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Review Article

The defence of body weight: a physiological basis for weight regain after weight loss

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Abstract

Although weight loss can usually be achieved by restricting food intake, the majority of dieters regain weight over the long-term. In the hypothalamus, hormonal signals from the gastrointestinal tract, adipose tissue and other peripheral sites are integrated to influence appetite and energy expenditure. Diet-induced weight loss is accompanied by several physiological changes which encourage weight regain, including alterations in energy expenditure, substrate metabolism and hormone pathways involved in appetite regulation, many of which persist beyond the initial weight loss period. Safe effective long-term strategies to overcome these physiological changes are needed to help facilitate maintenance of weight loss. The present review, which focuses on data from human studies, begins with an outline of body weight regulation to provide the context for the subsequent discussion of short- and long-term physiological changes which accompany diet-induced weight loss.

Key words: appetite, diet, hypothalamus, obesity, weight gain, weight loss

INTRODUCTION

Although weight loss can usually be achieved through dietary restriction and/or increased physical activity, the overwhelming majority of people regain the weight that they have lost over the long-term. A meta-analysis concluded that 4.5 years after completing a structured weight-loss programme comprising a hypocaloric diet with or without exercise, the average weight loss maintained was 3 kg (representing a 3.2% reduction in initial weight) [1]. The proportion of people who successfully maintain weight loss varies depending on the definition of 'weight loss maintenance' from less than 3% (for maintaining 100% of reduced weight at all annual visits for 4–5 years after completion of a weight-loss programme [2]) to 28% (for maintaining a loss of at least 10% of initial body weight at 4 years [3]). Wing and Hill [4] propose defining successful weight loss maintenance as "intentionally losing at least 10% of initial weight and keeping it off for at least 1 year". According to this definition, 20.6% of 228 overweight people in a random-digit-dial telephone survey in the U.S.A. reported being successful weight-loss maintainers [4]. Why is diet-induced weight loss so difficult to maintain?

The present review, which focuses on data from human studies, begins with an outline of body weight regulation to provide the context for the subsequent discussion of short- and long-term physiological changes which accompany diet-induced weight loss. A number of comprehensive reviews of the topic which have included insights from animal models of obesity have been published elsewhere [5,6].

BODY WEIGHT REGULATION

Given the considerable variation in food intake from day to day, the body weight of most adults remains remarkably stable over time. Although large weight changes can be brought about in humans and animals through dietary restriction or overfeeding, when free feeding is resumed, body weight and adiposity return accurately to baseline levels [7,8]. This homoeostatic regulation of body weight occurs primarily in the hypothalamus, and results from integration of peripheral signals conveying information about both short-term food intake and long-term energy balance. It seems that this system protects us against weight loss more vigorously than from weight gain [9,10], which is clearly beneficial for survival during periods when food is scarce, as it was throughout most of human evolution, and is still in many parts of the world. However, for an obese person living in an

Abbreviations: AgRP, agouti-related peptide; ARC, arcuate nucleus; CCK, cholecystokinin; CRH, corticotrophin-releasing hormone; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; LAGB, laparoscopic adjustable gastric banding; MCH, melanin-concentrating hormone; NPY, neuropeptide Y; NREE, non-resting energy expenditure; NWCR, National Weight Control Registry; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PVN, paraventricular nucleus; PYY, peptide YY; REE, resting energy expenditure; RQ, respiratory quotient; RYGB, Roux-en-Y gastric bypass; SNS, sympathetic nervous system; T_3, 3,3′,5-tri-iodothyronine; rT_3, reverse T_3; T_4, thyroxine; TEE, total energy expenditure; TEF, thermic effect of feeding; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

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environment in which high-calorie food is widely available, it means that weight loss achieved through dietary restriction is extremely difficult to maintain.

Homoeostatic regulation

The ARC (arcuate nucleus) of the hypothalamus is the primary brain region involved in the homoeostatic control of food intake. Within the ARC are two distinct but interconnected groups of neurons with opposing effects on energy balance. Neurons which co-express NPY (neuropeptide Y) and AgRP (agouti-related peptide) stimulate food intake, whereas neurons expressing POMC (pro-opiomelanocortin) have the opposite effect. Projections from the ARC travel to other hypothalamic regions, including the PVN (paraventricular nucleus) where TRH (thyrotropin-releasing hormone), CRH (corticotrophin-releasing hormone) and oxytocin are produced (hunger-suppressing), and the lateral hypothalamus, which is the source of MCH (melanin-concentrating hormone) and orexins (hunger-stimulating).

Peripheral signals reflecting long- and short-term energy balance are processed centrally to influence the relative activity between the two ARC circuits. The hormones leptin (from adipose tissue) and insulin (from the pancreas) are involved in the long-term regulation of energy balance, whereas short-term signals send information to the brain on a meal-to-meal basis and include hormones from the gastrointestinal tract and pancreas, such as ghrelin, CCK (cholecystokinin), GLP-1 (glucagon-like peptide-1), amylin, PP (pancreatic polypeptide) and PYY (peptide YY), along with several others, including many almost certainly yet to be described (Table 1). This peripheral information is transmitted via the bloodstream and the vagus nerve to the hypothalamus and hindbrain (including the area postrema and the nucleus of the solitary tract). Reciprocal pathways project between these areas, allowing integration of signals to regulate food intake and energy expenditure (Figure 1) [12]. The homoeostatic regulation of body weight has been discussed in more detail elsewhere [11].

Table 1 Peptides and hormones involved in appetite regulation

Location	Anorexigenic	Orexigenic
Central		
Hypothalamus	POMC [13]	NPY [14]
	Nesfatin-1 [15]	AgRP [16]
	TRH [17]	Orexins [18]
	CRH [19]	MCH [20]
	Oxytocin [21]	Endocannabinoids [22]
	Serotonin [23]	Opioids [24]
	Histamine [25]	
	Urocortin [26]	
Peripheral		
Gastrointestinal tract	CCK [27]	Ghrelin [28]
	GLP-1 [29]	
	PYY [30]	
	Oxyntomodulin [31]	
	Enterostatin [32]	
	Bombesin [33]	
	Uroguanylin [34]	
Pancreas	Amylin [35]	
	Insulin [36]	
	PP [37]	
Adipocytes	Leptin [38]	

Hedonic influence on appetite

If appetite were controlled solely by homoeostatic mechanisms, we would eat only to meet nutritional requirements, which is clearly not the case. In addition to homoeostatic pathways, the hypothalamus receives inputs from the cortex and reward circuits in the limbic system ('hedonic' pathways) related to the sight, smell and taste of food, along with emotional and social factors, which are all integrated to have an impact upon energy intake and expenditure. The hedonic pathways can override the homoeostatic system, increasing the desire to consume palatable energy-dense food even when energy stores and food supply are abundant.

There is evidence of significant interactions between homoeostatic and hedonic pathways of appetite regulation. Leptin has been shown to influence taste and reward pathways [39–41], and ghrelin stimulates the mesolimbic dopaminergic pathway and increases consumption of sweet foods [42,43]. In addition, stimulation of the CB1 (cannabinoid 1) receptor, which is widely distributed in hypothalamic nuclei and brainstem regions known to be crucial in the homoeostatic control of appetite [44], increases not only food intake, but a preference for palatable foods [45], indicating an influence on feeding also via non-homoeostatic reward pathways.

PHYSIOLOGICAL ADAPTATIONS TO WEIGHT LOSS

There is accumulating evidence that diet-induced weight loss brings about compensatory changes in several biological pathways involved in the utilization and storage of energy, and the regulation of appetite, which collectively predispose to weight regain (summarized in Table 2). Some of these changes are more pronounced during dynamic weight loss than after stabilization at a reduced body weight. However, recent studies have shown that many of these changes represent not only a transient response to dynamic weight loss, but persist for 1 year or more following initial weight reduction.

Energy expenditure

In humans, the three principal components of TEE (total energy expenditure) are REE (resting energy expenditure; comprised of processes such as maintaining transmembrane ion gradients and resting cardiopulmonary activity), TEF (thermic effect of feeding; the energy required to digest, transport and deposit nutrients), and NREE (non-resting energy expenditure; mainly in the form of physical activity). In weight-stable adults, REE, TEF and NREE make up approximately 60, 10 and 30% respectively of TEE [46].

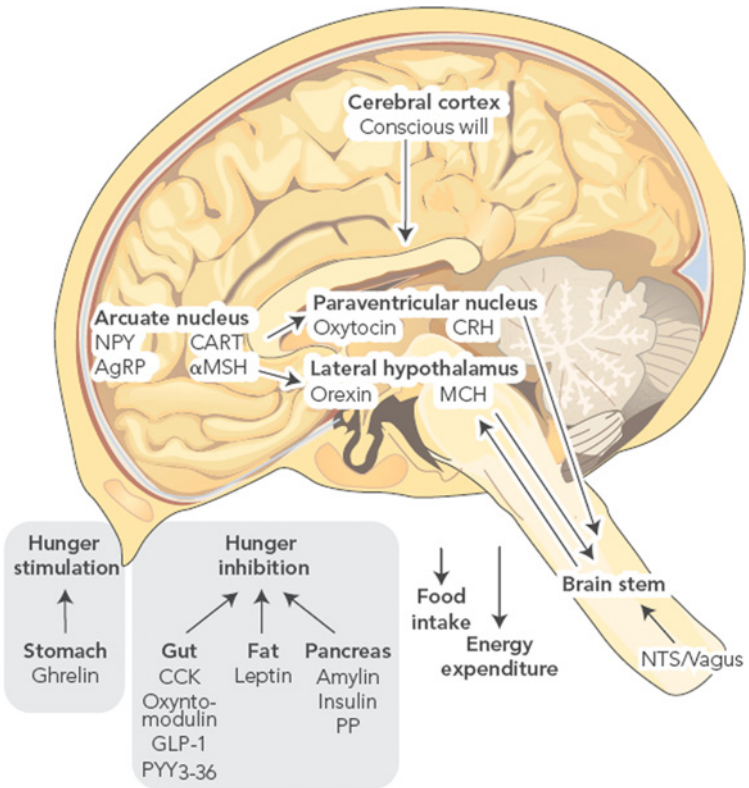

Figure 1 **Selected pathways involved in body weight regulation**
CART, cocaine- and amphetamine-regulated transcript; αMSH, α-melanocyte-stimulating hormone. This Figure was reproduced from Proietto J. Why is treating obesity so difficult? Justification for the role of bariatric surgery. Med. J. Aust. 2011; 195(3): 144–146. © Copyright 2011 *The Medical Journal of Australia* – reproduced with permission.

Table 2 **Physiological changes after diet-induced weight loss**

Factor	Expected effect
↓Energy expenditure	Increase energy storage
↓Fat oxidation	
↓Thyroid hormones	
↑Cortisol	
↑GIP	Increase food intake
↓Leptin	
↓PYY	
↓Amylin	
↓Insulin	
↑Ghrelin	
↑Appetite	
Altered neural activation	
↑Pancreatic polypeptide	?Reduce food intake

Diet-induced loss of 10% of body weight leads to a reduction in TEE to a level 15% below that which can be accounted for by the alterations in body mass and composition, in both lean and obese persons [46]. The degree to which REE actually declines is controversial [47–49]; however, a greater than predicted reduction in NREE accounts for the majority of the decrease in TEE and appears to be largely due to increased efficiency of skeletal muscle, particularly at low workloads [50,51]. This disproportionate decline in TEE has been shown to persist for more than 1 year in subjects who maintain a reduced body weight [52].

Substrate metabolism

Substrate metabolism is heavily dependent on a number of factors, including energy balance (i.e. weight stability compared with dynamic weight change), physical activity and nutritional status (i.e. dietary macronutrient composition, and whether measured in fed or fasted state) [53,54]. Studies in rodent models of diet-induced obesity allow examination of the metabolic state during obesity development, treatment and relapse, which is not feasible in humans. In diet-induced obese rats, dietary energy restriction is accompanied by a reduction in non-protein RQ (respiratory quotient), indicating a preference for the use of lipids over carbohydrates [55]. After maintenance of the reduced weight, fuel utilization shifts to a preference for carbohydrate use, which continues during weight regain [55]. Increased carbohydrate oxidation spares dietary fat for deposition. A number of human studies have also demonstrated that weight-stable formerly obese subjects have lower fasting or 24-h rates of fat oxidation compared with matched control subjects, or an impaired ability to appropriately increase fat oxidation in response to a high-fat diet [56–61]. This may lead to positive fat balance and negative carbohydrate balance [57,60], which has been proposed to stimulate

feeding to restore glycogen reserves [62]. Longitudinal studies have suggested that a high fasting or 24-h RQ (indicating low fat oxidation) is associated with weight gain over time [63–65]. After cessation of a weight-loss programme, a significant correlation has been shown in weight-stable reduced-obese women between changes in RQ and weight regain during the follow-up period ($r = 0.89$, $P < 0.01$) [66]. In contrast with lower basal and 24-h fat oxidation, fat oxidation may be higher during low-level exercise (i.e. exercise commensurate with activities of daily living) following diet-induced weight loss compared with pre-weight loss values [50,67], which is associated with a reduction in the ratio of skeletal muscle glycolytic to fatty acid oxidative enzyme activity [67]. It has been suggested that this may be related to the increase in skeletal muscle efficiency, in that the more metabolically efficient slow-twitch muscle fibres derive a greater proportion of energy from fat oxidation than the primarily glycolytic (and less efficient) fast-twitch fibres, although alterations in fibre type were not demonstrated in skeletal muscle biopsies [67].

Autonomic nervous system

Obesity is associated with resting SNS (sympathetic nervous system) overactivity ('sympathetic overdrive') [68,69]. There is evidence that this may not only be the result of obesity [66,70–73], but may also be contributing to its development [74,75]. Chronic SNS overactivity may lead to reduced sensitivity or down-regulation of adrenoreceptors [76], and it has been hypothesized that consequent blunting of SNS responsiveness may impair energy expenditure, post-post-prandial thermogenesis and fat oxidation [77,78]. In obese subjects, diet-induced weight loss has consistently been shown to be accompanied by significant reductions in sympathetic activity and an increase in cardiac parasympathetic function [73,79–81]. The increase in cardiac parasympathetic tone is attenuated during prolonged ($\geqslant$4 months) weight-loss maintenance and weight regain [81–83], whereas a recent study showed divergent effects of weight-loss maintenance on markers of sympathetic function, with a sustained reduction in whole-body noradrenaline spillover, but a rebound in muscle sympathetic nerve activity, implying either a further reduction in sympathetic outflow in another organ or tissue bed, or a mismatch between sympathetic nerve firing and noradrenaline overflow during weight-loss maintenance [83].

Hypothalamic–pituitary–thyroid axis

Under normal circumstances, TRH (thyrotropin-releasing hormone) from the paraventricular nucleus of the hypothalamus stimulates the release of TSH (thyroid-stimulating hormone) from the anterior pituitary, resulting in the production and release of T_4 (thyroxine) and T_3 (3,3′,5-tri-iodothyronine) by the thyroid gland. T_4 is converted into the more biologically active T_3 in peripheral target tissues. Thyroid hormones play an important role in energy expenditure [84,85]. In adults receiving T_4 replacement for the treatment of hypothyroidism, REE is significantly negatively correlated with TSH and is sensitive to small changes in thyroxine dosage, even when thyroid hormone levels are maintained within the normal range [84]. Some of this increase in REE may be due to mitochondrial uncoupling in skeletal muscle, which has been shown to occur in the presence of increased circulating thyroid hormone levels [86]. The importance of thyroid hormones to adaptive thermogenesis has been demonstrated in thyroidectomized rats, which become hypothermic when exposed to cold. T_4 replacement prevents this, unless conversion of T_4 into T_3 in brown adipose tissue is blocked [87]. Energy restriction has generally been found to suppress the hypothalamic–pituitary–thyroid axis, characterized by impaired secretion of TSH in response to TRH, reductions in circulating TSH and T_3 and increased production of the inactive rT_3 (reverse T_3), with variable effects on total and free T_4 [72,88–93]. Alterations in T_3, rT_3 and T_4 have been described to return towards baseline during maintenance of the reduced weight in some [90,91,94,95], but not all [72,96], studies.

Hypothalamic–pituitary–adrenal axis

CRH is released from the PVN in response to stress and acts in the anterior pituitary to stimulate the release of ACTH (adrenocorticotropic hormone), resulting in production of cortisol, mineralocorticoids and androgens from the adrenal glands. Cortisol excess (for example in Cushing's syndrome) leads to weight gain, particularly central adiposity, and a significant correlation has been reported between increases in appetite and fasting plasma cortisol after a weight-loss programme in obese men and women [97]. A study in rats has demonstrated that cortisol inhibits the suppressive action of leptin on food intake and body weight [98]. Increased circulating cortisol, and reduced dexamethasone suppression or diurnal variation of cortisol production, have been demonstrated [91,99–102], although not consistently [103] in both lean and obese humans following reduction in food intake, particularly with greater degrees of energy restriction. Alterations in cortisol metabolism are reversible upon return to unrestricted feeding [99].

Appetite-regulating adipocyte and gastrointestinal hormones

Following weight loss, changes occur in circulating concentrations of a multitude of peripheral hormones involved in appetite regulation. Although there are some inconsistencies, which are likely to be due to considerable heterogeneity in methodology between studies (including participant characteristics, dietary interventions, degree of weight loss, study duration and hormone fragments assayed), the majority of studies have found that diet-induced weight loss is accompanied by hormone changes which collectively promote weight regain and restoration of energy balance.

Leptin acts in the hypothalamus to reduce food intake and increase energy expenditure by reducing the expression of AgRP and NPY, and stimulating that of POMC [104–106]. When individuals are in energy balance at their usual weight, leptin secretion is proportional to fat mass [107]. In keeping with its proposed role as a signal of energy depletion [108], leptin levels decrease profoundly following dietary restriction [109–111] and are significantly lower during dynamic weight loss than during weight-loss maintenance [112]. Administration of leptin to people at their baseline weight has little effect on body weight and appetite [113], whereas leptin administration during an energy deficit reduces appetite [114], and in weight-stable weight-reduced

subjects, leptin 'replacement' to pre-weight loss levels reverses many of the adaptive physiological changes involving thyroid hormones, the autonomic nervous system, appetite, energy expenditure, skeletal muscle efficiency and regional brain activation [72,115,116].

Other hormonal perturbations resulting from diet-induced weight loss include increases in circulating ghrelin, GIP (gastric inhibitory polypeptide) and PP and reductions in PYY, CCK, insulin and amylin [59,111,117–122]. GLP-1 secretion has been variably reported to increase, decrease or remain unchanged following weight loss [111,123,124]. All of the abovementioned hormones inhibit food intake [27,29,30,35–37], other than ghrelin, which stimulates hunger [28], and GIP, which may have a role in energy storage [125]. As such, it can be seen that almost all of these changes would be expected to favour regain of lost weight, by increasing hunger, reducing satiety and promoting energy storage.

There is recent evidence that these hormonal changes are not merely a transient response to negative energy balance. In a study conducted by our research group [111], 50 overweight or obese men and women underwent a 10-week very-low-energy diet-based weight-loss programme, followed by a 12 month period during which they attempted to maintain their weight loss. Subjects were required to lose at least 10% of their initial weight and peripheral appetite-mediating hormones were measured in the 34 participants who completed the study at baseline, at the end of the weight loss period and 12 months later. Initial weight loss was (mean$\pm$S.E.M.) 13.5$\pm$0.5 kg (14% of baseline weight), and participants maintained a weight reduction of -7.9 ± 1.1 kg at 12 months. Weight loss was accompanied by significant reductions in circulating leptin, PYY, CCK, insulin and amylin, and increases in ghrelin, GIP and PP, which persisted 12 months later, even after the onset of weight regain.

Subjective appetite

In keeping with the expected effects of the hormonal adaptations to weight reduction, sustained increases in subjective appetite have been described following diet-induced weight-loss in obese adults [97,111]. Interestingly, there is evidence that dietary weight loss increases not only appetite itself (i.e. increases in hunger, desire to eat and prospective food consumption) [97,111], but also the perceived rewarding properties of food [126] and the preference for high-calorie food. One study compared the taste preferences of normal-weight, obese and formerly obese subjects for liquid solutions with various sugar and fat content. The formerly obese group had previously lost a mean of 31 kg with a low-calorie diet and had been maintaining a loss of at least 13.6 kg for at least 1 year prior to the study. The normal-weight group found a solution containing 20% lipid and <10% sucrose optimal, the obese group preferred a high-fat solution and the formerly obese group preferred solutions high in both fat and sugar [127]. Several studies have reported that changes in appetite after weight loss are related to alterations in circulating leptin [97,110,128].

Regional brain activation

Studies using functional brain imaging techniques have provided valuable insight into alterations in brain activity patterns in response to food stimuli in obese subjects after diet-induced weight loss. One study found increased neural activity in the limbic (reward) system and areas involved in executive function and decision-making, whereas reduced activity was seen in the hypothalamus and areas involved in the emotional control of food intake, integrative cognitive control functions and motor planning, compared with baseline in reduced-obese subjects [116]. This may indicate a state of increased responsiveness to food reward with decreased control of food intake. Others have shown that, when presented with food stimuli, reduced-obese individuals have altered activation in several brain areas involved in the control of complex aspects of eating behaviour compared with obese and lean controls, including the insula, inferior visual cortex, posterior cingulate cortex, posterior hippocampus and amygdala [129,130]. In one study, regional cerebral blood flow increased in the middle insula increased in response to tasting a liquid meal in obese and post-obese subjects, but not in lean individuals [130]. In another, activation of the insula and inferior visual cortex in response to images of palatable food compared with non-food images was not as robust in reduced-obese as in lean individuals in the eucaloric state. However, after 2 days of overfeeding, food responses in the insula and hypothalamus were significantly attenuated in the lean, but not reduced-obese, subjects, suggesting a possible impairment in ability to sense a positive energy balance following weight loss [129]. Among other activities, the insula is involved in mediating the desirability of food [131]. Activation in this area in response to images of high-calorie foods is stimulated by ghrelin [132] and attenuated by administration of leptin in reduced-obese or congenitally leptin-deficient adults [116,133].

In a study which compared nine formerly obese people with 20 obese non-dieters, the successful dieters were found to have greater activation in the dorsal prefrontal cortex (an area involved in the cognitive control of behaviour) and less activation in the orbitofrontal cortex (an area involved in determining the reward value of sensory and visceral inputs) after a meal than non-dieters. This pattern of activation was associated with the higher levels of dietary restraint found in the successful dieters [134].

STRATEGIES FOR SUCCESSFUL WEIGHT LOSS MAINTENANCE

In the 'obesogenic' environment which prevails in most of the developed world, the multitude of physiological adaptations to weight loss which aim to restore body weight are a hindrance to obese dieters, most of whom will regain weight over time. Despite this, there are individuals who manage to maintain significant weight losses over the long-term. Most of the published data regarding these uniquely successful weight loss maintainers comes from the NWCR (National Weight Control Registry), a database of more than 4000 adults in the U.S.A., who have maintained weight losses of at least 13.6 kg (30 lb) for at least 1 year. Members, of whom 97% are Caucasian and 80% women, are recruited via newspaper and magazine advertisements, and data are self-reported [135]. Participants have lost an average of

30 kg, and have maintained the minimum 13.6 kg weight loss for an average of 5.5 years [135], and 83% report a trigger for their weight loss, most commonly a medical or emotional event [136]. Analyses of strategies reported by registry members to maintain weight loss have revealed a number of key behaviours common to the majority of participants. (i) Eating a low-calorie low-fat diet with minimal variation. Participants reported consuming a mean of 1306 (women) to 1685 (men) kcal/day, with <25% of calories coming from fat. This is around 30% less than the energy and fat intakes reported by respondents in the NHANES III (Third National Health and Nutrition Examination Survey) [137]. In addition, the majority of NWCR participants consume a diet with minimal variety in food groups and adhere to this without variation on weekends or holidays. Those who do not are more likely to regain weight [138,139]. (ii) Eating breakfast every day (78%) [136]. (iii) Frequent self-monitoring. 78% of NWCR members weigh themselves at least once a week, and 50% count calories or grams of fat [136]. (iv) Undertaking regular exercise (91%), equivalent to walking 45 km (28 miles)/week or around 1 h/day of moderately intense activity [136]. NWCR members spend more time engaged in physical activity, particularly in high-intensity activity, than people who are stable at their baseline weight, whether lean or obese [136,140]. (v) Limiting television viewing. A total of 62% report watching television for fewer than 10 h/week compared with the national reported U.S.A. average of 28 h [141].

Given that the compensatory adaptations to weight loss lead to a reduction in energy expenditure and increased propensity to fat storage, consistent application of the combination of above-mentioned behaviours would seem an ideal way to prevent weight regain after weight loss. However, for any person, long-term rigid adherence to the dietary and exercise strategies described by NWCR participants would be exceedingly difficult, let alone for weight-reduced individuals, in whom appetite has increased, in a setting where they are surrounded by food, particularly if the environment is not conducive to using physical activity as a means of transport. This is highlighted by the fact that even within the successful NWCR group, small weight regains are common and very few individuals reduce their weight again following regain [142].

The durable success of bariatric surgical procedures such as LAGB (laparoscopic adjustable gastric banding) and RYGB (Roux-en-Y gastric bypass) is likely to be related to the fact that appetite is reduced post-operatively, in contrast with the appetite changes which accompany non-surgical methods of weight loss [143,144]. Hormonal adaptations encouraging weight regain are similar following LAGB and diet-induced weight loss, and the mechanism for appetite suppression following LAGB is not fully understood [145]. A hormone profile which favours appetite suppression is seen after RYGB [118,146,147].

FUTURE DIRECTIONS

Recent attention has focused on the potential contribution of gut flora to energy absorption and fat deposition, and diet-induced weight loss induces changes in the prevalence of various species of gut micro-organisms [148–151]. Whether this has any role in facilitating weight regain is yet to be determined.

Although evidence of physiological adaptations to weight loss which encourage weight regain continues to accumulate, there are currently no non-surgical treatments available with demonstrated long-term safety and efficacy to circumvent these changes and assist weight-reduced obese people who are unable to maintain weight loss. In recent months, the U.S.A. Food and Drug Administration has approved two appetite-suppressing medications for the treatment of obesity: lorcaserin (a serotonin 2C receptor agonist) and the combination of phentermine and topiramate (Qsymia), although post-marketing studies of long-term cardiovascular safety are required. It seems logical that restoration of appetite-regulating hormones to pre-weight loss values may facilitate weight-loss maintenance and, indeed, many of the biological perturbations which accompany weight loss are attenuated following administration of leptin in doses calculated to replicate pre-weight loss levels [72,115,116,152]. In obese subjects consuming an energy-restricted diet, a combination of analogues of leptin (metreleptin) and amylin (pramlintide) was found to have synergistic effects on weight loss compared with treatment with either alone [153]. However, in 2011, a randomized clinical trial was stopped prematurely due to safety concerns and development of the combination therapy has since been discontinued (Takeda Pharmaceutical Company Ltd press release; http://takeda.com/press/article_42791.html). Other pharmacological agents currently undergoing clinical trials for the treatment of obesity include the GLP-1 analogue liraglutide and the combination of naltrexone and bupropion (Contrave) [154,155]. The growing evidence of sustained physiological adaptations to weight loss which encourage weight regain justifies the long-term use of medications with demonstrated long-term safety and efficacy to suppress appetite and assist with weight-loss maintenance.

REFERENCES

1 Anderson, J. W., Konz, E. C., Frederich, R. C. and Wood, C. L. (2001) Long-term weight-loss maintenance: a meta-analysis of US studies. Am. J. Clin. Nutr. **74**, 579–584
2 Kramer, F. M., Jeffery, R. W., Forster, J. L. and Snell, M. K. (1989) Long-term follow-up of behavioral treatment for obesity: patterns of weight regain among men and women. Int. J. Obes. **13**, 123–136
3 Christiansen, T., Bruun, J. M., Madsen, E. L. and Richelsen, B. (2007) Weight loss maintenance in severely obese adults after an intensive lifestyle intervention: 2- to 4-year follow-up. Obesity **15**, 413–420
4 Wing, R. R. and Hill, J. O (2001) Successful weight loss maintenance. Annu. Rev. Nutr. **21**, 323–341
5 Maclean, P. S., Bergouignan, A., Cornier, M-A. and Jackman, M. R. (2011) Biology's response to dieting: the impetus for weight regain. Am. J. Physiol. Regul. Integ. Comp. Physiol. **301**, R581–R600
6 Sainsbury, A. and Zhang, L. (2009) Role of the arcuate nucleus of the hypothalamus in regulation of body weight during energy deficit. Mol. Cell. Endocrinol. **316**, 109–119
7 Bernstein, I. L, Lotter, E. C., Kulkosky, P. J., Porte, Jr, D. and Woods, S. C. (1975) Effect of force-feeding upon basal insulin levels of rats. Proc. Soc. Exp. Biol. Med. **150**, 546–548

8 Pasquet, P. and Apfelbaum, M. (1994) Recovery of initial body weight and composition after long-term massive overfeeding in men. Am. J. Clin. Nutr. **60**, 861–863
9 Schwartz, M. W., Woods, S. C., Seeley, R. J., Barsh, G. S., Baskin, D. G and Leibel, R. L. (2003) Is the energy homeostasis system inherently biased toward weight gain? Diabetes **52**, 232–238
10 Siervo, M., Fruhbeck, G., Dixon, A., Goldberg, G. R., Coward, W. A., Murgatroyd, P. R., Prentice, A. M. and Jebb, S. A. (2008) Efficiency of autoregulatory homeostatic responses to imposed caloric excess in lean men. Am. J. Physiol. Endocrinol. Metab. **294**, E416–E424
11 Schwartz, M. W., Woods, S. C., Porte, Jr, D., Seeley, R. J. and Baskin, D. G. (2000) Central nervous system control of food intake. Nature **404**, 661–671
12 Proietto, J. (2011) Why is treating obesity so difficult? Justification for the role of bariatric surgery. Med. J. Aust. **195**, 144–146
13 Krude, H., Biebermann, H. and Gruters, A. (2003) Mutations in the human proopiomelanocortin gene. Ann. N.Y. Acad. Sci. **994**, 233–239
14 Billington, C. J., Briggs, J. E., Grace, M. and Levine, A. S. (1991) Effects of intracerebroventricular injection of neuropeptide Y on energy metabolism. Am. J. Physiol. **260**, R321–R327
15 Oh-I, S., Shimizu, H., Satoh, T., Okada, S., Adachi, S., Inoue, K., Eguchi, H., Yamamoto, M., Imaki, T., Hashimoto, K. et al. (2006) Identification of nesfatin-1 as a satiety molecule in the hypothalamus. Nature **443**, 709–712
16 Rossi, M., Kim, M. S., Morgan, D. G., Small, C. J., Edwards, C. M., Sunter, D., Abusnana, S., Goldstone, A. P., Russell, S. H., Stanley, S. A. et al. (1998) A C-terminal fragment of Agouti-related protein increases feeding and antagonizes the effect of α-melanocyte stimulating hormone *in vivo*. Endocrinology **139**, 4428–4431
17 Vijayan, E. and McCann, S. M. (1977) Suppression of feeding and drinking activity in rats following intraventricular injection of thyrotropin releasing hormone (TRH). Endocrinology **100**, 1727–1730
18 Sakurai, T., Amemiya, A., Ishii, M., Matsuzaki, I., Chemelli, R. M., Tanaka, H., Williams, S. C., Richardson, J. A., Kozlowski, G. P., Wilson, S. et al. (1998) Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell **92**, 573–585
19 Britton, D. R., Koob, G. F., Rivier, J. and Vale, W. (1982) Intraventricular corticotropin-releasing factor enhances behavioral effects of novelty. Life Sci. **31**, 363–367
20 Shimada, M., Tritos, N. A., Lowell, B. B., Flier, J. S. and Maratos-Flier, E. (1998) Mice lacking melanin-concentrating hormone are hypophagic and lean. Nature **396**, 670–674
21 Arletti, R., Benelli, A. and Bertolini, A. (1989) Influence of oxytocin on feeding behavior in the rat. Peptides **10**, 89–93
22 Di Marzo, V., Goparaju, S. K., Wang, L., Liu, J., Batkai, S., Jarai, Z., Fezza, F., Miura, G. I., Palmiter, R. D., Sugiura, T. and Kunos, G. (2001) Leptin-regulated endocannabinoids are involved in maintaining food intake. Nature **410**, 822–825
23 Blundell, J. E. (1977) Is there a role for serotonin (5-hydroxytryptamine) in feeding? Int. J. Obes. **1**, 15–42
24 Jalowiec, J. E., Panksepp, J., Zolovick, A. J., Najam, N. and Herman, B. H. (1981) Opioid modulation of ingestive behavior. Pharmacol. Biochem. Behav. **15**, 477–484
25 Sakata, T., Fukagawa, K., Ookuma, K., Fujimoto, K., Yoshimatsu, H., Yamatodani, A. and Wada, H. (1988) Modulation of neuronal histamine in control of food intake. Physiol. Behav. **44**, 539–543
26 Spina, M., Merlo-Pich, E., Chan, R. K., Basso, A. M., Rivier, J., Vale, W. and Koob, G. F. (1996) Appetite-suppressing effects of urocortin, a CRF-related neuropeptide. Science **273**, 1561–1564
27 Muurahainen, N., Kissileff, H. R., Derogatis, A. J. and Pi-Sunyer, F. X. (1988) Effects of cholecystokinin-octapeptide (CCK-8) on food intake and gastric emptying in man. Physiol. Behav. **44**, 645–649
28 Wren, A. M., Seal, L. J., Cohen, M. A., Brynes, A. E., Frost, G. S., Murphy, K. G., Dhillo, W. S., Ghatei, M. A. and Bloom, S. R. (2001) Ghrelin enhances appetite and increases food intake in humans. J. Clin. Endocrinol. Metab. **86**, 5992–5995
29 Flint, A., Raben, A., Astrup, A. and Holst, J. J. (1998) Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J. Clin. Invest. **101**, 515–520
30 Batterham, R. L., Cowley, M. A., Small, C. J., Herzog, H., Cohen, M. A., Dakin, C. L., Wren, A. M., Brynes, A. E., Low, M. J., Ghatei, M. A. et al. (2002) Gut hormone PYY_{3-36} physiologically inhibits food intake. Nature **418**, 650–654
31 Cohen, M. A., Ellis, S. M., le Roux, C. W., Batterham, R. L., Park, A. J., Patterson, M., Frost, G. S., Ghatei, M. A. and Bloom, S. R. (2003) Oxyntomodulin suppresses appetite and reduces food intake in humans. J. Clin. Endocrinol. Metab. **88**, 4696–4701
32 Erlanson-Albertsson, C. and York, D. (1997) Enterostatin–a peptide regulating fat intake. Obes. Res. **5**, 360–372
33 Muurahainen, N. E., Kissileff, H. R. and Pi-Sunyer, F. X. (1993) Intravenous infusion of bombesin reduces food intake in humans. Am. J. Physiol. **264**, R350–R354
34 Valentino, M. A., Lin, J. E., Snook, A. E., Li, P., Kim, G. W., Marszalowicz, G., Magee, M. S., Hyslop, T., Schulz, S. and Waldman, S. A. (2011) A uroguanylin-GUCY2C endocrine axis regulates feeding in mice. J. Clin. Invest. **121**, 3578–3588
35 Chapman, I., Parker, B., Doran, S., Feinle-Bisset, C., Wishart, J., Lush, C. W., Chen, K., Lacerte, C., Burns, C., McKay, R. et al. (2007) Low-dose pramlintide reduced food intake and meal duration in healthy, normal-weight subjects. Obesity **15**, 1179–1186
36 Porte, Jr, D. and Woods, S. C. (1981) Regulation of food intake and body weight in insulin. Diabetologia **20** (Suppl), 274–280
37 Batterham, R. L., le Roux, C. W., Cohen, M. A., Park, A. J., Ellis, S. M., Patterson, M., Frost, G. S., Ghatei, M. A. and Bloom, S. R. (2003) Pancreatic polypeptide reduces appetite and food intake in humans. J. Clin. Endocrinol. Metab. **88**, 3989–3992
38 Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L. and Friedman, J. M (1994) Positional cloning of the mouse obese gene and its human homologue. Nature **372**, 425–432
39 Fulton, S., Woodside, B. and Shizgal, P. (2000) Modulation of brain reward circuitry by leptin. Science **287**, 125–128
40 Kawai, K., Sugimoto, K., Nakashima, K., Miura, H. and Ninomiya, Y. (2000) Leptin as a modulator of sweet taste sensitivities in mice. Proc. Natl. Acad. Sci. U.S.A. **97**, 11044–11049
41 Shalev, U., Yap, J. and Shaham, Y. (2001) Leptin attenuates acute food deprivation-induced relapse to heroin seeking. J. Neurosci. **21**, RC129
42 Naleid, A. M., Grace, M. K., Cummings, D. E. and Levine, A. S. (2005) Ghrelin induces feeding in the mesolimbic reward pathway between the ventral tegmental area and the nucleus accumbens. Peptides **26**, 2274–2279
43 Disse, E., Bussier, A-L., Veyrat-Durebex, C., Deblon, N., Pfluger, P. T., Tschop, M. H., Laville, M. and Rohner-Jeanrenaud, F. (2010) Peripheral ghrelin enhances sweet taste food consumption and preference, regardless of its caloric content. Physiol. Behav. **101**, 277–281
44 Jelsing, J., Larsen, P. J. and Vrang, N. (2008) Identification of cannabinoid type 1 receptor expressing cocaine amphetamine-regulated transcript neurons in the rat hypothalamus and brainstem using *in situ* hybridization and immunohistochemistry. Neuroscience **154**, 641–652
45 Koch, J. E. and Matthews, S. M. (2001) Delta9-tetrahydrocannabinol stimulates palatable food intake in Lewis rats: effects of peripheral and central administration. Nutr. Neurosci. **4**, 179–187

46 Leibel, R. L., Rosenbaum, M. and Hirsch, J. (1995) Changes in energy expenditure resulting from altered body weight. N. Engl. J. Med. **332**, 621–628
47 Flatt, J. P. (2007) Exaggerated claim about adaptive thermogenesis. Int. J. Obes. **31**, 1626
48 Doucet, E., St-Pierre, S., Almeras, N., Despres, J. P., Bouchard, C. and Tremblay, A. (2001) Evidence for the existence of adaptive thermogenesis during weight loss. Br. J. Nutr. **85**, 715–723
49 Schwartz, A., Kuk, J. L., Lamothe, G. and Doucet, E (2012) Greater than predicted decrease in resting energy expenditure and weight loss: results from a systematic review. Obesity, doi: 10.1038/oby.2012.34
50 Rosenbaum, M., Vandenborne, K., Goldsmith, R., Simoneau, J-A., Heymsfield, S., Joanisse, D. R., Hirsch, J., Murphy, E., Matthews, D., Segal, K. R. and Leibel, R. L. (2003) Effects of experimental weight perturbation on skeletal muscle work efficiency in human subjects. Am. J. Physiol. Regul. Integr. Comp. Physiol. **285**, R183–R192
51 Doucet, E., Imbeault, P., St-Pierre, S., Almeras, N., Mauriege, P., Despres, J-P., Bouchard, C. and Tremblay, A. (2003) Greater than predicted decrease in energy expenditure during exercise after body weight loss in obese men. Clin. Sci. **105**, 89–95
52 Rosenbaum, M., Hirsch, J., Gallagher, D. A. and Leibel, R. L. (2008) Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight. Am. J. Clin. Nutr. **88**, 906–912
53 Melanson, E. L., Gozansky, W. S., Barry, D. W., Maclean, P. S., Grunwald, G. K. and Hill, J. O. (2009) When energy balance is maintained, exercise does not induce negative fat balance in lean sedentary, obese sedentary, or lean endurance-trained individuals. J. Appl. Physiol. **107**, 1847–1856
54 Bergouignan, A., Gozansky, W. S., Barry, D. W., Leitner, W., MacLean, P. S., Hill, J. O., Draznin, B. and Melanson, E. L. (2012) Increasing dietary fat elicits similar changes in fat oxidation and markers of muscle oxidative capacity in lean and obese humans. PLoS ONE **7**, e30164
55 MacLean, P. S., Higgins, J. A., Johnson, G. C., Fleming-Elder, B. K., Peters, J. C. and Hill, J. O. (2004) Metabolic adjustments with the development, treatment, and recurrence of obesity in obesity-prone rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. **287**, R288–R297
56 Ballor, D. L., Harvey-Berino, J. R., Ades, P. A., Cryan, J. and Calles-Escandon, J. (1996) Decrease in fat oxidation following a meal in weight-reduced individuals: a possible mechanism for weight recidivism. Metab., Clin. Exp. **45**, 174–178
57 Astrup, A., Buemann, B., Christensen, N. J. and Toubro, S. (1994) Failure to increase lipid oxidation in response to increasing dietary fat content in formerly obese women. Am. J. Physiol. **266**, E592–E599
58 Buemann, B., Toubro, S. and Astrup, A. (1998) Substrate oxidation and thyroid hormone response to the introduction of a high fat diet in formerly obese women. Int. J. Obes. **22**, 869–877
59 Raben, A., Andersen, H. B., Christensen, N. J., Madsen, J., Holst, J. J. and Astrup, A. (1994) Evidence for an abnormal postprandial response to a high-fat meal in women predisposed to obesity. Am. J. Physiol. **267**, E549–E559
60 Larson, D. E., Ferraro, R. T., Robertson, D. S. and Ravussin, E. (1995) Energy metabolism in weight-stable postobese individuals. Am. J. Clin. Nutr. **62**, 735–739
61 Filozof, C. M., Murua, C., Sanchez, M. P., Brailovsky, C., Perman, M., Gonzalez, C. D. and Ravussin, E. (2000) Low plasma leptin concentration and low rates of fat oxidation in weight-stable post-obese subjects. Obes. Res. **8**, 205–210
62 Flatt, J. P. (1987) The difference in the storage capacities for carbohydrate and for fat, and its implications in the regulation of body weight. Ann. N.Y. Acad. Sci. **499**, 104–123
63 Seidell, J. C., Muller, D. C., Sorkin, J. D. and Andres, R. (1992) Fasting respiratory exchange ratio and resting metabolic rate as predictors of weight gain: the Baltimore Longitudinal Study on Aging. Int. J. Obes. **16**, 667–674
64 Zurlo, F., Lillioja, S., Esposito-Del Puente, A., Nyomba, B. L., Raz, I., Saad, M. F., Swinburn, B. A., Knowler, W. C., Bogardus, C. and Ravussin, E. (1990) Low ratio of fat to carbohydrate oxidation as predictor of weight gain: study of 24-h RQ. Am. J. Physiol. **259**, E650–E657
65 Marra, M., Scalfi, L., Covino, A., Esposito-Del Puente, A. and Contaldo, F. (1998) Fasting respiratory quotient as a predictor of weight changes in non-obese women. Int. J. Obes. **22**, 601–603
66 Muscelli, E., Emdin, M., Natali, A., Pratali, L., Camastra, S., Gastaldelli, A., Baldi, S., Carpeggiani, C. and Ferrannini, E. (1998) Autonomic and hemodynamic responses to insulin in lean and obese humans. J. Clin. Endocrinol. Metab. **83**, 2084–2090
67 Goldsmith, R., Joanisse, D. R., Gallagher, D., Pavlovich, K., Shamoon, E., Leibel, R. L. and Rosenbaum, M. (2010) Effects of experimental weight perturbation on skeletal muscle work efficiency, fuel utilization, and biochemistry in human subjects. Am. J. Physiol. Regul. Integr. Comp. Physiol. **298**, R79–R88
68 Eikelis, N. and Esler, M. (2005) The neurobiology of human obesity. Exp. Physiol. **90**, 673–682
69 Grassi, G., Dell'Oro, R., Quarti-Trevano, F., Scopelliti, F., Seravalle, G., Paleari, F., Gamba, P. L. and Mancia, G. (2005) Neuroadrenergic and reflex abnormalities in patients with metabolic syndrome. Diabetologia **48**, 1359–1365
70 Eikelis, N., Schlaich, M., Aggarwal, A., Kaye, D. and Esler, M. (2003) Interactions between leptin and the human sympathetic nervous system. Hypertension **41**, 1072–1079
71 Paolisso, G., Manzella, D., Tagliamonte, M. R., Rizzo, M. R., Gambardella, A. and Varricchio, M. (1999) Effects of different insulin infusion rates on heart rate variability in lean and obese subjects. Metab., Clin. Exp. **48**, 755–762
72 Rosenbaum, M., Goldsmith, R., Bloomfield, D., Magnano, A., Weimer, L., Heymsfield, S., Gallagher, D., Mayer, L., Murphy, E. and Leibel, R. L. (2005) Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. J. Clin. Invest. **115**, 3579–3586
73 Straznicky, N. E., Lambert, E. A., Lambert, G. W., Masuo, K., Esler, M. D. and Nestel, P. J. (2005) Effects of dietary weight loss on sympathetic activity and cardiac risk factors associated with the metabolic syndrome. J. Clin. Endocrinol. Metab. **90**, 5998–6005
74 Masuo, K., Kawaguchi, H., Mikami, H., Ogihara, T. and Tuck, M. L. (2003) Serum uric acid and plasma norepinephrine concentrations predict subsequent weight gain and blood pressure elevation. Hypertension **42**, 474–480
75 Masuo, K., Mikami, H., Ogihara, T. and Tuck, M. L. (1997) Sympathetic nerve hyperactivity precedes hyperinsulinemia and blood pressure elevation in a young, nonobese Japanese population. Am. J. Hypertens. **10**, 77–83
76 Scheidegger, K., O'Connell, M., Robbins, D. C. and Danforth, E. Jr (1984) Effects of chronic β-receptor stimulation on sympathetic nervous system activity, energy expenditure, and thyroid hormones. J. Clin. Endocrinol. Metab. **58**, 895–903
77 Greenfield, J. R. and Campbell, L. V. (2008) Role of the autonomic nervous system and neuropeptides in the development of obesity in humans: targets for therapy? Curr. Pharm. Des. **14**, 1815–1820
78 Julius, S., Valentini, M. and Palatini, P. (2000) Overweight and hypertension: a 2-way street? Hypertension **35**, 807–813
79 Arone, L. J., Mackintosh, R., Rosenbaum, M., Leibel, R. L. and Hirsch, J. (1995) Autonomic nervous system activity in weight gain and weight loss. Am. J. Physiol. **269**, R222–R225

80 Grassi, G., Seravalle, G., Colombo, M., Bolla, G., Cattaneo, B. M., Cavagnini, F. and Mancia, G. (1998) Body weight reduction, sympathetic nerve traffic, and arterial baroreflex in obese normotensive humans. Circulation **97**, 2037–2042
81 Rissanen, P., Franssila-Kallunki, A. and Rissanen, A. (2001) Cardiac parasympathetic activity is increased by weight loss in healthy obese women. Obes. Res. **9**, 637–643
82 Laaksonen, D. E., Laitinen, T., Schonberg, J., Rissanen, A. and Niskanen, L. K (2003) Weight loss and weight maintenance, ambulatory blood pressure and cardiac autonomic tone in obese persons with the metabolic syndrome. J. Hypertens. **21**, 371–378
83 Straznicky, N. E., Grima, M. T., Eikelis, N., Nestel, P. J., Dawood, T., Schlaich, M. P., Chopra, R., Masuo, K., Esler, M. D., Sari, C. I. et al. (2011) The effects of weight loss versus weight loss maintenance on sympathetic nervous system activity and metabolic syndrome components. J. Clin. Endocrinol. Metab. **96**, E503–508
84 al-Adsani, H., Hoffer, L. J. and Silva, J. E. (1997) Resting energy expenditure is sensitive to small dose changes in patients on chronic thyroid hormone replacement. J. Clin. Endocrinol. Metab. **82**, 1118–1125
85 Bianco, A. C., Maia, A. L., da Silva, W. S. and Christoffolete, M. A. (2005) Adaptive activation of thyroid hormone and energy expenditure. Biosci. Rep. **25**, 191–208
86 Mitchell, C. S., Savage, D. B., Dufour, S., Schoenmakers, N., Murgatroyd, P., Befroy, D., Halsall, D., Northcott, S., Raymond-Barker, P., Curran, S. et al. (2010) Resistance to thyroid hormone is associated with raised energy expenditure, muscle mitochondrial uncoupling, and hyperphagia. J. Clin. Invest. **120**, 1345–1354
87 Bianco, A. C. and Silva, J. E. (1987) Intracellular conversion of thyroxine to triiodothyronine is required for the optimal thermogenic function of brown adipose tissue. J. Clin. Invest. **79**, 295–300
88 Marine, N., Hershman, J. M., Maxwell, M. H., Dornfeld, L. P. and Schroth, P. (1991) Dietary restriction on serum thyroid hormone levels. Am. J. Med. Sci. **301**, 310–313
89 Romijn, J. A., Adriaanse, R., Brabant, G., Prank, K., Endert, E. and Wiersinga, W. M. (1990) Pulsatile secretion of thyrotropin during fasting: a decrease of thyrotropin pulse amplitude. J. Clin. Endocrinol. Metab. **70**, 1631–1636
90 Wadden, T. A., Mason, G., Foster, G. D., Stunkard, A. J and Prange, A. J. (1990) Effects of a very low calorie diet on weight, thyroid hormones and mood. Int. J. Obes. **14**, 249–258
91 Torgerson, J. S., Carlsson, B., Stenlof, K., Carlsson, L. M., Bringman, E. and Sjostrom, L. (1999) A low serum leptin level at baseline and a large early decline in leptin predict a large 1-year weight reduction in energy-restricted obese humans. J. Clin. Endocrinol. Metab. **84**, 4197–4203
92 Kozlowska, L. and Rosolowska-Huszcz, D. (2004) Leptin, thyrotropin, and thyroid hormones in obese/overweight women before and after two levels of energy deficit. Endocrine **24**, 147–153
93 O'Brian, J. T., Bybee, D. E., Burman, K. D., Osburne, R. C., Ksiazek, M. R., Wartofsky, L. and Georges, L. P. (1980) Thyroid hormone homeostasis in states of relative caloric deprivation. Metab., Clin. Exp. **29**, 721–727
94 Weinsier, R. L., Nagy, T. R., Hunter, G. R., Darnell, B. E., Hensrud, D. D. and Weiss, H. L. (2000) Do adaptive changes in metabolic rate favor weight regain in weight-reduced individuals? An examination of the set-point theory. Am. J. Clin. Nutr. **72**, 1088–1094
95 Hukshorn, C. J., Menheere, P. P. C. A., Westerterp-Plantenga, M. S. and Saris, W. H. M. (2003) The effect of pegylated human recombinant leptin (PEG-OB) on neuroendocrine adaptations to semi-starvation in overweight men. Eur. J. Endocrinol. **148**, 649–655
96 Naslund, E., Andersson, I., Degerblad, M., Kogner, P., Kral, J. G., Rossner, S. and Hellstrom, P. M. (2000) Associations of leptin, insulin resistance and thyroid function with long-term weight loss in dieting obese men. J. Intern. Med. **248**, 299–308
97 Doucet, E., Imbeault, P., St-Pierre, S., Almeras, N., Mauriege, P., Richard, D. and Tremblay, A. (2000) Appetite after weight loss by energy restriction and a low-fat diet-exercise follow-up. Int. J. Obes. Relat. Metab. Disord. **24**, 906–914
98 Zakrzewska, K. E., Cusin, I., Sainsbury, A., Rohner-Jeanrenaud, F. and Jeanrenaud, B. (1997) Glucocorticoids as counterregulatory hormones of leptin: toward an understanding of leptin resistance. Diabetes **46**, 717–719
99 Johnstone, A. M., Faber, P., Andrew, R., Gibney, E. R., Elia, M., Lobley, G., Stubbs, R. J. and Walker, B. R. (2004) Influence of short-term dietary weight loss on cortisol secretion and metabolism in obese men. Eur. J. Endocrinol. **150**, 185–194
100 Tomiyama, A. J., Mann, T., Vinas, D., Hunger, J. M., Dejager, J. and Taylor, S. E. (2010) Low calorie dieting increases cortisol. Psychosom. Med. **72**, 357–364
101 Galvao-Teles, A., Graves, L., Burke, C. W., Fotherby, K. and Fraser, R. (1976) Free cortisol in obesity; effect of fasting. Acta Endocrinol. **81**, 321–329
102 Edelstein, C. K., Roy-Byrne, P., Fawzy, F. I. and Dornfeld, L. (1983) Effects of weight loss on the dexamethasone suppression test. Am. J. Psychiatry **140**, 338–341
103 Ho, J. T., Keogh, J. B., Bornstein, S. R., Ehrhart-Bornstein, M., Lewis, J. G., Clifton, P. M. and Torpy, D. J. (2007) Moderate weight loss reduces renin and aldosterone but does not influence basal or stimulated pituitary-adrenal axis function. Horm. Metab. Res. **39**, 694–699
104 Pelleymounter, M. A., Cullen, M. J., Baker, M. B., Hecht, R., Winters, D., Boone, T. and Collins, F. (1995) Effects of the obese gene product on body weight regulation in ob/ob mice. Science **269**, 540–543
105 Schwartz, M. W., Seeley, R. J., Woods, S. C., Weigle, D. S., Campfield, L. A., Burn, P. and Baskin, D. G. (1997) Leptin increases hypothalamic pro-opiomelanocortin mRNA expression in the rostral arcuate nucleus. Diabetes **46**, 2119–2123
106 Stephens, T. W., Basinski, M., Bristow, P. K., Bue-Valleskey, J. M., Burgett, S. G., Craft, L., Hale, J., Hoffmann, J., Hsiung, H. M. and Kriauciunas, A. (1995) The role of neuropeptide Y in the antiobesity action of the obese gene product. Nature **377**, 530–532
107 Considine, R. V., Sinha, M. K., Heiman, M. L., Kriauciunas, A., Stephens, T. W., Nyce, M. R., Ohannesian, J. P., Marco, C. C., McKee, L. J. and Bauer, T. L. (1996) Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N. Engl. J. Med. **334**, 292–295
108 Ahima, R. S., Prabakaran, D., Mantzoros, C., Qu, D., Lowell, B., Maratos-Flier, E. and Flier, J. S. (1996) Role of leptin in the neuroendocrine response to fasting. Nature **382**, 250–252
109 Havel, P. J., Kasim-Karakas, S., Mueller, W., Johnson, P. R., Gingerich, R. L. and Stern, J. S. (1996) Relationship of plasma leptin to plasma insulin and adiposity in normal weight and overweight women: effects of dietary fat content and sustained weight loss. J. Clin. Endocrinol. Metab. **81**, 4406–4413
110 Keim, N. L., Stern, J. S. and Havel, P. J. (1988) Relation between circulating leptin concentrations and appetite during a prolonged, moderate energy deficit in women. Am. J. Clin. Nutr. **68**, 794–801
111 Sumithran, P., Prendergast, L. A., Delbridge, E., Purcell, K., Shulkes, A., Kriketos, A. and Proietto, J. (2011) Long-term persistence of hormonal adaptations to weight loss. N. Engl. J. Med. **365**, 1597–1604

112 Rosenbaum, M., Nicolson, M., Hirsch, J., Murphy, E., Chu, F. and Leibel, R. L. (1997) Effects of weight change on plasma leptin concentrations and energy expenditure. J. Clin. Endocrinol. Metab. **82**, 3647–3654

113 Heymsfield, S. B., Greenberg, A. S., Fujioka, K., Dixon, R. M., Kushner, R., Hunt, T., Lubina, J. A., Patane, J., Self, B., Hunt, P. and McCamish, M. (1999) Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. JAMA, J. Am. Med. Assoc. **282**, 1568–1575

114 Westerterp-Plantenga, M. S., Saris, W. H., Hukshorn, C. J. and Campfield, L. A. (2001) Effects of weekly administration of pegylated recombinant human OB protein on appetite profile and energy metabolism in obese men. Am. J. Clin. Nutr. **74**, 426–434

115 Kissileff, H. R., Thornton, J. C., Torres, M. I., Pavlovich, K., Mayer, L. S., Kalari, V., Leibel, R. L. and Rosenbaum, M. (2012) Leptin reverses declines in satiation in weight-reduced obese humans. Am. J. Clin. Nutr. **95**, 309–317

116 Rosenbaum, M., Sy, M., Pavlovich, K., Leibel, R. L. and Hirsch, J. (2008) Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. J. Clin. Invest. **118**, 2583–2591

117 Chearskul, S., Delbridge, E., Shulkes, A., Proietto, J. and Kriketos, A. (2008) Effect of weight loss and ketosis on postprandial cholecystokinin and free fatty acid concentrations. Am. J. Clin. Nutr. **87**, 1238–1246

118 Cummings, D. E., Weigle, D. S., Frayo, R. S., Breen, P. A., Ma, M. K., Dellinger, E. P. and Purnell, J. Q. (2002) Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N. Engl. J. Med. **346**, 1623–1630

119 Essah, P. A., Levy, J. R., Sistrun, S. N., Kelly, S. M. and Nestler, J. E. (2010) Effect of weight loss by a low-fat diet and a low-carbohydrate diet on peptide YY levels. Int. J. Obes. **34**, 1239–1242

120 Pfluger, P. T., Kampe, J., Castaneda, T. R., Vahl, T., D'Alessio, D. A., Kruthaupt, T., Benoit, S. C., Cuntz, U., Rochlitz, H. J., Moehlig, M. et al. (2007) Effect of human body weight changes on circulating levels of peptide YY and peptide YY3–36. J. Clin. Endocrinol. Metab. **92**, 583–588

121 Reinehr, T., de Sousa, G., Niklowitz, P. and Roth, C. L. (2007) Amylin and its relation to insulin and lipids in obese children before and after weight loss. Obesity **15**, 2006–2011

122 Reinehr, T., Enriori, P. J., Harz, K., Cowley, M. A. and Roth, C. L. (2006) Pancreatic polypeptide in obese children before and after weight loss. Int. J. Obes. **30**, 1476–1481

123 Adam, T. C. M., Lejeune, M. P. G. M. and Westerterp-Plantenga, M. S. (2006) Nutrient-stimulated glucagon-like peptide 1 release after body-weight loss and weight maintenance in human subjects. Br. J. Nutr. **95**, 160–167

124 Verdich, C., Toubro, S., Buemann, B., Lysgard Madsen, J., Holst, J. J. and Astrup, A. (2001) The role of postprandial releases of insulin and incretin hormones in meal-induced satiety-effect of obesity and weight reduction. Int. J. Obes. **25**, 1206–1214

125 Hauner, H., Glatting, G., Kaminska, D. and Pfeiffer, E. F. (1988) Effects of gastric inhibitory polypeptide on glucose and lipid metabolism of isolated rat adipocytes. Ann. Nutr. Metab. **32**, 282–288

126 Cameron, J. D., Goldfield, G. S., Cyr, M-J. and Doucet, E. (2008) The effects of prolonged caloric restriction leading to weight-loss on food hedonics and reinforcement. Physiol. Behav. **94**, 474–80

127 Drewnowski, A., Brunzell, J. D., Sande, K., Iverius, P. H. and Greenwood, M. R. (1985) Sweet tooth reconsidered: taste responsiveness in human obesity. Physiol. Behav. **35**, 617–622

128 Heini, A. F., Lara-Castro, C., Kirk, K. A., Considine, R. V., Caro, J. F. and Weinsier, R. L. (1998) Association of leptin and hunger-satiety ratings in obese women. Int. J. Obes. **22**, 1084–1087

129 Cornier, M.-A., Salzberg, A. K., Endly, D. C., Bessesen, D. H., Rojas, D. C. and Tregellas, J. R. (2009) The effects of overfeeding on the neuronal response to visual food cues in thin and reduced-obese individuals. PLoS ONE **4**, e6310

130 DelParigi, A., Chen, K., Salbe, A. D., Hill, J. O., Wing, R. R., Reiman, E. M. and Tataranni, P. A. (2004) Persistence of abnormal neural responses to a meal in postobese individuals. Int. J. Obes. **28**, 370–377

131 Gordon, C. M., Dougherty, D. D., Rauch, S. L., Emans, S. J., Grace, E., Lamm, R., Alpert, N. M., Majzoub, J. A. and Fischman, A. J. (2000) Neuroanatomy of human appetitive function: A positron emission tomography investigation. Int. J. Eat. Disord. **27**, 163–171

132 Malik, S., McGlone, F., Bedrossian, D. and Dagher, A. (2008) Ghrelin modulates brain activity in areas that control appetitive behavior. Cell Metab. **7**, 400–409

133 Baicy, K., London, E. D., Monterosso, J., Wong, M-L., Delibasi, T., Sharma, A. and Licinio, J. (2007) Leptin replacement alters brain response to food cues in genetically leptin-deficient adults. Proc. Nat. Acad. Sci. U.S.A. **104**, 18276–18279

134 DelParigi, A., Chen, K., Salbe, A. D., Hill, J. O., Wing, R. R., Reiman, E. M. and Tataranni, P. A. (2007) Successful dieters have increased neural activity in cortical areas involved in the control of behavior. Int. J. Obes. **31**, 440–448

135 Klem, M. L., Wing, R. R., McGuire, M. T., Seagle, H. M. and Hill, J. O. (1997) A descriptive study of individuals successful at long-term maintenance of substantial weight loss. Am. J. Clin. Nutr. **66**, 239–246

136 Wyatt, H. R., Phelan, S., Wing, R. R. and Hill, J. O. (2005) Lessons from patients who have successfully maintained weight loss. Obesity Management **1**, 56–61

137 Shick, S. M., Wing, R. R., Klem, M. L., McGuire, M. T., Hill, J. O. and Seagle, H. (1998) Persons successful at long-term weight loss and maintenance continue to consume a low-energy, low-fat diet. J. Am. Diet. Assoc. **98**, 408–413

138 Gorin, A. A., Phelan, S., Wing, R. R. and Hill, J. O. (2004) Promoting long-term weight control: does dieting consistency matter? Int. J. Obes. **28**, 278–281

139 Raynor, H. A., Jeffery, R. W., Phelan, S., Hill, J. O. and Wing, R. R. (2005) Amount of food group variety consumed in the diet and long-term weight loss maintenance. Obes. Res. **13**, 883–890

140 Phelan, S., Roberts, M., Lang, W. and Wing, R. R. (2007) Empirical evaluation of physical activity recommendations for weight control in women. Med. Sci. Sports Exercise **39**, 1832–1836

141 Raynor, D. A., Phelan, S, Hill, J. O. and Wing, R. R. (2006) Television viewing and long-term weight maintenance: results from the National Weight Control Registry. Obesity **14**, 1816–1824

142 Phelan, S., Hill, J. O., Lang, W., Dibello, J. R. and Wing, R. R. (2003) Recovery from relapse among successful weight maintainers. Am. J. Clin. Nutr. **78**, 1079–1084

143 Borg, C. M., le Roux, C. W., Ghatei, M. A., Bloom, S. R., Patel, A. G. and Aylwin, S. J. B. (2006) Progressive rise in gut hormone levels after Roux-en-Y gastric bypass suggests gut adaptation and explains altered satiety. Br. J. Surg. **93**, 210–215

144 Dixon, A. F. R., Dixon, J. B. and O'Brien, P. E. (2005) Laparoscopic adjustable gastric banding induces prolonged satiety: a randomized blind crossover study. J. Clin. Endocrinol. Metab. **90**, 813–819

145 Burton, P. R. and Brown, W. A. (2011) The mechanism of weight loss with laparoscopic adjustable gastric banding: induction of satiety not restriction. Int. J. Obes. **35** (Suppl. 3), S26–S30

146 Korner, J., Bessler, M., Cirilo, L. J., Conwell, I. M., Daud, A., Restuccia, N. L. and Wardlaw, S. L. (2005) Effects of Roux-en-Y gastric bypass surgery on fasting and postprandial concentrations of plasma ghrelin, peptide YY, and insulin. J. Clin. Endocrinol. Metab. **90**, 359–365

147 Morinigo, R., Moize, V., Musri, M., Lacy, A. M., Navarro, S., Marin, J. L., Delgado, S., Casamitjana, R. and Vidal, J. (2006) Glucagon-like peptide-1, peptide YY, hunger, and satiety after gastric bypass surgery in morbidly obese subjects. J. Clin. Endocrinol. Metab. **91**, 1735–1740

148 Backhed, F., Ding, H., Wang, T., Hooper, L. V., Koh, G. Y., Nagy, A., Semenkovich, C. F. and Gordon, J. I. (2004) The gut microbiota as an environmental factor that regulates fat storage. Proc. Nat. Acad. Sci. U.S.A. **101**, 15718–15723

149 Duncan, S. H., Lobley, G. E., Holtrop, G., Ince, J., Johnstone, A. M., Louis, P. and Flint, H. J. (2008) Human colonic microbiota associated with diet, obesity and weight loss. Int. J. Obes. **32**, 1720–1724

150 Ley, R. E., Turnbaugh, P. J., Klein, S. and Gordon, J. I. (2006) Microbial ecology: human gut microbes associated with obesity. Nature **444**, 1022–1023

151 Turnbaugh, P. J., Ley, R. E., Mahowald, M. A., Magrini, V., Mardis, E. R. and Gordon, J. I. (2006) An obesity-associated gut microbiome with increased capacity for energy harvest. Nature **444**, 1027–1031

152 Chan, J. L., Heist, K., DePaoli, A. M., Veldhuis, J. D. and Mantzoros, C. S. (2003) The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men. J. Clin. Invest. **111**, 1409–1421

153 Ravussin, E., Smith, S. R., Mitchell, J. A., Shringarpure, R., Shan, K., Maier, H., Koda, J. E. and Weyer, C. (2009) Enhanced weight loss with pramlintide/metreleptin: an integrated neurohormonal approach to obesity pharmacotherapy. Obesity **17**, 1736–1743

154 Astrup, A., Rossner, S., Van Gaal, L., Rissanen, A., Niskanen, L., Al Hakim, M., Madsen, J., Rasmussen, M. F. and Lean, M. E. J. (2009) Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet **374**, 1606–1616

155 Greenway, F. L., Dunayevich, E., Tollefson, G., Erickson, J., Guttadauria, M., Fujioka, K. and Cowley, M. A. (2009) Comparison of combined bupropion and naltrexone therapy for obesity with monotherapy and placebo. J. Clin. Endocrinol. Metab. **94**, 4898–4906

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