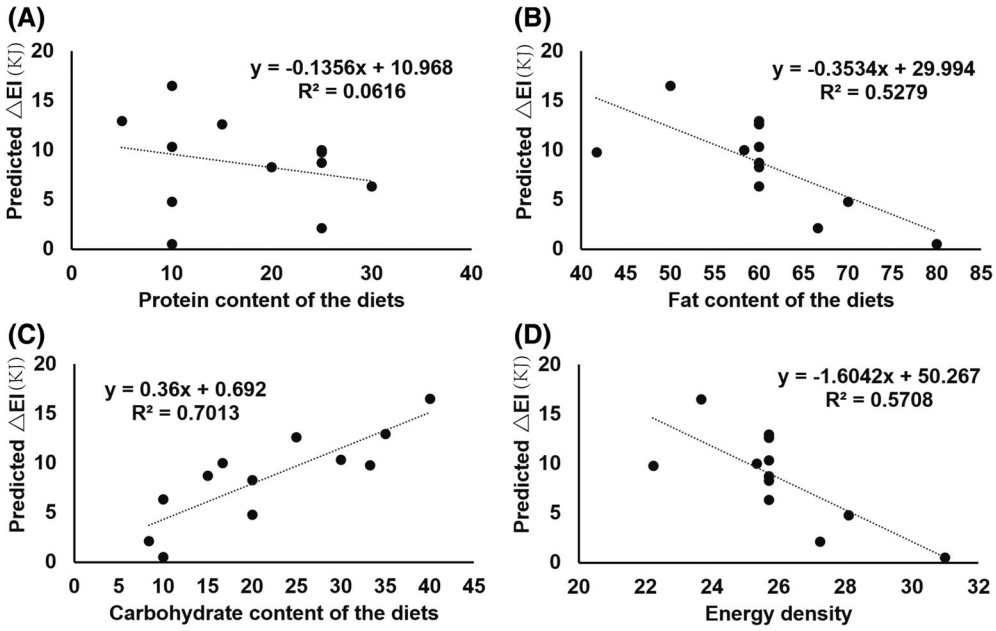

FIGURE 5 Regression between predicted energy intake (EI) relative to baseline (kilojoules) when the mice had gained 7 g of body weight and dietary macronutrient content. (A) Protein, (B) fat, (C) carbohydrate (percent), and (D) the energy density of diets (kilojoules).

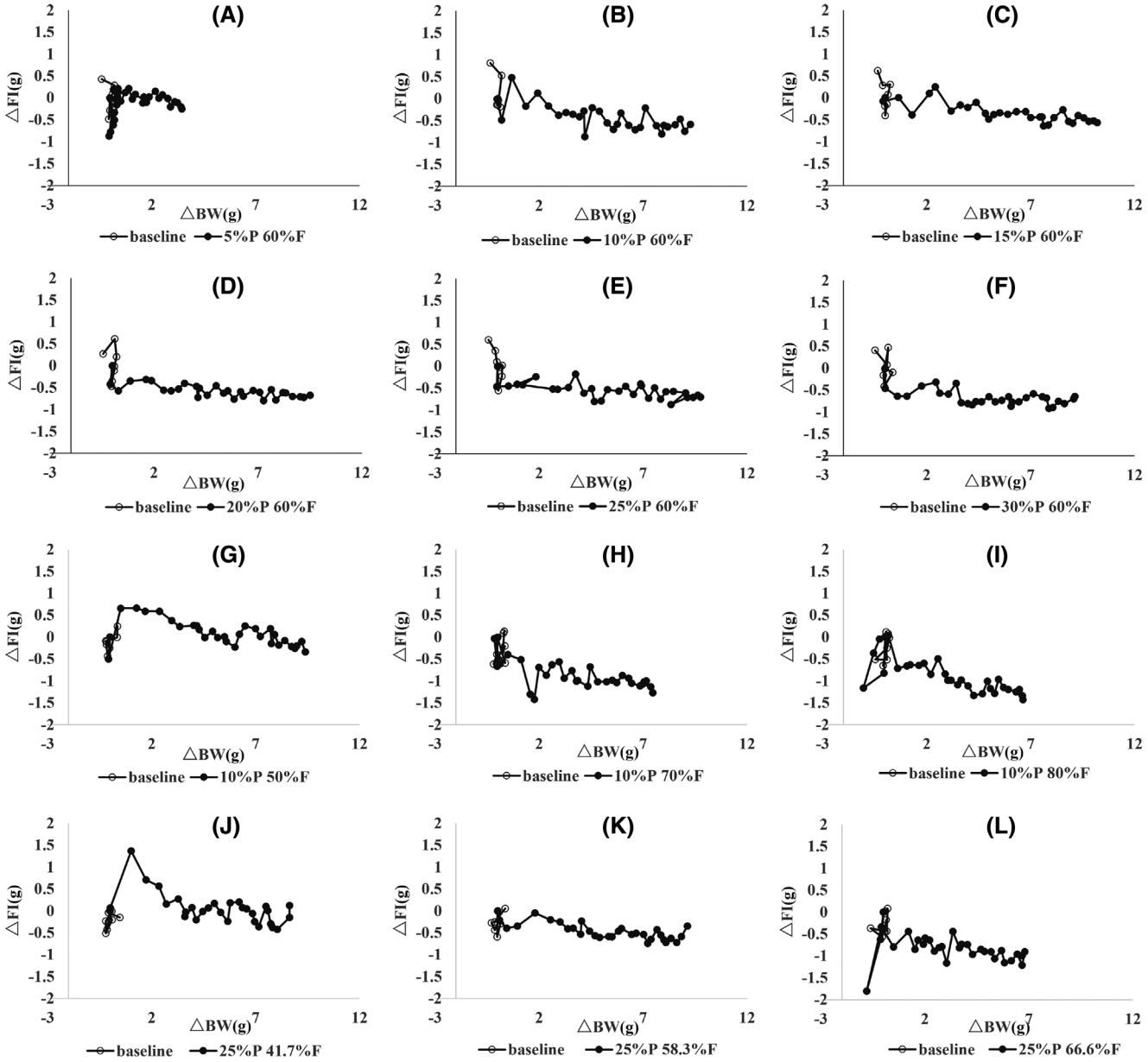

FIGURE 6 Trends of day-to-day changes in weight of food intake (△FI; grams) against changes in body weight (BW; grams) relative to baseline for mice fed with diets varying in fat content from 40% to 80%.

(Figure 6A–L); therefore, energy intake increased. This appeared to match the passive overconsumption model better than hedonic overdrive. However, if the passive overconsumption model was correct, then the peak energy intake after the diet was changed should have been mostly influenced by the energy density of the food in a strong positive correlation. In other words, the peak only existed because the energy density of the higher-fat foods was greater. There was, in contrast to this expectation, a weak, nonsignificant negative relationship ($r^2 = 0.06$) between energy density and the peak energy intake (Figure 4B). Furthermore, when we added energy density into the predictive model along with the macronutrient compositions, it did not enter as a significant factor. Studies in humans have suggested that energy density may be a strong driver of intake [44, 45], but only when the energy density is lower than a threshold of about 7.3 kJ/g [21]. All of the diets used here were dry diets with high fat content (40%–80% by calories) and thereby had energy densities greater than 20 kJ/g; therefore, the lack of an impact of energy density and passive overconsumption may not be surprising.

The passive overconsumption model also predicts that individuals should continue to eat the same weight of food throughout the time that they are gaining weight. However, the time tracks of the weight of intake show that they did not do this. In all but one case (60% fat, 5% protein, and 35% carbohydrate), the weight of food consumed declined over time. Although energy density was a strong predictor of the energy intake after the mice had gained 7 g of body weight ($r^2 = 0.57$) the relationship was negative, reflecting the balance of carbohydrates and fat, and opposite of the direction predicted from the passive overconsumption model. One interpretation of the decline

in intake after the peak is that the animals were attempting to regulate their body weight. However, the data are not consistent with this interpretation. The decline in intake occurred very quickly after the peak intake, i.e., before there was any appreciable body weight increase. Moreover, they never reduced their intake to a point at which body weight started to decline, suggesting that the reduced intake does not perform a function of body weight regulation.

In conclusion, none of the models provided an exact description of what happened. The hedonic overdrive model seemed to best fit the changes in consumption following the diet switch. However, after the initial peak in intake, the animals continuously adjusted the weight of food they ate downward, potentially attempting to compensate for the fact that they were overconsuming calories. This pattern of partial compensation over time is also observed in long-duration covert manipulations of energy density in humans [46, 47]. That trend is not predicted by a simple version of the hedonic model, but other, more complex models could be envisaged in which reward declines with time on the diet. On all diets, the mice were still overconsuming after 30 days of exposure, and the level of overconsumption with the different diets still seemed to fit the hedonic model. By day 30, on all diets, they were consuming substantially less weight of food but still more calories relative to the baseline intake. This pattern of intake is replicated in humans consuming high-fat diets [48]. They consume less weight of food but more calories. Recent work has suggested that this decrease may be governed by projections from the cerebellum that dampen the reward value of foods [49]. The fact that the mice here, and humans in other studies, ate a lower weight of food but a greater amount of calories and, in doing, so gained weight, is a direct refutation of the mass balance model of obesity [50, 51].

What remains a mystery is what prevents the male mice studied here (and both sexes of humans) from lowering their intake a little further so that they would be completely in balance and not further accumulating. This could be achieved, on average, across all the diets that we studied by the mice eating 0.34-g (SD = 0.19 g) less food per day (about 10% of the baseline intake). This suggests that, if there is a calorie counter modulating intake, it is at best imprecise and susceptible to error when foods have high fat contents. Alternatively, our interpretation that the intake decline is because the mice are aiming to compensate for calorie overconsumption may be incorrect. Finally, given that we now identified hedonic overdrive as a key feature driving male mouse overconsumption when exposed to high-fat diets, why female C57BL/6 mice do not have the same magnitude of response as males would seem a profitable area for future investigation. This is particularly the case because some studies have suggested that female rats may be more susceptible to hedonic eating when sated than males [52, 53]. The molecular basis of what happens in the brains of mice during the different phases of response after high-fat diet exposure would seem a profitable area of future investigation. We have already shown such patterns after 3 months of exposure [1], but not during the dynamic phases immediately following the change in diet identified herein. The main limitation of this work is that the pattern we observed did not match exactly any of the models proposed a priori. However, we were unable to come up with a convincing explanation for the discrepancy among the data and the models. More sophisticated models are required to understand more fully what is happening when mice are exposed to high-fat diets. Also, it is unclear how closely these findings translate to food intake patterns in humans.

AUTHOR CONTRIBUTIONS

John R. Speakman directed the project; conceived and designed the experiments; contributed to the analysis; and co-wrote the manuscript. Lin Gao analyzed the data and co-wrote the manuscript. Sumei Hu, Dengbao Yang, Li Li, Lu Wang, Jacques Togo, Yingga Wu, Baoguo Li, Min Li, Guanlin Wang, Xueying Zhang, Yanchao Xu, Moshen Mazidi, Elspeth Couper, Andrew Whittington-Davies, and Chaoqun Niu were involved in the initial experimental design and performed body weight and food intake measurements.

CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

ORCID

Lin Gao https://orcid.org/0009-0007-1586-7503
John R. Speakman https://orcid.org/0000-0002-2457-1823

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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