Brief communication

MOLECULAR METABOLISM

High fat diet causes rebound weight gain

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ABSTRACT

Obesity is at epidemic proportions but treatment options remain limited. Treatment of obesity by calorie restriction (CR) despite having initial success often fails due to rebound weight gain. One possibility is that this reflects an increased body weight (BW) set-point. Indeed, high fat diets (HFD) reduce adult neurogenesis altering hypothalamic neuroarchitecture. However, it is uncertain if these changes are associated with weight rebound or if long-term weight management is associated with reversing this.

Here we show that obese mice have an increased BW set-point and lowering this set-point is associated with rescuing hypothalamic remodelling. Treating obesity by CR using HFD causes weight loss, but not rescued remodelling resulting in rebound weight gain. However, treating obesity by CR using non-HFD causes weight loss, rescued remodelling and attenuates rebound weight gain. We propose that these phenomena may explain why successful short-term weight loss improves obesity in some people but not in others.

Keywords Obesity; Neurogenesis; Hypothalamus; Calorie restriction; Rebound weight gain

1. INTRODUCTION

Obesity is at epidemic proportions in many developed nations, but treatment options remain limited. The homoeostatic body weight (BW) set-point theory is strongly supported by the counter-measures that are enabled to resist weight loss under calorie restriction (CR) [1], and the subsequent return to their original body weight after dieting is terminated, called rebound weight gain [2]. However, such robust homoeostatic regulation is difficult to reconcile with environmental influences on BW; feeding mice a high fat diet (HFD) induces obesity (DIO) which can be reversed by feeding regular chow [3]. One proposed solution to this paradox is that the BW set-point is altered by environmental factors via changes in the neuroarchitecture of the homoeostatic energy balance circuit [4] and indeed, the properties of homoeostatic energy balance are altered by HFD and restored by feeding regular chow [3]. Recently, remodelling of the hypothalamus has been identified in obese mice and humans [5] and we have discovered that dietary regulation of hypothalamic neurogenesis alters hypothalamic neuroarchitecture [6].

Treatment of obesity by reducing calorie intake, despite having a good success rate in promoting initial weight-loss, has a generally poor outcome for long-term weight control [7]. Indeed the large scale Diabetes Prevention Program [8] and its follow up the Look Ahead trial [9] demonstrate that the short-term success of lifestyle change in lowering obesity is offset in the long-term by rebound weight gain. The mechanisms underlying long-term rebound weight gain remain unclear although the homoeostatic BW set-point theory suggests that obese subjects have a higher BW set-point reflecting an underlying defect of the homoeostatic energy balance circuit. Those individuals who achieve long-term weight management after caloric restriction (CR) may have successfully lowered their set-point while rebound weight gain may result from a failure to lower the raised set-point during the period of restriction. However, it is uncertain if obese individuals do have an increased BW set-point and if successful long-term weight management is associated with reversing this.

Here we follow up on our recent study of dietary regulation of proliferative remodelling in the murine hypothalamus [6] and find that obese mice do have an increased BW set-point and that lowering this set-point is associated with rescuing proliferative remodelling. We show that hypothalamic remodelling and long-term BW control are distinct from short-term BW changes, and propose that these phenomena may explain why successful short-term weight loss improves obesity in some people but not in others.

2. RESULTS AND DISCUSSION

2.1. Both calorie restriction and HFD reduce hypothalamic proliferative remodelling

The hypothalamic energy balance circuit is remodelled by ongoing adult neurogenesis; in lean mice old neurons are replaced by newborn neurons [6]. However, neurogenesis is reduced in both diet induced obesity (DIO) and genetic obesity; in obese mice newborn neurons are not generated and old neurons are retained [6]. This change is not permanent, and inducing weight loss in DIO animals by CR rescues proliferative remodelling in the hypothalamic niche [6]. However, it is unclear if this rescue is complete, and the extent to which macronutrient composition of diet during CR affects the extent of rescue. To test the extent of proliferative remodelling during weight loss and the role of dietary macronutrients in this process, we fed 6 week old mice HFD for 10 weeks to induce obesity. We then treated these 16 week old DIO mice with diets rich in a single macronutrient high protein (HPD), high carbohydrate

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Diet	%Energy Fat	%Energy Protein	%Energy Carbohydrate	Gross energy (kJ/g)	Manufacturer	Reference
HFD	45	20	35	20.1	Research Diets	D12451
HCD	10	20	70	16.3	Research Diets	D12450B
HPD	13.2	42.6	44.3	15.9	Teklad	TD90018
KD	93.4	4.7	1.8	30.1	Bio-Serv	F3666
Chow	9.1	22.0	68.9	13.8	Special diets services	801722

Table 1: Composition of the diets used (data as provided by manufacturer).

(HCD), ketogenic (KD = high fat and low protein and carbohydrate) or maintained them on HFD for 4 weeks (see Table 1 for diet details). Diet treated mice where further sub-divided by feeding either ad-lib (AL) or CR at −30% of daily energy intake with a final group size of 7 mice per diet/feeding regime combination. The extent of proliferative remodelling in the arcuate nucleus (ARC)/median eminence (ME) niche was measured by BrdU incorporation during the last week of treatment (Figure 1).

As expected DIO mice maintained on ad-lib HFD did not lose weight while DIO mice treated with HFD-CR lost weight (Figure 1a). Treatment of DIO mice with non-HFD diets either ad-lib or under CR also caused weight loss (Figure 1a). When fed ad-lib, macronutrient composition had a significant effect on final BW ($p < 0.001$), but had no effect on final BW under CR (Figure 1b). For all diets, CR of DIO mice resulted in a final BW similar to chow fed controls treated with CR (Figure 1b).

DIO mice fed HFD with 45% of energy derived from fat (Table 1) had a significantly reduced proliferative remodelling compared to chow fed controls (Figure 1c). This is in agreement with our previous finding in mice fed HFD with 58% of energy derived from fat [6] suggesting that reduced proliferative remodelling is a general feature of mice fed HFDs. Treating DIO mice with ad-lib HPD, HCD and KD led to a significant recovery of proliferative remodelling, although this recovery did not reach the level seen in ad-lib controls (Figure 1c). Likewise, treating DIO mice with HPD, HCD and KD under CR led to a significant recovery of proliferative remodelling (Figure 1c). This recovery of proliferative remodelling under CR was significantly less than seen in ad-lib fed mice ($p < 0.001$). The finding that CR inhibits proliferative remodelling compared to ad-lib feeding was confirmed in chow fed controls; CR significantly inhibited hypothalamic proliferative remodelling in non-obese mice (Figure 1c).

While CR had a significant inhibitory effect on recovery of proliferative remodelling there was no compounding effect of individual dietary macronutrients ($p = 0.865$, HCD, HPD and KD). However, DIO mice fed HFD-CR showed no recovery of proliferative remodelling despite weight loss, indicating a significant ($p < 0.001$) and specific effect of HFD on the rescue of proliferative remodelling (Figure 1c).

To further investigate the effect of CR and HFD on proliferative remodelling, alongside ad-lib fed DIO and control mice we pair-fed mice HCD or HFD from 6 to 20 weeks of age, with hypothalamic remodelling measured by BrdU incorporation at 20 weeks as above. Each pair-fed mouse was fed a single daily meal containing the age matched energy intake of ad-lib fed controls (Control AL in Figure 1) i.e. 0%CR (Supplementary Figure 1). This experiment revealed that HFD consumption under pair-feeding (0%CR) did not result in either weight gain or weight loss while hypothalamic proliferative remodelling was reduced to the level seen in both HFD ad-lib fed DIO mice and DIO mice treated with HFD 30%CR. This data confirms that this pattern of proliferative remodelling reflects HFD consumption and not current BW. Remarkably, HCD pair-fed mice (0%CR) had a similar final BW to HCD ad-lib controls but the moderately reduced level proliferative remodelling seen in control mice treated with HCD 30%CR (Supplementary Figure 1). These data suggest that the moderate reduction in hypothalamic proliferative remodelling seen in CR treated

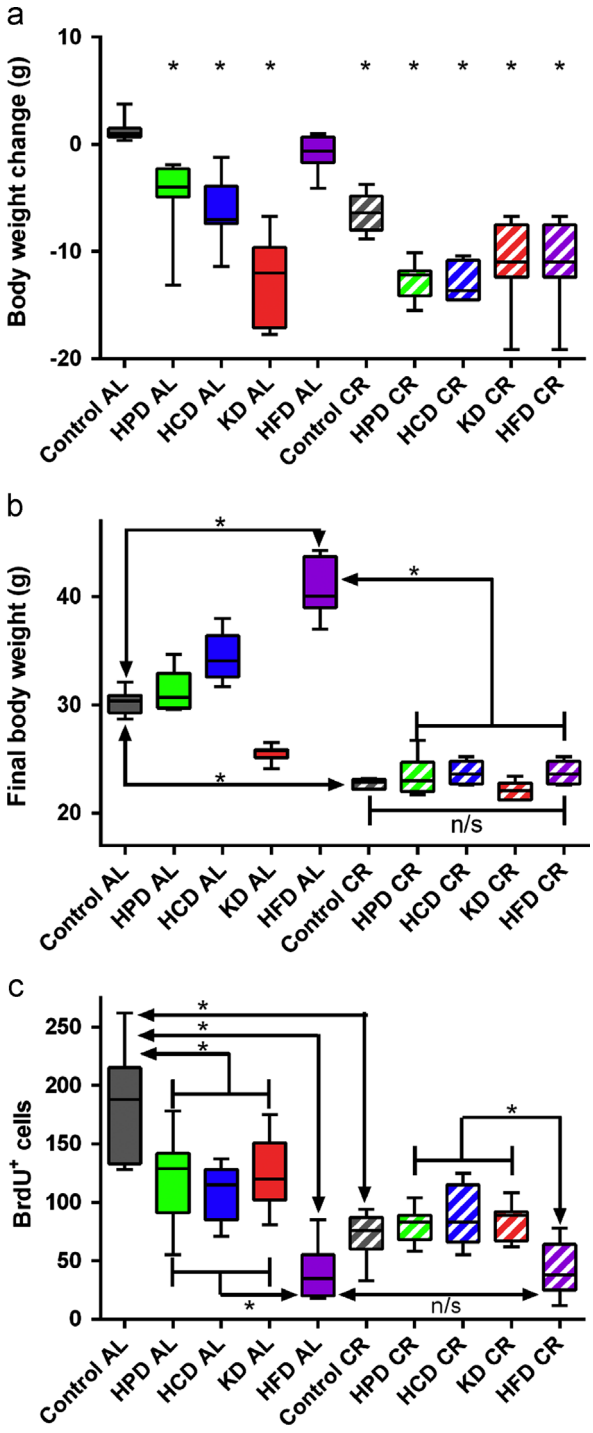

Figure 1: Calorie restriction of obese mice using HFD fails to rescue hypothalamic proliferative remodelling. 16 week old obese mice were treated using 4 diets for 4 weeks, either ad-lib (AL) or at 70% of normal daily calorie intake of lean controls (CR). (a) Treatment of obese mice caused significant BW loss in all groups except mice fed HFD AL. (b) Treating obese mice by CR resulted in identical final BW irrespective of macronutrient composition, while AL treatment resulted in differential final BW dependent on macronutrient composition. (c) Although CR with HFD lowered BW, it did not rescue hypothalamic proliferative remodelling. Non-HFD diets rescued proliferative remodelling irrespective of dietary macronutrient composition under both CR and AL. However, CR inhibited the rescue of proliferative remodelling compared to AL treatment ($p < 0.001$). CR also reduced proliferative remodelling in lean controls. The rescue of hypothalamic proliferative remodelling during treatment of obesity was incomplete in all groups and did not reach the level seen in control mice not previously exposed to HFD. (*$p < 0.05$, graphs show box plots, N = 7 mice per group).

