

Title: Mechanisms of weight regain.

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Abstract

Weight regain following weight loss is frequent problem that people with obesity face. This weight recidivism is often attributed to the lack of compliance with appropriate food habits and exercise. On the contrary, it is known that body weight and fat mass are regulated by numerous physiological mechanisms, far beyond voluntary food intake and physical exercise. Thus, the aim of this paper is to review the main peripheral and central mechanisms involved in weight regain.

Gut hormone secretion profiles impact upon predisposition to weight regain according to an individual variability, although it is recognised a usual pattern of compensatory changes: a reduction in anorectic hormones secretion and an increase in orexigenic hormone. These changes lead to both increased appetite and reward value of food leading to increased energy intake. In addition, resting energy expenditure after weight loss is lower than expected according to body composition changes. This gap between observed and predicted energy expenditure following weight loss is named metabolic adaptation, which has been suggested to explain partly weight regain.

This complicated scenario, beyond patient motivation, makes weight regain a challenge in long-term management interventions in patients with obesity.

Keywords: weight regain, gut hormones, metabolic adaptation, reward

Introduction

Obesity is a chronic progressive disease with a high tendency to recidivism. Weight regain is frequent after any attempts of voluntary weight loss [1]. Weight regain is frequently attributed to the lack of compliance of the patients [2]. This simplistic interpretation is based on the false assumption that body weight is entirely under volitional control and that weight loss is only a matter of self-control [3]. Weight regain was indeed attributed to the lack of motivation and self-control of the patients, thus increasing the pervasive stigmatization of people with obesity as lazy and unreliable persons [3].

On the contrary, we now know that body weight and fat mass are regulated by numerous physiological mechanisms, far beyond voluntary food intake and physical exercise. Moreover, a large body of experimental evidence has shown that voluntary attempts to lose weight activated potent biologic mechanisms that tend to stop weight loss and restore previous body weight and fat mass levels [4]. In this paper, a brief overview will be provided on some of the peripheral and central mechanisms believed to be relevant in weight regain.

The role of gut hormones in weight regain following dietary weight loss

Ensuring an adequate energy intake to meet the body's needs is essential for survival. Gut hormones have been identified as key regulators of energy homeostasis acting on homeostatic and hedonic brain circuits to drive eating behaviour. These physiological circuits evolved in conditions where energy availability was sparse. Energy restriction activates powerful compensatory drives aimed at resisting weight loss and defending the higher body weight. Altered gut hormone secretion profiles are a key part of this physiological drive to restore energy reserves and contribute to weight regain following dietary weight loss.

A study by Sumithran et al. provided key insights into the role of gut hormones in driving weight regain. 50 participants with severe obesity were followed up for 52 weeks after a 10-week very low energy diet (VLED) [5]. Mean weight loss was 13.5 ± 0.5 kg at 10 weeks and 7.9 ± 1.1 kg after 52 weeks. Increased hunger levels, as well as desire and urge to eat were reported. At the end of the 10-week VLED circulating levels of the anorectic hormones, Peptide YY3-36 (PYY), cholecystokinin (CCK) and amylin, were significantly reduced, together with decreased insulin and leptin levels. In contrast, circulating levels of the orexigenic hormone ghrelin and levels of glucose-dependent insulinotropic polypeptide (GIP) and pancreatic polypeptide (PP) increased. By 52 weeks, body weight had returned to pre-intervention level, however, unfavourable gut hormone changes combined with increased hunger levels persisted [5].

Compensatory changes in gut hormone profiles with reduction in anorectic hormone secretion (circulating GLP-1, PYY, CCK, amylin) and leptin levels, coupled with reduced satiety have also been reported in other studies [6-8]. Increased ghrelin levels, leading to increased hunger and an augmented desire to eat are also reported [9]. **Table 1** summarises the known effects of dietary weight loss on gut hormones secretion profiles.

Hormone	Overall effect of energy restriction on circulating levels [6]	Specific diets/circumstances
Ghrelin	↑	↔/↓ during ketosis [10]
GIP	↑	
PP	↑	
GLP-1	↓	↔ in low carbohydrate diet [13]
PYY	↓/↔	
CCK	↓	
Neurotensin	↓	
Amylin	↓	

Table 1: Summary of effects of dietary weight loss on gut hormone secretion profiles.

Furthermore, the composition of diets used to achieve weight loss also impact upon gut hormones secretion profiles. For example, diets designed to induce ketogenesis, either by carbohydrate elimination and high protein consumption or through calorie restriction, may halt weight-loss related rises in ghrelin and suppress hunger, while ketosis is maintained [10]. Interestingly, administration of a ketone ester drink was shown to suppress ghrelin levels, as well as perceived hunger and desire to eat in normal weight adults [11]. However, even with ketogenic diets, increased ghrelin levels and hunger occur with re-introduction of a varied diet [12]. In a study in adults with obesity comparing GLP-1 secretion with a low-carbohydrate versus low-fat diet, GLP-1 remained stable in the low-carbohydrate group, but reduced in the low-fat diet, despite comparable weight loss [13].

However, gut hormone responses to energy restriction are variable and may be linked to weight loss maintenance outcomes. In a study using a 8-week VLED with a mean weight loss of 13% followed by a 52-week weight-maintenance programme, weight loss maintenance was associated with higher circulating postprandial PYY and GLP-1 levels [14]. Another study in adults with obesity demonstrated that weight regain was more likely with lower fasting GLP-1 and greater reduction in GLP-1 after weight loss [15]. Furthermore, a study using a 8-week VLED and a year-long weight maintenance follow-up programme in participants with obesity who maintained 17% weight loss at 1 year, compared gut hormone profiles to those of a normal weight individuals [16]. Results showed increases in ghrelin, along with increases in both hunger and fullness, which after weight loss were comparable to those in healthy weight controls. Postprandial concentrations of active GLP-1, total PYY, and CCK remained lower in individuals with obesity at all time points compared with controls. These findings suggest that that individual variability, likely driven by genetic variability, in gut hormone secretion profiles in response to weight loss impacts upon predisposition to weight regain. Moreover, functional brain MRI (fMRI) studies have demonstrated that reductions in body weight are associated with increased reward and reduced emotional and cognitive control with regard to food intake [17]. A brain fMRI study in adults with overweight and obesity undergoing a calorie-restricted diet, found that weight loss-induced increased ghrelin and reduced leptin levels correlated with increased brain activation of reward-related areas while viewing food cues [18]. Furthermore, the degree of food-cue reactivity assessed using fMRI brain imaging, has been shown to

correlate with the amount of weight lost through lifestyle interventions and to predict the likelihood of weight regain [19].

Gut hormones exert their effects on multiple organs and tissues, forming a key part of a highly complicated network of physiological body weight regulations. Weight loss through dietary restriction therefore undoubtedly also impacts upon the other components of this highly complex system, including bile acid secretion, adipose tissue and the intestinal microbiome. Weight loss leads to adipocytes reducing in size with a consequent increase in the extracellular matrix (ECM). This results in mechanical stress, leading to inflammation and oxidative stress [20]. Conditions of ongoing energy restriction may not allow for ECM remodelling, inhibiting further reduction in adipocyte size and driving the cells to return to their original size, thereby contributing to weight regain [21]. Bile acids and intestinal microbiome are closely interlinked and both have been shown to respond to dietary changes leading to weight loss, such as a VLCD. However, the long-term impact of these changes on weight loss maintenance and regain are not yet established [22-24].

Understanding the genetic and physiological drivers that underlie variability in response to energy restriction interventions and their anticipated physiological sequelae will lead to the development of more effective strategies for weight loss and weight loss maintenance.

Metabolic adaptation

Resting energy expenditure (REE) accounts for 60-70% of 24 hours energy expenditure in humans and it is mainly determined by body composition. By using population specific equations, REE can be predicted with a certain accuracy from fat-free mass (FFM) levels [25]. The loss of FFM that accompanied both voluntary and involuntary weight loss is therefore associated to an expected reduction of REE. Unfortunately, REE reduced after weight loss more than expected according to body composition changes. This gap between observed and predicted energy expenditure following weight loss is named metabolic adaptation [25].

Metabolic adaptation was firstly observed in voluntary starvation experiments [26] and it has been later better conceptualized by Leibel, Rosenbaum & Hirsch in 1995 [25]. These authors, repeatedly measured 24-hour total energy expenditure, resting and non-resting energy expenditure, and the thermic effect of feeding in 18 volunteers with obesity and 23 subjects who never had obesity. The subjects were studied at their usual body weight and after losing weight by underfeeding. Stabilization of body weight at a level 10% below the initial weight was associated with negative observed-minus-predicted values for total energy expenditure and non-resting and resting energy expenditure. The magnitude of this metabolic adaptation was clinically significant (around 300 kcal/day for total energy expenditure) [25]. The existence of metabolic adaptation was confirmed in 16 people with class III obesity undergoing an intensive diet and exercise intervention as part of “The Biggest Loser” weight loss competition [27].

Metabolic adaptation has been observed also after bariatric and metabolic surgery. Knut et al. compared metabolic adaptation in 13 pairs of matched patients with obesity that underwent Roux-en-Y Gastric Bypass (RYGB) surgery or participated in “The Biggest Loser” competition: in both groups, REE decreased significantly more than expected based on body

composition changes, with the gap being related to the degree of energy imbalance and changes in circulating leptin [28]. A 12-month persistent metabolic adaptation in response to RYGB-induced weight loss has been confirmed in 11 adolescents with extreme obesity [29]. Tam et al. analysed metabolic adaptation in 14 patients treated with RYGB and in 13 patients treated with sleeve gastrectomy and found a greater-than-expected reduction of REE not explained by changes in body composition at 6 weeks after surgery in both groups. The suppression in REE after Laparoscopic Sleeve Gastrectomy (LSG) and RYGB remained up to 2 years, even after weight loss plateaued [30]. Finally, the existence of metabolic adaptation 12 months after surgery was confirmed in a larger sample of 154 patients treated by LSG [31]. In this latter study, a weak but significant inverse correlation between the level of metabolic adaptation and the degree of weight or FM loss in the first year after sleeve gastrectomy was observed, supporting the hypothesis that a greater metabolic adaptation could be partly responsible for a lower weight loss after surgery [31].

Most of the previous studies evaluated and detected metabolic adaptation shortly after weight loss. The fade of metabolic adaptation in the long-term and its importance as a mechanism favouring weight regain is still matter of debate. Fothergill et al. re-evaluated body composition and REE in 14 of the 16 subjects participating in “The Biggest Loser” competition 6 years after the original study [32]. In this group, weight loss at the end of the competition was 58.3 ± 24.9 kg and REE decreased by 610 ± 483 kcal/day. After 6 years, 41.0 ± 31.3 kg of the lost weight was regained, while REE still was 704 ± 427 kcal/day below baseline, with a metabolic adaptation of 499 ± 207 kcal/day [32]. These data suggest that metabolic adaptation could persist over time and after substantial weight regain. Weight regain was not significantly correlated with metabolic adaptation at the competition’s end, but those subjects maintaining greater weight loss at 6 years also experienced greater concurrent metabolic slowing [32]. Authors concluded that, even if the magnitude of short-term metabolic adaptation was not associated to weight regain, maintaining long-term weight loss requires vigilant combat against persistent metabolic adaptation that acts to proportionally counter ongoing efforts to reduce body weight [32]. More data about the persistence of metabolic adaptation in the long-term after weight loss are required.

Reward

Hunger, food craving, and the anticipation and enjoyment of eating are all psychological experiences that are underpinned by interactions between peripheral (outlined above) and central/neuro-biology. Appetite regulation involves a complex interplay between hunger/satiety, reward processes and cognitive control processes [33]. In the brain these processes are ascribed to interacting hypothalamic and mesocorticolimbic neuro-circuitry [34].

Due to food being essential for survival, we have evolved efficient motivational processes, which direct our attention and desire for food, and enjoyment of eating, which in turn can drive consumption beyond our metabolic requirement [35]. Our food reward system can override satiety signalling allowing us to eat when we do not feel hunger and undermine the ability to exert control overeating. This becomes problematic in modern westernised “obesogenic”

environments whereby energy-dense foods are easily accessed, and palatable foods are heavily marketed [36].

Berridge and colleagues have described what is regularly referred to as ‘wanting’ and ‘liking’ of foods [37-40]. These are separable psychological processes with overlapping, but distinct, neuro-circuitry. ‘Wanting’ refers to increased incentive salience of food, which is triggered by a food cue (e.g. the sight or smell of food) and generates a craving, or behavioural urge for food [41]. Preclinical studies have identified the neuro-architecture of ‘wanting’ as being located primarily in the mesocorticolimbic reward pathway comprising the nucleus accumbens shells, dorsal striatum and amygdala [34]. Neuro-chemically ‘wanting’ is understood to be underpinned primarily by dopamine, glutamate, opioid and endocannabinoid neurotransmission [42]. ‘Liking’ (pleasure) on the other hand is primarily generated in a sub-region of the mesocorticolimbic reward pathway (nucleus accumbens). Notably, dopamine does not appear to have a primary role in liking, instead ‘liking’ is primarily underpinned neuro-chemically by opioid and endocannabinoid activity [43].

In human behavioural research, increased cravings for food have been associated with increased BMI [44]. Furthermore, cravings for food and responsivity to food cues increase in people who are adhering to an energy restricted diet, and this effect is more pronounced in people living with obesity [45,46]. Taken together this suggests that people living with obesity may find greater difficulty in coping with consequences of dieting. This suggests a biological vulnerability for weight gain in people living with obesity which results in eating behaviours that lead to energy overconsumption, such as preference for high fat foods (liking) and strong hedonic attraction to palatable foods [47].

Food cue reactivity paradigms using fMRI have suggested that people living with obesity show neurobiological vulnerabilities, which may increase risk of overconsumption [48]. For example, Dimitropoulos et al. observe increased mesocorticolimbic (lateral orbitofrontal cortex, caudate, anterior cingulate) activity in people with obesity relative to controls whilst viewing high-calorie and low-calorie foods [49]. However, many of these cross-sectional studies with small sample sizes report inconsistent results. Due to this, meta-analyses of passive viewing studies suggest that there is little consistent evidence for simple activation differences between people with obesity and controls in passive viewing paradigms [50].

Similarly, behavioural studies of attentional bias (selective capture and holding of attention) posit that incentive salience of foods are reflected by an attentional bias for food cues over non-food cues. Many studies in this area have been conducted, however the totality of the data, as recently meta-analysed [51], suggest that whilst craving for food, hunger, and food intake are associated with increased attentional bias, BMI is not. Thus, attentional bias reflects state changes in motivational value of food, rather than this being a trait of people living with obesity.

Given the complexity of obesity, it is not surprising that cross sectional studies have showed inconsistencies in neurobiological vulnerabilities for weight gain. There is clearly much individual variability in reward-related weight gain. More complex prospective studies using fMRI paradigms have been used to start to identify neurobiological markers for weight gain in individuals who are at greater risk of weight gain – i.e. predictors of weight gain. Such studies suggest that individuals at risk of obesity show a hyper-responsivity of reward neurocircuitry to high-calorie food tastes [48]. For example, Geha et al. showed that elevated responses to

high-calorie milkshake taste in nucleus accumbens, ventral pallidum, hypothalamus and thalamus predicted increased weight gain over a 12-month period [52]. Similarly, future weight-gain has been predicted by reward-related (nucleus accumbens, orbitofrontal cortex) activation in response to food cues and anticipation of foods [53]. However, equally there are studies which do not replicate these results [48]. In terms of weight-regain, novel neuroimaging designs are now beginning to be used to assess how differences in reward processing predicts successful/unsuccessful weight maintenance following weight-loss. For example, Simon et al. [54] shows that weight-maintainers and weight-regainers both show similar reward reactivity to expectation and receipt of food rewards. However, this activation remained in the satiated state in weight-regainers, but not weight-maintainers. This suggests a role for sustained reward system activity in weight-regain. However much more research is required in this area to elucidate specific mechanisms.

Research on the predictive markers for weight-gain and weight-regain based on reward pathway responsivity is still in its relative infancy, and there are studies that show equivocal findings. It becomes clear that reward processes are powerful motivators of food intake. However, these are not necessarily associated with changes in trait reward function in all people with obesity. There is a high likelihood that many people living with obesity have a reward-related neurobiological vulnerability to overconsumption, and this must be understood if we are to reduce blame and stigma around heavier body weight. Studies into reward reactivity in humans serve to highlight the complexities of obesity, and so identifying individual barriers to weight loss and specific individual problems must be identified in personalised weight management plans in order to have the best chances of achieving and maintaining weight loss.

Conclusion

The evidence presented in this review confirms that the inexorable trend to weight regain observed after weight loss is not simplistically attributable to the loss of patients motivation or compliance, but it is driven by potent biological mechanisms that tend to stimulate food intake (gut hormones) and depress energy expenditure (metabolic adaptation). The combined action of these peripheral mechanisms provides a pressure to overeating that open the way to the effects driven by the central mechanisms linked to the pleasure and the reward for food (**Figure 1**). This picture needs to be taken into account in designing long-term management interventions in patients with obesity. These compensatory mechanisms that we have described potentially contribute to weight regain after bariatric surgery. However, additional longitudinal studies are required in order to delineate the underlying mechanisms. A better insight of the molecular mechanisms sustaining weight regain could suggest new potential targets for pharmacologic interventions.

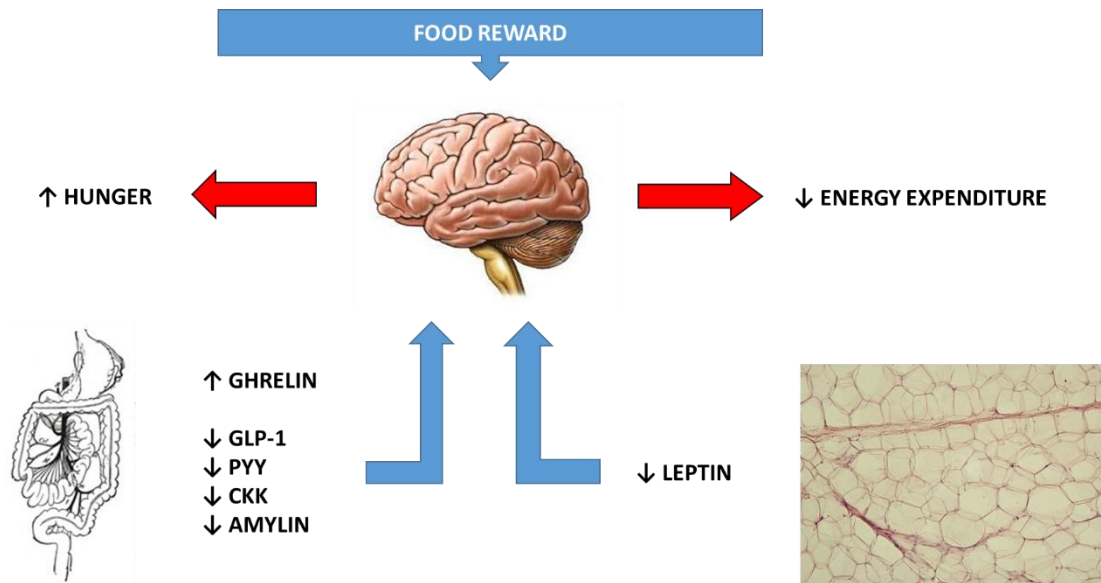


Figure 1. When body weight reduction occurs, secretion of orexigenic hormones in the gastrointestinal tract tends to increase, whereas anorexigenic hormones production slows down. The loss of fat mass is signaled by leptin levels reduction. The combined effects of these peripheral signals at the level of the hypothalamic neurons controlling weight and energy balance cause an increase in hunger and a decrease in energy expenditure, creating a more favourable substrate for the action of the central mechanisms linked to the pleasure and the reward for food.

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