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Metabolic Adaptations during Negative Energy Balance and their Potential Impact on Appetite and Food Intake

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Abstract

This review examines the metabolic adaptations that occur in response to negative energy balance and their potential putative or functional impact on appetite and food intake. Sustained negative energy balance will result in weight loss, with body composition changes similar for different dietary interventions if total energy and protein intake are equated. During periods of underfeeding, compensatory metabolic and behavioural responses occur that attenuate the prescribed energy deficit. While losses of metabolically active tissue during energy deficit results in reduced energy expenditure, an additional down-regulation in expenditure has been noted that cannot be explained by changes in body tissue (e.g. adaptive thermogenesis). Sustained negative energy balance is also associated with an increase in oregixgenic drive and changes in appetite-related peptides during weight loss that may act as cues for increased hunger and food intake. It has also been suggested that losses of fat-free mass could also act as an orexigenic signal during weight loss, but more data is needed to support these findings and the signalling pathways linking fat-free mass and energy intake remains unclear. Taken together, these metabolic and behavioural compensatory responses to weight loss point to a highly complex and dynamic energy balance system in which perturbations to individual components can cause co-ordinated and inter-related compensatory responses. The strength of these compensatory responses is individually subtle, and early identification of this inter-individual variability may help identify individuals that respond well or poorly to an intervention.

1.0 Introduction

A negative energy balance will result in weight loss if sustained over time[1]. Despite the apparent simplicity of energy balance i.e. energy intake (EI) vs. energy expenditure (EE), most weight loss maintenance attempts are unsuccessful and weight loss recidivism is high[2-5]. The development of strategies that promote successful weight loss and prevent weight regain therefore remains a priority. While a lack of sustained weight loss can in part be explained by a failure to adhere to dietary and physical activity guidelines[6, 7], compensatory metabolic and behavioural responses to energy deficit also act to undermine weight loss and promote weight regain[8, 9]. A better understanding of the compensatory responses to energy deficit and surfeit are needed if more effective long-term weight maintenance strategies are to be developed. However, such strategies are complicated by the large inter-individual variability typically seen in body weight responses to weight loss interventions[10-12], and the lack of robust predictors of this response variability[13].

The mechanisms that oppose a negative energy balance are inter-related and complex, individually subtle and often difficult to quantify[9, 13]. Metabolic and behavioural determinants of energy balance interact in a co-ordinated fashion during energy deficit and surfeit, but the mechanisms through which physiology drives behaviour are rarely acknowledged in the context of weight loss and weight regain[13]. Methodological limitations associated with the measurement of EI and EE have long frustrated energy balance research, and have limit our understanding of the putative signals that link physiology to behaviour. These limitations have also contributed to debate over the primary cause of weight gain and secular trends in obesity prevalence[14]. However, given the fundamental relationships between components of EE, body composition and EI, it might argued that successful weight loss and weight loss maintenance strategies will only be developed if the inter-relationships between physiology and behaviour are explicitly acknowledged and incorporated in their design[15, 16].

To this end, there is renewed interest in integrative models of energy balance regulation that consider the dynamic relationships between body composition, EE and physiological function, and the way these interactions influence appetite and EI[17-20]. Recent research has focused on the functional associations between components of body composition, EE and EI, and indicate that fat-free mass (FFM) and resting metabolic rate (RMR) are associated with a drive to eat that reflects the energetic demand of metabolically active tissue[21-26]. However, it is unclear how changes in body composition and EE during weight loss influence appetite control. Therefore, the main aims of the present review are to i) examine the metabolic adaptations that occur in response to negative

energy balance, and ii) to consider the putative or functional effects that these adaptations may have on appetite control and EI.

2.0 Energy Balance: A Dynamic Regulatory System

It has been suggested that an energy deficit of 3500 kcal would lead to 1 pound of lost body weight (~454 grams)[27], but this simplistic approach is known to overestimate weight loss[28]. The '3500 kcal per pound' rule assumes that the composition of weight lost would be 100% body fat (based on the assumption that the energy value of 1 gram of fat is 9 kcal and adipocytes are composed of 85-90% of triglyceride) and fails to account for dynamic changes in the biological components of EE seen with weight loss (e.g. reductions in RMR and the energy cost of muscular activity). Therefore, even though the energy content of fat remains constant (i.e. 3500kcal per 1lb or ~454g), a concomitant reduction in EE during weight loss will attenuate the prescribed energy deficit and lead to a lower than predicted weight loss (as the actual energy deficit will be lower than that prescribed via dietary restriction for example)[29]. Large inter-individual variability in weight loss and other physiological behavioural responses are also apparent following lifestyle (diet or exercise)[8, 12], pharmacological[12] and surgical[30] weight loss interventions. The clinical significance[31] and statistical methods[32] used to quantify such variability have been debated, but this inter-individual variability in treatment response appears to be a biological norm[33].

Although adherence to a prescribed intervention is likely to contribute to such variability[7], metabolic and behavioural compensatory adaptations will also underlie differences in treatment response. This is evidenced by the lower than expected weight loss typically observed in studies that predict changes in bodyweight based on 'static' mathematical models (e.g. the '3500 kcal per pound' rule), and it should not be assumed that a linear relationship exists between the prescribed energy deficit and actual weight loss. Rather, energy balance should be viewed as a dynamic regulatory system in which perturbation to an individual component may produce co-ordinated responses in other components of the system that act to attenuate the gap between EI and EE. For instance, compensatory responses to negative energy balance such as a greater than predicted decreases in RMR[11, 34, 35] and increased muscular efficiency[36, 37] have been observed (relative to that predicted based on changes in metabolically active tissue). Additionally, spontaneous increases in EI have also been reported following caloric restriction[38, 39]. Thus, the apparent simplicity of energy balance belies a dense and complex network of inter-related biological, nutritional, psychological and behavioural determinants of EI and EE[16], and multiple regulatory systems and

feedback loops that operate concurrently to influence energy homeostasis (see Fig. 1). It is also tempting to try and explain overconsumption and weight gain solely in terms of a failure in innate biological or homeostatic regulation. However, such biological reductionism fails to adequately acknowledge the importance of psychological and behavioural aspects of energy balance during weight gain or loss[40]. Psychological factors such as cognitive restraint remain robust predictors of EI when considered alongside physiological determinants of EI (such as body composition and RMR), and indeed, have the potential to play a mediating role between physiological and behavioural outcomes[41].

Figure 1 here

Compensation to energy imbalance appears asymmetrical, with the forces that resist weight loss stronger than the ones that resist weight gain (Fig. 2)[42]. This asymmetry may help account for the apparent ease at which people gain weight but typically fail to sustain weight loss over the long term[43]. However, studies examining compensation to controlled over rather than underfeeding are less common[44], and considerable inter-individual variability in the magnitude of weight gain and the extent of compensation also exists with overfeeding[45]. While EE and its components may change in response to energy imbalance in a quantitatively important manner, changes in appetite and EI may have a greater capacity to perturb energy balance and body composition[46]. For example, Polidori et al.[47] recently estimated that the increase in appetite seen following a 52- week placebo- controlled trial using canagliflozin (a sodium glucose co- transporter inhibitor) was approximately three times greater than the corresponding change in EE (~100 kcal/day vs. ~30 kcal/day per kilogram of weight lost). Elevations in EE may also provide "limited auto-regulatory capacity" to dissipate excess EI during periods of energy surfeit, with Siervo et al.[48] reporting that total daily EE increased by just 11.4% after progressive overfeeding (3 wks at 120%, 3 wks at 140% and 3 wks at 160% of baseline intake). Such findings would point to the relative importance of appetite and EI as the primary means to compensate for energy deficit and surfeit in humans.

Figure 2 here

In relation to our understanding of the peripheral physiological mechanism involved in the regulation of appetite, there is a growing number of gut peptides purported to play unique roles in hunger and satiety signalling[49]. However, not all of these peptides have a close association with the temporal profiles of hunger and fullness[50], and eating behaviour reflects the combined influence of multiple hormonal and metabolic stimuli (as depicted in the satiety cascade[51]). An area that has been a target of recent interest is the role of FFM and RMR in appetite control, with studies

demonstrating that FFM and RMR play important roles in the excitatory drive to eat in weight stable individuals[46, 52, 53]. It remains unclear though how the functional relationships between body composition, EE and EI operate during periods of negative energy balance and weight loss. Decreases in body composition and EE will influence energy balance by reducing total daily EE during weight loss, but such responses may also promote changes in EI that further attenuate the energy gap. As such, a clear understanding of these adaptations and their impact on bodyweight and appetite regulation during negative energy balance could be a key factor in improving weight maintenance.

3.0 Metabolic Adaptations in Response to Negative Energy Balance

3.1 Resting energy expenditure

RMR, used interchangeably with resting EE and basal metabolic rate in this review, represents the energy requirements to fuel the body's basic functions in a resting state. It is thought to account for up to 70% of total daily EE, depending on physical activity and exercise levels[54, 55]. It has been postulated that changes in RMR could influence weight loss and maintenance success since associations between a lower RMR and future weight gain have been observed[56, 57], although this hypothesis has been questioned[58]. RMR is primarily determined by the quantity of FFM, which accounts for 63%[59] and up to 75% of variability between individuals[46]. Factors such as fat-mass (FM), age and sex also contribute to the between-subject variability in RMR[59], but an unknown component typically remains in models examining between-subject differences in RMR.

There is a decrease in RMR during periods of negative energy balance that occurs primarily as a result of losses of metabolically active tissue[46, 59, 60]. However, during the first stages of fasting / starvation (i.e. ~2 days), a transient increase in RMR (5-10%) can be observed[61], possibly due to an increase gluconeogenesis as this is a more energy-demanding pathway[62]. There also appears to be an additional downregulation in EE not explained by changes in FFM or FM[63-65], even after adjusting for losses in organ mass[66]. This phenomenon has been termed adaptive thermogenesis, and is usually defined as a greater than predicted decrease in EE after adjusting for changes in body composition[36]. A 5-10% lower than predicted decrease in RMR has been observed following weight loss which could subvert continued weight loss or weight maintenance[34, 35, 65, 67], although the existence and functional significance of adaptive thermogenesis has been questioned[64, 68]. It is worth noting that studies examining the presence of adaptive thermogenesis typically only adjust for changes in FFM as a single homogenous tissue compartment, and assume that losses in FFM are uniform across its constituent components (e.g. skeletal muscle and organs) and that tissue

hydration loss remains constant during underfeeding. However, reductions in organ mass during weight loss have been reported[34, 69, 70], and it may be that after accounting for changes in more energy-demanding structures such as the heart and kidneys, which expend approximately 440 kcal per kg in contrast to 13 kcal per kg for skeletal muscle[71], adaptive thermogenesis becomes negligible. For instance, after 10% weight loss, it was observed that from a total decrease in RMR (-136.4 kcal = 7.7%), 40% was attributed to adaptive thermogenesis (~55 kcal) after accounting for changes in organ mass[66]. Reduced sympathetic nervous system output, impaired thyroid activity (lower free triiodothyronine) and a fall in insulin secretion have been suggested as possible mechanisms for adaptive thermogenesis[60, 64, 72], but the underlying causes remain to be fully understood. From a biological standpoint, it makes sense that the body reacts in order to reduce the energy gap induced by "voluntary starvation", becoming more efficient in response to food restriction. However, it is not fully understood whether adaptive thermogenesis is a permanent consequence of weight loss or is reversed after a period of weight stability at a newly reduced body weight[35, 73].

3.2 Non-resting energy expenditure

3.2.1 Thermic effect of feeding

The thermic effect of feeding, representing the energy expended above RMR[74], represents 10-15% of an individual's total EE[54]. During periods of negative energy balance there is some evidence that the thermic effect of feeding decreases for the same given meal[75, 76]. For instance, after an 11-week hypocaloric diet (protein supplement modified fast) that lead to a ~12kg weight loss, 5 obese women showed a decrease of ~19.1% in the thermic effect of feeding in response to a fixed meal (60% of RMR) over a 300 minute period[77]. However, after removing one outlier (57.5% reduction), only a 9.8% decrease was observed (i.e. 5-10 kcal). Furthermore, after 20 days of energy deficit (760 kcal per day) in 10 young and 9 older men, a decrease of 13% and 23.6%, respectively, was observed after measuring the thermic effect of feeding for 4 hours in response to a meal comprised of 25% of total daily EI[75]. Even though there may be a decrease in the thermic effect of feeding during periods of negative energy balance, the extent to which changes in the thermic effect of feeding contribute to resistance to weight loss and promote weight gain is unclear. Furthermore, it should be noted that depending on meal composition, measuring the thermic effect of feeding for less than 6 hours may give an incomplete estimate[78].

3.2.2 Non-exercise activity thermogenesis and non-exercise physical activity

As with the thermic effect of feeding, changes in physical activity (or the EE associated with such activity) during periods of negative energy balance are yet to be fully understood. When considering the changes in physical activity during periods of negative energy balance, it is important to distinguish between metabolic and behaviour adaptations. For instance, non-exercise activity thermogenesis (NEAT) refers to the EE of a determined activity[79]. However, quantifying the number of steps or the amount of time spend in sedentary or vigorous activities refers to non-exercise physical activity. This is an important distinction because NEAT is not a volitional component, while non-exercise physical activity levels could be influenced by behaviour change interventions.

An increase in NEAT has been observed during periods of overfeeding with weight gain ranging from 1.4 kg to 7.2 kg after 8 weeks in an energy surplus of 1000 kcal/d[79]. A decrease in non-exercise physical activity and NEAT during periods of energy deficit has also been observed[80, 81], but a recent systematic review indicated that the majority of evidence does not support a reduction in non-exercise physical activity with weight loss[82]. It could be that as observed by Levine[79] during phases of overfeeding where some individuals were more resistant to body fat storage, a large variability between individuals is present during periods of underfeeding making one more resistant or responsive to weight loss, permitting the identification of specific phenotypes (e.g. susceptible vs resistant). In line with this, Reinhardt[83] reported that the change in EE following a 24-hour period of either fasting or overfeeding (200%) was associated with weight loss during a subsequent 6 week period of dietary energy restriction. A smaller reduction in 24-h EE during fasting, and a larger response to overfeeding, was found to be associated with greater weight loss over the 6 weeks.These findings led the authors to suggest that individuals could be categorised as displaying either “thrift” or “spendthrift” EE phenotypes, with spendthrift individuals losing more weight during the intervention as they displayed an attenuated reduction in EE during weight loss. An increase in muscular efficiency (i.e. lower EE for the same activity) has also been observed following weight loss[34-37]. For instance, a 26.5% increase in muscular efficiency during a graded cycle ergometer protocol was observed after 10% weight loss[37]. However, whether between-subject differences in muscular efficiency following weight loss contribute to resistant or susceptible weight loss phenotypes is unclear.

4.0 Impact of Metabolic Adaptations on Energy Intake

While a compensatory change in one component of total daily EE during negative energy balance may have limited impact on subsequent weight loss, compensation in multiple components of total daily EE may exert stronger influence. It is also plausible that changes in EE may be accompanied, or indeed, trigger responses in eating behaviour. Marked weight loss is associated with both a decrease in EE and an increase in orexigenic drive[84, 85]. In the past it was thought that the long-term metabolic influences on EI and EE were mainly due to changes in FM and peripheral leptin concentrations[86]. A reduction in leptin is thought to promote increased hunger and EI via a down-regulation in pro-opiomelancortin and α-melanocyte-stimulating hormone expression, and an up-regulation in neuropeptide Y and agouti-related protein expression[87]. There is also limited evidence in humans that changes in fasting leptin concentrations are associated with changes in subjective appetite[88-90] and food reward[91] during dietary and exercise-induced weight loss, respectively. Exogenous leptin administration in a weight reduced state also reverses the adaptive suppression of multiple metabolic, autonomic and neuroendocrine functions[92, 93], and potentially improves satiety[94].

Changes in appetite-related peptides during weight loss may also act as physiological cues for increased EI during energy deficit. Decreased concentrations of anorexigenic hormones and increased concentrations of orexigenic hormones following short-term energy deficit (2-7 days), that would favour an increase in EI, have been observed with and without concomitant reductions in body weight[38, 95-98]. Furthermore, an increase in the orexigenic hormone ghrelin[99], and a reduction in the fasting[100-104] and postprandial[100, 103-105] concentrations of the anorexigenic hormones cholecystokinin, peptide YY, and glucagon-like peptide-1 have been reported following longer-term dietary weight loss. Limited evidence also suggests that these changes in appetite-related peptides may persist in the weight reduced state[106-108], with Sumatran et al.[106] reporting that 8% weight loss, induced by a very low calorie diet, lead to persistent changes circulating appetite-related hormones and increased hunger 12 months after weight loss. However, persistent changes in appetite-related peptides during weight loss maintenance are not always reported[109]. Taken together, these metabolic responses to weight loss appear to create a 'biological pressure'[110] that promotes increased EI and weight regain. However, it is now increasingly recognised that the energetic demand of metabolically active tissue[111] and metabolic processes also creates a functional drive to eat[112]. This drive from metabolic energy need acts alongside the tonic inhibition arising from leptin and insulin and the acute modulating influence of episodic gut peptides in the overall expression of appetite and food intake.

4.1 Functional associations between body composition, energy expenditure and food intake

A conceptual model highlighting a drive to eat based on energy needs has previously been proposed[113], but only now are studies beginning to fully recognise EE and its main determinants (e.g. body composition and activity-related EE) as important excitatory features of homeostatic appetite control. Interestingly, previous research had already reported that lean tissues were associated with EI and hunger[22, 114]. Almost 30 years ago, Lissner[22] observed that EI was associated with lean mass, but not FM, while Cugini[114] reported 10 years later the potential role of FFM as a driver of appetite by observing that hunger sensations were positively associated to FFM, but negatively to FM (a finding consistent with other research demonstrating an inhibitory effect of FM on appetite through the action of leptin that promotes a reduction in hunger and EI[115-117]).

More recently, several studies have observed associations between FFM and EI, with higher levels of FFM associated with greater EI in individuals at or close to energy balance[21, 23, 53, 112, 118-120]. For instance, after 12 weeks of imposed aerobic exercise (5 sessions per week), a positive association was observed between self-selected meal size and daily EI with FFM both at baseline and post-intervention in 58 individuals (β=0·33, P<0·01 and β= 0·28, P<0·02 respectively). Interestingly, there were no correlations between meal size or EI and FM or BMI. This result is confirmed by the findings of Cameron[120], in which after adjusting for age, sex, height and physical activity, FFM (β=21.9, p=0.007) and skeletal muscle (β=25.8, p=0.02), but not FM, were predictors of EI in 304 post-pubertal adolescents. Additionally, Weise[21] observed an association between FFM index and daily EI in 184 individuals. The relationship between FFM and EI seems to be mediated by RMR[52] (Fig. 3), suggesting that the influence of FFM on EI is primarily due to the energetic demand (EE) that it creates in terms of energy turnover. Additionally, Piaggi[118] observed that the association between FFM and EI was mediated by total daily EE (P=0.01, partial R^2=7%), indicating EE per se may exert influence over food intake. However, given skeletal muscle's role as an endocrine organ, specific signalling pathways linking FFM to appetite and EI cannot be ruled out.

Figure 3 here

4.2 Do changes in fat-free mass or energy expenditure act as an orexigenic signal during weight loss?

While the aforementioned studies indicate robust associations between FFM, RMR and EI under conditions of energy balance, these data are typically cross-sectional in nature and do not provide evidence of the mechanisms that drive EI during weight loss or gain. While evidence is limited at present, associations between changes in FFM and EI have been reported during periods of weight change. For example, during Ancel keys' Minnesota semi-starvation experiment [121], a group of 32 healthy individuals went through a period of 24 weeks of semi-starvation (~25% weight loss), followed by 12 weeks of controlled refeeding and 8 weeks of ad libitum refeeding. Twelve of these participants completed all phases of this intervention. During the 8 weeks of ad libitum re-feeding a significant hyperphagic response was observed (n = 12), which only abated after FFM was completely restored. Interestingly, there was evidence of 'fat overshoot' in which FM increased significantly above baseline values. This observation is not exclusive to this intervention. For instance, after losing approximately 12% of initial bodyweight, Nindl[122] also observed a hyperphagic response in 10 healthy young men until FFM levels were restored. However, even though this restoration of FFM was noted at week 5, it was accompanied by an above baseline increase in FM. This happens because after a period of underfeeding, restoration seems to be faster for FM than for FFM. Additionally, in a more recent intervention[123], after 5 weeks of a very-low calorie diet or 12 weeks of a low-calorie diet, there was a significant association between percentage of FFM loss during the weight loss phase and weight regain (r=0.325, P=0.018).

Although there is renewed interest in the role of FFM and its associated energetic demand on food intake, the idea that lean tissue acts as a driver of appetite and food intake has been previously suggested e.g. the protein-stat[124] and aminostatic[125] theories of appetite regulation, respectively. Millward's protein-stat theory suggests lean mass, and in particular skeletal muscle, is tightly regulated and that food intake (dietary protein) is directed to meet the needs of lean tissue growth and maintenance[124]. This theory is based on the existence of an 'aminostatic' feedback mechanism in which food intake is adjusted in response to amino acid availability to meet the protein demands of lean tissue growth and maintenance. When coupled with the metabolic demand for fuel, Millward suggests that appetite control allows 'substrate intake to match overall nutrient demand'[124]. However, evidence to date to support such a feedback mechanism remains limited. As noted by Stubbs et al.[46], there are also some interesting parallels between the differential recovery trajectories of FM and FFM and the hyperphagia seen during the Minnesota study, and the changes in whole body 'catch-up growth' in undernourished children (i.e. repletion of body weight for a given growth trajectory). When a child's individualised pattern of growth is impeded by

malnutrition (or infection), a period of catch-up growth is typically observed in body weight for height, and, height for age[126]. Of note though, catch-up growth in body weight for height occurs before any catch-up growth in height for age is seen, and the catch-up growth in body weight for height is accompanied by a marked increase in appetite and EI that subsequently declines once a normal body weight for height is achieved[126].

These data suggest that while FFM may have an impact in the control of EI due to its energy requirements, it is also possible that there could be feedback signalling between deficits in FFM and appetite control (as a means of increasing EI in attempt to restore FFM levels). However, a challenge in this area is to reconcile the differing relationships between FFM and EI under conditions of energy balance and energy deficit (see Stubbs et al.[46] or Dulloo, Miles-Chan & Schutz[127] for a detailed discussion), and to identify the signalling pathways that link EE and EI. Notwithstanding, this data linking FFM and EE to hunger and EI may have relevance in the design of weight loss and weight loss maintenance strategies, with emphasis placed on the importance of preserving FFM during periods of energy restriction. Preservation of FFM during periods of energy restriction (via greater protein intakes[128, 129], slower weight loss rates[123] and performing exercise[130] for example) might help offset the increase in orexigenic drive seen with weight loss, but to date, this remains speculative and more data is needed in order to fully comprehend the impact of metabolic adaptations on appetite and EI during periods of negative energy balance.

4.3 Cross-talk between energy expenditure and energy intake- implications for weight loss?

Given the apparent cross-talk between components of EE and EI, it is plausible to suggest that some individuals may demonstrate coordinated adaptive metabolic (EE) and behavioural (EI) responses during energy deficit that act synergistically to attenuate perturbations to energy balance. In other words, people that show greater than predicted decreases in RMR may also present with a greater hyperphagic response following negative energy balance. Case in point, even though average weight loss was small [-1.3 kg (-7.7 to 3.8 kg)], Hopkins et al.[11] observed a negative association between the extent of adaptive thermogenesis and ad libitum EI ($r=-0.45$; $R^2=0.20$, $p=0.01$). These findings support those of Tremblay et al.[72] who showed a strong positive association between adaptive thermogenesis and hunger ($r=0.73$, $p<0.05$) after reanalysing the data from a previous study where 54 overweight women followed a calorie restricted diet (~-700 kcal/d) for 4-months[131] leading to a mean weight loss of ~5% (-4 kg). These responses would favour the defence of body weight rather than promoting weight loss, and contribute to the inter-individual variability seen in

weight loss. While the underlying mechanisms still need to be determined, common biological signals such as leptin have been causally implicated in adaptive thermogenesis and compensatory appetite responses following energy deficit, and support the previously mentioned distinction between resistant and susceptible individuals suggested by Reinhardt[83]. Regarding the thermic effect of feeding, some authors have observed associations between this EE component and appetite or EI[132]. Since protein has a greater thermic effect of feeding (20-30% in comparison to 0-3% for fat and 5-10% for carbohydrates)[133] and impact on satiety[134] in comparison to the remaining macronutrients, it could be that this component of total EE might be associated with appetite control. However, a meta-analysis failed to support any link between the thermic effect of feeding and satiety [132].

It could be postulated that some individuals could be more resistant to weight loss (and prone to weight gain), presenting greater co-ordinated behavioural and metabolic responses that oppose weight loss and weight loss maintenance. If a "weight loss resistance" phenotype exists, it could be characterized by a greater than predicted decrease in RMR, as well a smaller thermic effect of feeding for the same meal and EE for the same activity (i.e. greater muscular efficiency). Additionally, these responses could act in a synergistic way with greater increases in hunger and appetite, as well lower satiety and satiation, prompting an individual to regain lost weight. However, more data incorporating a multi-component analysis assessing changes in body composition, EE, appetite and EI are needed to fully comprehend the cross-talk in the energy balance system and determine whether distinct phenotypes are present. Identification of inter-individual variability in compensation during the initial stages of an intervention may act as a marker of longer-term success, but whether the identification of such phenotypes leads to more personalised and efficacious weight loss interventions remains unclear.

5.0 Conclusions

Even though the regulation of energy balance appears simple when considered in relation to thermodynamic theory i.e. energy in vs energy out, energy balance is a highly complex dynamic system involving multiple feedback signals from individual components of EE and EI. Under conditions of energy deficit, and to a lesser extent energy surfeit, individual components of energy balance can act in a co-ordinated fashion to resist perturbations elsewhere in the energy balance system. The strength of these metabolic and behavioural compensatory responses appears to be individually subtle, and in part, underlie the heterogeneity seen in body weight responses to weight

loss interventions. The potency of such compensatory mechanisms means that effective strategies that promote sustained weight loss and weight loss maintenance have proved remarkably elusive to date. While it is clear that individuals differ in the susceptibility to weight loss (and their subsequent ability to sustain this lower body weight), robust predictors of treatment response remain elusive.

While biological reductionism and a failure in innate biological regulatory mechanisms often dominates discussions around the putative causes of weight gain, psychological and behavioural aspects of energy balance are of equal importance when trying to account for overconsumption. Indeed, there is renewed interest in integrative models of energy balance regulation that consider the dynamic relationships between body structure, physiological function, and the way these interactions influence key psychological and behavioural determinants of energy balance such as appetite. Recent research has focused on the functional associations between components of body composition, EE and EI, and indicate that FFM and RMR are associated with a drive to eat that reflects the energetic demands of metabolically active tissue. Future research should examine how the functional relationships between body composition, appetite and EI operate during periods of negative energy balance, and the implications that changes in body composition and EE have on appetite control and EI.

AUTHORSHIP

All authors contributed to the writing and editing of the manuscript.

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CONFLICTS OF INTEREST

None.

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LEGENDS FOR FIGURES

Figure 1: Schematic overview of energy balance and the nutritional, psychological, behavioural and physiological influences on total daily energy intake and energy expenditure. Reference values for organ and tissue contribution to metabolic rate taken from Elia[135], while determinants of resting metabolic rate taken from Johnstone et al.[59]. TDEI, total daily energy intake. TDEE, total daily energy expenditure. CHO, carbohydrate. NEPA, Non-exercise physical activity. NEAT, non-exercise adaptive thermogenesis. CCK, cholecystokinin. PP, pancreatic polypeptide. PYY, peptide YY. GLP-1, glucagon-like peptide-1. FFA, free-fatty acid. AA, amino acid. FFM, fat-free mass. RMR, resting metabolic rate. AEE, activity energy expenditure. TEF, thermic effect of food.

Figure 2: Overview of physiological and behavioural responses during: a) energy deficit and b) energy surfeit. In panel a and b it is possible to observe an asymmetrical response between periods of energy deficit and surfeit in which there is a greater force resisting weight loss than weight gain. Figure adapted from Melby et al.[9]. EI, energy intake. EE, energy expenditure. TDEE, total daily energy expenditure. RMR, resting metabolic rate. PAEE, physical activity energy expenditure. TEF, thermic effect of food. FFM, fat-free mass. FM, fat mass.

Figure 3: Path diagram for the mediation model with the standardized parameter coefficients for the direct effects of fat mass and fat-free mass on resting metabolic rate and resting metabolic rate on energy intake, the indirect effect of fat mass and fat-free mass on energy intake mediated by resting metabolic rate and the squared multiple correlations (R^2) for resting metabolic rate and energy intake (adapted from Hopkins et al.[18]). RMR, resting metabolic rate. NS, non-significant.