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Factors influencing individual variability in high fat diet-induced weight gain in out-bred MF1 mice

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HIGHLIGHTS

- Individual variability in high fat diet-induced weight loss was studied in MF1 mice.
- Pre-existing differences and changes in compensation were investigated.
- Fat free mass and sex predicted around 12% of the variability in body mass.
- Food intake during the 1st week of high fat feeding predicted 20% of the variability.
- Mice that gained more weight on high fat diet lost more when dietary restricted.

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ABSTRACT

Easy access to high-energy palatable foods has been suggested to have contributed to the world-wide obesity epidemic. However, within these 'obesogenic' environments many people manage to remain lean. Mice also show variability in their weight gain responses to high-fat diet (HFD) feeding and their weight loss responses to calorically restricted (CR) feeding. In this study we investigated which factors contribute to determining susceptibility to HFD-induced obesity in mice, and whether the responses in weight gain on HFD are correlated with the responses to CR. One-hundred twenty four mice were exposed to 30% CR for 28 days followed by a 14 day recovery period, and subsequent exposure to 60% HFD for 28 days. Responses in various metabolic factors were measured before and after each exposure (body mass; BM, body composition, food intake; FI, resting metabolic rate; RMR, physical activity, body temperature and glucose tolerance; GT).
Weight changes on HFD ranged from −1 to 26%, equivalent to −0.2 g to 10.5 g in absolute mass. Multiple regression models showed that fat free mass (FFM) of the mice before exposure to HFD predicted 12% of the variability in weight gain on HFD ($p < 0.001$). Also, FI during the first week of HFD feeding predicted 20% of the variability in BM and fat mass (FM) gain 4 weeks later. These data may point to a role for the reward system in driving individual differences in FI and weight gain. Weight gain on the HFD was significantly negatively correlated to weight loss on CR, indicating that animals that are poor at defending against weight gain on HFD, were also poor at defending against CR-induced weight loss. Changes in FM and FFM in response to HFD or CR were not correlated however.

1. Introduction

The 'obesogenic' environment of modern society, with its high abundance of palatable energy-dense foods, has led to a gradual increase in the number of people that suffer from obesity and related diseases [12,23]. However, the response amongst people exposed to such 'obesogenic' environments is highly variable; some people are susceptible to weight gain while others remain lean [3]. Studying this individual variability in responses could reveal processes of individual weight regulation and establish the biological factors that make people either susceptible or resistant to weight gain, which is crucial to increase our understanding of the aetiology of obesity. For example, in male Sprague Dawley rats on pure macronutrient or high fat diets, measures of weight gain, energy intake or fat preference are shown to vary considerably in direct proportion to ultimate body fat gain ([28,39,49], also see [55] in mice).

Substantial individual variability in weight loss is also observed in response to caloric restriction (CR) (e.g., humans [1,5], mice [47]). For instance, weight loss ranged from 1 to 36% in mice that had exposed to 30% CR for 4 weeks [47]. In this previous study, ~70% of the variation

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in weight loss could be attributed to individual variability in baseline food intake (FI), activity and resting metabolic rate (RMR) and changes in activity in response to CR. It is currently unclear if weight changes in response to high fat feeding (HFD) and CR are linked; i.e., are individuals that are poor at defending against weight gain also poor at defending against weight loss? Or does an individual that defends itself well against weight loss, defend itself poorly against weight gain? The dual intervention point model [33,42] suggests that body mass (BM) is regulated by an upper and lower intervention point above and below which physiological mechanisms are activated to maintain BM in the preferred range [42]. It is hypothesised that the upper and lower intervention points are potentially set by the risk of predation and starvation respectively, and it is assumed that they are independent. This model would thus predict no correlation between responses to over and undernutrition. Alternatively, the general model of intake regulation [8], which hypothesises that energy intake is regulated by compensated factors (e.g., stomach content, hunger) and uncompensated factors (e.g., time of day, social factors), may predict a negative relationship between weight loss and gain. This model assumes that BM is maintained at a constant level until changes occur to a compensated or uncompensated factor, in response to which a new level of BM is reached and maintained. The magnitude of the change in BM depends on the magnitude of the individual response to the altered factor and individuals that respond strongly to changes in factors may be expected to be susceptible to both HFD and CR, whereas other individuals may be resistant to both.

Animal models have been developed that include HFD-induced obesity-prone and -resistant animals (rats [28,30,31,35] and mice [20]) and these animals have been shown to differ in their energy intake, glucose tolerance (GT), expression of (an)orexigenic neuropeptides and responses to CR [4,20,31,37]. These responses are generally observed after obesity has developed, and it is thus unclear whether they are the cause of differences in weight gain between animals fed HFDs, or a consequence of variable responses to the HFD. In addition, within these groups of animals (obesity resistant vs. obesity prone) individual variability in responses to HFD remains. Whether the extent to which individual variability prior to exposure of animals to HFD predisposes or protects individuals from weight gain has not been extensively studied in animal models (e.g., [3,28,55]). Zhang et al. [55] showed that pre-existing differences in baseline physical activity levels, lean BM and body fatness were all predictors of weight gain in C57Bl/6 mice when exposed to a HFD, but that baseline FI, body temperature (Tb) and lean BM were not. Some of the variation in these traits at baseline could be traced back to nutritional history during development.

The aim of this study was to investigate whether variation in pre-existing traits relevant to energy balance and body composition could predict variability in weight gain in response to HFD feeding. In addition, we aimed to establish whether individual responses in weight gain and weight loss are linked. We used an outbred mouse strain (i.e., MF1) to study these effects. MF1 mice vary considerably in their responses to CR and HFD and they develop age-related obesity on standard low-fat laboratory diets (10% kcal from fat); i.e., fat content is ~30% of BM at 6 months of age, compared to 10% in adult mice at 10 weeks of age [16]. These mice therefore provide a suitable model to investigate variability in responses to CR and HFD induced weight changes (see also [47]). Baseline FI, fat mass (FM), fat free mass (FFM), RMR, general physical activity, Tb and GT were selected as potential predictors. These predictors were selected because previous studies have suggested that individual variability in the tendency to gain weight is associated with high FI, low RMR and low activity [36,44,54,55] and that there is an inverse relationship between Tb and obesity [29,38,45]. In addition to pre-existing variation in these traits, changes that occur in traits in response to high fat feeding may also contribute to the variability in HF diet-induced weight gain. Therefore we also studied whether variability in changes in RMR, Tb and/or activity in response to HFD feeding could predict HFD-induced weight gain. To elucidate whether preference for the HFD (due to the palatability of the food) [2,10,11] contributed to weight gain, FI during the first week of HF feeding was also included as a predictor in these models, and food preference tests were performed.

2. Methods & procedures

2.1. Animals and housing

Male and female outbred MF1 mice were obtained from Harlan Ltd. UK at 4 weeks of age (parental generation, n = 46) or bred in house (first generation of offspring, F1, n = 78). Mice were maintained in a temperature controlled room (21 ± 1 °C) under a 12:12-h light–dark cycle, with lights on at 5:00 h and a "dawn/dusk" period of 20 min at either end of the light period. After a breeding event at 10 weeks of age all mice (males and females) were individually housed in standard cages containing shredded paper and a red dome-shaped house for enrichment. Out of the females used in this study (n = 65) 53 gave birth and weaned successful litters and the others (n = 12) were unsuccessful. Animals had ad libitum access to food (D12450B, 10% kcal fat, 18.36 kJ g^{-1}, Research Diets, New Brunswick, USA) and water. All mice (n = 124) were implanted intraperitoneally with temperature transmitters (PDT-4000 E-Mitter, Mini Mitter Company Inc., USA) under general anaesthesia (mixture of isoflurane and oxygen). Males were implanted at 14 weeks of age and females at 17–18 weeks of age at least 10 days after their litters had been weaned. Mice were allowed at least 12 days to recover from the surgery before the start of the experiment. All procedures concerning animal care and treatment were approved by the ethical committee for the use of experimental animals of the University of Aberdeen, and licensed by the UK Home Office.

2.2. Experimental procedure

Baseline measurements (BL) started at the age of 19–20 weeks and were taken over a period of 4 weeks (days −28 to −1). During this time mice had ad libitum access to food (D12450B) and water. FI of all mice was then restricted to 70% of their individual BL FI (calculated in grammes over the last week of BL) for a period of 28 days (caloric restriction, CR; days 0–28). Food rations were weighed and delivered daily between 16:00 and 17:00. After the CR phase animals received ad libitum food for a period of 2 weeks to recover from CR (RC, days 29–42). Mice then received ad libitum high fat diet (D12492, 60% kcal from fat, Research Diets, New Brunswick, USA) for a period of 4 weeks (HF, days 43–70).

BM and FI were measured each day between 16:00 and 17:00 (1 h before lights off) throughout the experimental periods; i.e., BL, CR, RC and HF phases. Data on BM, FI, RMR, body composition, physical activity and Tb from the BL and CR phase of this experiment have been published previously [47] in a paper investigating predictors of individual variability in diet-induced weight loss.

2.3. Food preference test

A food preference test was performed on day −27 of the BL period. Animals were given a choice of 4 diets over a 24 h period: 1.) high carbohydrate (HC) diet (CRM (P), 66:22:12% kcal from carbohydrates:protein:fat (C:P:F), 18.4 kJ g^{-1}, Special Diets Services, BP Nutrition, Witham, UK), 2.) medium fat (MF) diet (D12451, 35:20:45% kcal C:P:F, 20.2 kJ g^{-1}, Research Diets), 3.) high fat (HF) diet (D12492, 20:20:60% kcal C:P:F, 23.9 kJ g^{-1}, Research Diets, New Brunswick, USA) or 4.) custom-made high protein (HP) diet (DX04080301, 30:60:10% kcal C:P:F, 21.1 kJ g^{-1}, Research Diets). Animals were offered 10.0 ± 0.1 g of each diet in small petri-dishes that were randomly distributed over the cage floor and the amount of food left from each diet after 24 h was measured to calculate how much food was consumed from each diet.