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REVIEW ARTICLE

Potential effects of fat mass and fat-free mass on energy intake in different states of energy balance

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Abstract

Recently models have attempted to integrate the functional relationships of fat mass (FM) and fat-free mass (FFM) with the control of human energy intake (EI). Cross-sectional evidence suggests that at or close to EB, FFM is positively related to hunger and EI, whereas FM either shows a weak negative or no association with ad libitum EI. Further analysis suggests that the effects of FFM and FM on EI may be mediated by resting metabolic rate (RMR). These studies suggest that energy turnover is associated with EI and the largest determinant of energy requirements in most humans is FFM. During chronic positive EBs both FM and FFM expand (but disproportionately so), increasing energy demands. There is little evidence that an expanding FM exerts strong negative feedback on longer term EI. However, during chronic negative EBs FM, FFM and RMR all decrease but appetite increases. Some studies suggest that proportionate loss of FFM during weight loss predicts subsequent weight regain. Taken together these lines of evidence suggest that changes in the size and functional integrity of FFM may influence appetite and EI. Increases in FFM associated with either weight gain or high levels of exercise may 'pull' EI upwards but energy deficits that decrease FFM may exert a distinct drive on appetite. The current paper discusses how FM and FFM relationships influence appetite regulation, and how size, structure and functional integrity of FFM may drive EI in humans (i) at EB (ii) during positive EB and (iii) during negative EB.

Key points

- At or close to EB, FFM is positively associated with EI, whereas FM is either not associated or weakly negatively associated with ad libitum EI.
- Associations between FFM, FM and EI are mediated by RMR, suggesting that basal energy turnover may represent an indirect, tonic mechanism that relates energetic demands to EI.
- There is little evidence that expanding FM exerts strong negative feedback on EI, but increased FFM associated with weight gain may 'pull' EI upwards.
- During energy deficits or when growth is retarded, there may be an 'active' drive exerted by FFM on EI when FFM is in deficit and its functional integrity is threatened.

Introduction

For decades there has been considerable interest in the regulation of energy intake (EI) [1, 2], energy expenditure (EE) [1, 3] and body weight [2, 3] in animals and humans to understand energy and nutrient requirements across the life course in health and disease, and appreciate responses to energy imbalances during starvation, semi-starvation and the development and treatment of human obesity. The energy balance (EB) equation is ostensibly simple, but due to its dynamic, interactive nature, much more difficult to measure and explain than one might suppose from a simple reading of the laws of themodynamics [4]. It is reasonable to say that almost every component of EI, EE and body composition have at times been proposed as the basis for models of EI or EB regulation in humans. Models have

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focused inter alia on adaptive changes in EE [5, 6], the role of macronutrients or body composition compartments [7, 8] and specific nutrients as neurotransmitter precursors [9], as potential levers of EI or EE and EB. Although there was general recognition that physiology and behaviour interact to influence EB in the 1970s–80s [10, 11], the study of EB still largely fails to adequately integrate physiological and behavioural determinants of EB in regulatory models.

At the present time, predominant models of EB regulation emphasise the role of adipose tissue signalling modulated by acute peripheral gastrointestinal signals [12, 13]. More recent integrative models of EB regulation based on the concept of functional body composition [14–17] consider how the physiological rules governing fat mass (FM) and fat-free mass (FFM) relationships may impact on physiological functioning, health and EB behaviours to explain (i) the inherent asymmetry of EB regulation, (ii) the tendency for most humans to gain weight under modern environmental conditions and (iii) weight regain in response to weight loss attempts [16, 17]. Understanding the relationship between body structure, function and behaviour in the context of EB offers a coherent framework to develop more effective intervention targets for the dual burden of malnutrition, and to integrate the structure of body components with functional outcomes in health and disease [17]. The current paper discusses how FM and FFM relationships influence appetite regulation, and how the size, structure and functional integrity of FFM may act as a driver of EI in humans. We consider recent models integrating the role of FM and FFM in appetite control to ask the question when and to what extent does FFM drive EI (i) at EB (ii) during positive EB (iii) during negative EB?

The energy balance equation

EB is the difference between the energy ingested and that expended and excreted over a given period of time. Thus, storage is equal to intake minus expenditure:

$$\begin{aligned}&\text{Energy intake} - (\text{Energy of faeces}) - (\text{Energy of urine})\\&-(\text{Energy of combustible gas}) - (\text{Heat produced})\\&= \text{Energy retained or secreted.}\end{aligned}$$

This equation [1] is frequently simplified to give:

$$\Delta\text{Energy intake} = \Delta\text{Energy expenditure} - \Delta\text{Energy}$$

In the mid-late tweentieth century research focused intensely on the expenditure side of the equation in the search for metabolic differences between lean and obese individuals [18]. Inter-individual differences in the (in) ability to adjust whole-body energy expenditure in response to differing energy and macronutrient intakes were suggested as mechanisms to explain why some individuals remain lean but others become obese when exposed to the same environmental conditions [19]. It was proposed that mechanisms of adaptive thermogenesis or luxuskonsumption exist that allow metabolic flexibility in the dissipation of excess EIs [5, 6], and this process was defective in the obese, which predisposed them to store rather than dissipate excess EI. It is now generally accepted that a defect in thermogenic energy dissipation is not the primary mechanism underlying obesity development [3, 20, 21], and there is little evidence of quantitatively significant differences in rates of EE between lean and obese individuals once body size and composition are accounted for [20]. Indeed, according to Forbes et al. [22, 23], it is actually energetically more costly for the obese to gain weight than lean individuals (as the obese gain proportionately more adipose tissue than lean individuals following excess EI, and per gram of tissue gained, the energy cost of adipose tissue gain is about six times greater than lean tissue). See also ref. [24] for a consideration of the implications for longer term weight change in relation to energy balance in lean and obese subjects. There is also little experimental support for the concept of adaptive thermogenesis as a major means of protection against weight gain in humans [3]. Overfeeding studies conducted under rigorously controlled conditions indicate that weight gains were as expected from standard thermodynamic and biochemical considerations [25–28]. However, there is considerable heterogeneity in the rate of weight gain during overfeeding [29], which may in part, reflect inter-individual variations in physical activity and/or partitioning the excess energy between FM and FFM [22, 30].

In relation to weight loss, the exact mechanisms that oppose energy deficits are multiple, complex, individually subtle and often difficult to quantify specifically, although they include changes in EE and physiological signals that may be concerned with appetite and EI [27, 31–34]. As there is some evidence for adaptation of whole-body metabolic rate during chronic undernutrition independent of changes in metabolically active tissue, the estimated maximum change of resting metabolic rate (RMR) under such conditions is ~5–10% [35]. Indeed, although EE and its components change in response to energy imbalances in a quantitatively important manner, it is likely that changes in EI have a greater capacity to produce relatively large alterations in EB and body composition [36].

Energy and nutrient balances and in the control of appetite

Numerous models of EB regulation predict that certain components of energy and nutrient balance act as negative feedback signals affecting appetite and body weight control. However, evidence in humans suggests that the metabolism

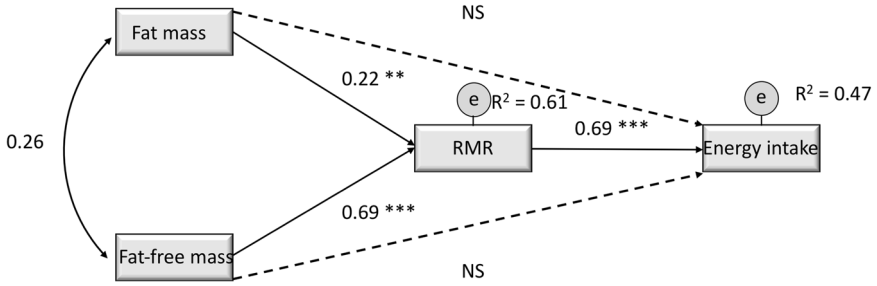

Fig. 1 Path diagram for the mediation model with the standardised parameter coefficients for the direct effects of fat mass (FM) and fat-free mass (FFM) on resting metabolic rate (RMR) and RMR on energy intake (EI), the indirect effect of FM and FFM on EI mediated by RMR and the squared multiple correlations (R^2) for RMR and EI. The mediation model indicates that the effect of FM and FFM on EI was fully mediated by RMR (from ref. [14])

or storage of specific individual macronutrients fails to exert powerful negative feedback on EI [37], but models that include all macronutrients do explain greater variance in EI [8]. In the late 1980s and early 1990s interest shifted to a focus on the regulation of macronutrient balance [21]. In terms of EB, this means that the metabolisable energy ingested is equal to EE in the physiological oxidation of the macronutrients plus or minus body fat, protein and glycogen. There appears to be a hierarchy in the immediacy with which recently ingested macronutrients are disposed of by oxidation, which is influenced, inter alia, by the body's capacity to store those macronutrients. Thus, alcohol has priority in the short-term over all other macronutrients [38]. The order of priority is then protein, carbohydrate (whose balance is regulated by a number of other factors) and fat (whose oxidation is determined by the balance-status of these other macronutrients) [39].

Because of the limited storage capacity for carbohydrates, changes in body composition over the longer term are more closely reflected by protein–energy relationships [22, 40, 41]. Protein or nitrogen: energy relationships have been the focus of considerable study in relation to growth and development [42, 43], pregnancy and lactation [44], farm animal production [45] and responses to chronic energy deficits in health [46–51] and disease [52]. However, despite the critical role of protein–energy relationships for survival time during severe undernutrition [40, 53], and the relationship between energy partitioning, tissue growth and appetite in animals [45], few have analysed energy expenditure (or its body compositional determinants) as major sources of feedback in human appetite control [37, 54]. This may in part relate to the discovery of leptin [55], which appeared to offer a molecular basis for Kennedy's 'lipostasis' concept [56] and provided the foundation for the current models of appetite and EB regulation based on the integration of acute gastrointestinal signals (including putative fore and hind gut signalling systems) and putative adipose tissue-derived tonic signalling [12, 13].

Body composition, energy expenditure and appetite control

Despite the intense focus on adipose-derived signals in EB regulation, a number of questions still exist regarding the applicability of this 'lipostatic' control system to the regulation of appetite in humans free from congenital leptin deficiency [57]. Indeed, despite extensive literature on leptin and other putative feedback signals arising from adipose tissue [58, 59], there appears to be limited evidence in humans of the extent to which changes in adipose tissue exert strong negative feedback on EI. Consequently, more recent models have attempted to integrate the role of FM and FFM in appetite and EB regulation [14, 15, 46, 48, 60, 61]. On the basis of studies measuring EI under controlled laboratory conditions at or close to energy balance, our research group [14] and others [62, 63] have demonstrated that FFM is a strong predictor of hunger and ad libitum day-to-day EI in lean and obese individuals. The effect of FFM on EI appears to reflect the energetic demand of metabolically active tissue, with the reported associations between FFM and EI mediated by RMR [14] and 24-h energy expenditure [64], respectively. In contrast, no associations [62, 65] or weak negative associations [63, 64, 66] have been reported between FM and EI in subjects at or close to EB.

Recent analyses and reviews by the Leeds group have highlighted the association in both lean and overweight adults between FFM and meal size, total daily EI and hunger [15, 61, 67]. These analyses have suggested that FM and BMI have no, or a weak negative association with daily EI. These relationships have been demonstrated by other groups, e.g. [63, 64] and by the same group using an independently collected data set (with no a priori hypothesis about relationships between body composition, RMR and EI) where total EB in ad libitum feeding subjects was carefully monitored [14]. These data suggest that some signal(s) associated with FFM may (directly or indirectly) exert a determining effect on EI. Similar relationships have

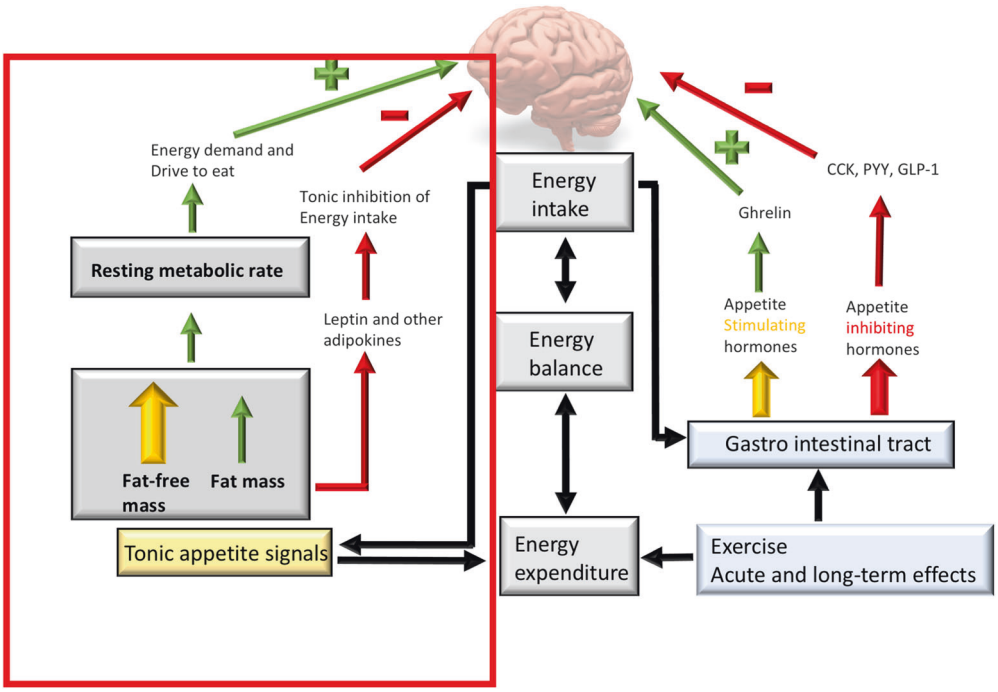

Fig. 2 Conceptual framework describing the major influences on appetite control in humans at or close to energy balance energy balance. Green arrows indicate processes that stimulate feeding, whereas the red arrows demote processes that inhibit feeding. In this framework, short-term episodic signals arise as a consequence and as part of the process of food consumption, digestion and absorption, whereas tonic (longer term) signals arise from body tissues and metabolism. The effect of fat mass on energy intake reflects a lipostatic view of appetite control; leptin is a key mediator of the inhibitory influence of fat on brain mechanisms. The metabolic demand for energy primarily arises from energy requirements generated by fat-free mass and its metabolically active components (heart, liver, brain, GI tract, skeletal muscle) as reflected in the resting metabolic rate. The overall strength of the drive for food is the balance between the tonic excitatory and inhibitory processes. It is proposed that, as adipose tissue accumulates in the body, the tonic inhibitory effect of fat on energy intake becomes weaker (due in part to leptin and insulin resistance). Therefore, as people become fatter it becomes more difficult to control appetite. Figure originally published in ref. [15]

been established between RMR and EI. Path analysis (Fig. 1) indicated that the association between FM and FFM was mediated by RMR at least under the experimental conditions of the study concerned [14]. Under conditions at or close to EB, FFM is the major determinant of RMR and RMR itself may represent a tonic drive to eat (hunger signal), although specific mechanisms by which FFM and hence RMR per se might drive hunger have yet to be identified [61].

Extrapolating these associations in a line of causation has led to the following conclusions:

1. FFM is the largest determinant of RMR, accounting for 70–75% of RMR in most humans [20, 68].
2. RMR is the largest component of total daily energy expenditure (50–70%), depending on physical activity levels and may represent a continuous tonic pull on appetite through hunger mechanisms.
3. FFM is positively associated with appetite, through the energetic demands of RMR [14, 15, 61]. In other words, metabolic body size is associated with daily EI.
4. FM is negatively or not associated with appetite or total daily energy intake under conditions at or near EB, and the strength of any negative feedback from adipose tissue decreases with increase in the size of FM [14, 15, 61, 63, 64]. In other words, low levels of FM may exert a stronger negative feedback on EI (per kg of FM) than high levels of FM. It is suggested that leptin and insulin resistance are responsible for this inverse relationship between the size of FM and any negative feedback it may exert on EI [67]. This effect could also be partially mediated by RMR as adipose tissue has a low metabolic rate (~4.5 kcal/kg/day; ~4–5% of RMR in reference man and woman), the contribution of FM to RMR would increase somewhat in the very obese. For reference, the metabolic rate coefficients for other major organs are: liver 200; brain 240; heart and kidneys 440; muscle 13 kcal/kg/day [69].
5. Energy expended in physical activity would exert a weaker effect on EI, and the effect of physical activity on EI may operate via multiple mechanisms (in addition to its contribution to energy requirements)

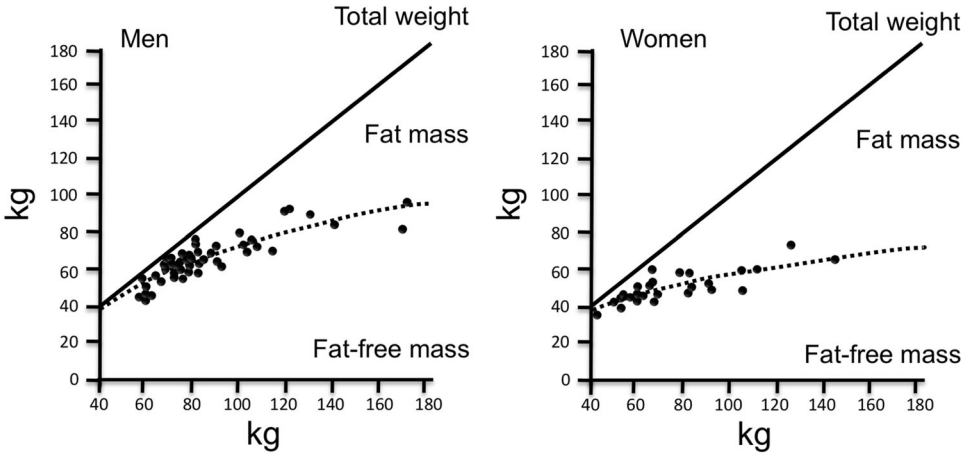

Fig. 3 The proportionate contribution of fat and fat-free mass (FFM) to a linear increase in weight in men and women. The putative effect of FFM or resting metabolic rate (RMR) on the drive to eat may decrease with increasing BMI as FFM and RMR increase at a decelerating rate with increase in weight, but the energy content of the body expands disproportionately as fat mass expands. (Figures reproduced from ref. [72])

[67].

6. The association between FFM, RMR and EI is loose and can easily be overridden by factors such as sedentariness or dietary energy density [14, 67]. These hypothetical relationships are depicted in Fig. 2.

Although cross-sectional studies appear to indicate robust associations between FFM, RMR and EI under conditions of EB, these data do not provide evidence of the mechanisms that drive EI during weight loss or gain. However, such studies do provide a hypothetical framework to consider how such mechanisms may operate under conditions of energy surfeit and energy deficit where changes in FM and FFM occur. Using the model proposed by Blundell and colleagues as a conceptual framework, evidence for a FFM-derived control mechanism of appetite is discussed below under conditions of positive and negative energy balance.

Appetite during positive energy balance

Humans and a variety of other mammals appear much more tolerant of positive than negative EBs. Humans share with many animal species the capacity to store large amounts of energy as fat, which is an important ecological strategy to survive uncertainties in the environmental supply of energy and nutrients. Human history has been punctuated by disruptions of the food supply caused by seasonality, droughts, flooding, failed harvests and war (see Keys [53], pp 3–17, for a history of documented human famine). It has been argued that alternations between periods of feast and famine have resulted in evolved physiological and behavioural programmes in humans that result in the deposition of reserves in adipose tissue when energy and nutrient-rich food was readily available [70]. Human adipose tissue contains around 33.1 MJ/kg [71] and is a highly efficient form of energy storage. Under natural ecological conditions, massive lipid reserves are rarely seen in most species, but there are many examples in laboratory or domesticated animals, and in modern humans. It appears that physiological and behavioural systems have been designed, through natural selection, to compensate for energy deficits in an environment where excess EIs are periodic and temporary situations, balanced by periods of limited supply. This suggests that accumulation of FM is unlikely to exert strong negative feedback to limit the excess EI that is causing it.

It is important to note that as weight is gained, both FM and FFM expand but at different rates. These relationships between FM and FFM are described in Fig. 3, and the implications for the Leeds model of body composition and appetite control are shown in Fig. 4a. In terms of the model, this suggests that:

1. Body weight gain leads to an expansion of FFM which increases RMR [20, 68]. Although this is not hypothesised to drive weight gain per se, a higher FFM and associated RMR may increase the background tonic drive to eat, favouring maintenance of a higher body weight.
2. Expansion of FM over the long term induces insulin and leptin resistance, expansion of FFM and, in extremis, some slight elevation of RMR, which could account for the apparent diminishing negative feedback from FM as adipose tissue expands.
3. It may be argued that any putative effect of FFM or RMR on the drive to eat may decrease with increasing BMI since FFM and RMR increase at a decelerating rate with increase in weight, but the energy content of the body expands disproportionately as fat mass expands. The gross energy of fat is 39.9 kJ/g and of average meat protein is 23.6 kJ/g. The exact values may vary considerably between subjects [71] (pp. 225–247). If we assume that FFM contains 20% protein and has an energy content of 4.7 KJ/g, a lean

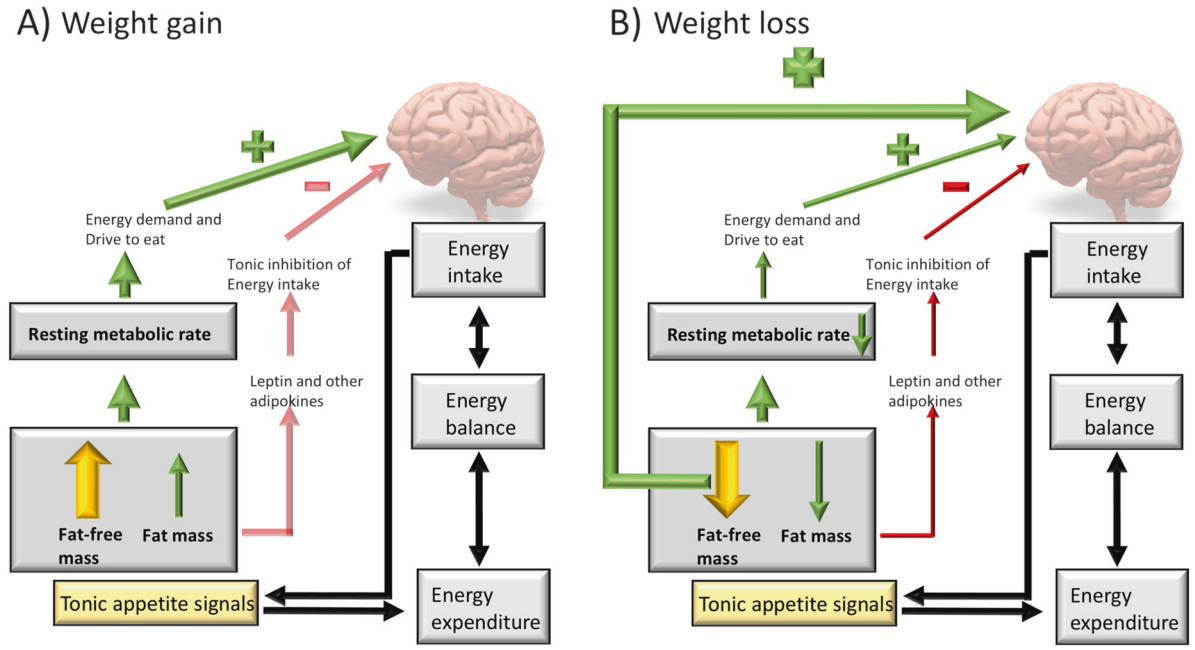

Fig. 4 **a** Conceptual framework describing the major potential influences on appetite control in humans during an incremental positive (**a**) and negative (**b**) energy balance leading to significant weight change. **a** Body weight gain leads to an expansion of fat-free mass (FFM) which increases the resting metabolic rate (RMR). This is not hypothesised to drive weight gain per se, because FFM and RMR tend to plateau as weight linearly increases, but the energy density of the body increases disproportionately with a linear increase in weight and as a greater percentage of weight gain is due to increments in fat mass. A higher FFM and associated RMR may increase the background tonic drive to eat, favouring maintenance of a higher body weight but not necessarily driving weight per se. Expansion of fat mass (FM) over the long-term induces insulin and leptin resistance, expansion of FFM and, in extremis, some slight elevation of RMR, which could account for the apparent diminishing negative feedback from FM as adipose tissue expands. Hypothesised effects of FFM or RMR on the drive to eat may actually decrease with increasing BMI since FFM and RMR increase at a decelerating rate with increase in weight, but the energy content of the body expands disproportionately as fat mass expands. It is more likely that other factors drive energy intake (EI) during very significant weight gain such as diet composition and hedonic responses to food. **b** A model that accounts for the potential effects of FFM, RMR and FM on appetite and EI needs to account for the apparent change of direction in the relationship between FM and FFM and appetite during positive and negative energy balances. If increased energy turnover is associated with increases in appetite and EI, how is it that during weight loss, decreases in FM, FFM and RMR are also associated with increases in appetite and EI? It may be that FM and FFM exert 'passive' and 'active' drives on appetite under situations of differing energy balance. At or near to energy balance (EB), FFM (and to a lesser extent, FM) may have a relatively passive role in driving EI, i.e. the FFM (and FM)-related energy demands associated with these tissue compartments creates a 'passive' or tonic pull on EI to meet the long-term energetic demands of metabolically active tissue and processes (Fig. 2). However, during energy deficit where FFM is threatened, dynamic losses of FFM may act as an 'active' orexigenic signal that stimulates increased EI (hunger and/or hyperphagia) to defend the functional integrity of FFM. The tonic inhibition of appetite by the presence of leptin is reduced. This distinction between passive and active roles of FFM may enable us to explain the roles of FFM in appetite control at different levels of energy balance

male subject who weighs 80 kg, of which 20 kg is fat the energy content of their weight would be $[(39.9\ \text{MJ/kg} \times 20) + (4.7\ \text{MJ/kg} \times 60)] = 1080\ \text{MJ}$. If this man weighed 120 kg, of which 48 kg was FM, his body energy content would be $[(39.9\ \text{MJ/kg} \times 48) + (4.7\ \text{MJ/kg} \times 72)] = 2{,}254\ \text{MJ}$. If his body weight expanded to 160 kg, of which 80 kg was fat his body energy content would be approximately $[(39.9\ \text{MJ/kg} \times 80) + (4.7\ \text{MJ/kg} \times 80)] = 3568\ \text{MJ}$. Thus, the energy content, cost and percentage of weight gained as FM increases with increasing weight. These estimates are taken from body composition data by Owen et al. [72] (Fig. 3). In other words, as FFM and RMR tend to plateau as weight linearly increases, the energy density of the body of the 160 kg man is more than three times that of the 80 kg man per kg of weight. EI per unit of FFM or RMR would need to be greater to achieve the weight of the 160 kg man than for the 80 kg man, implying that the effect of FFM or RMR on appetite would increase with increasing body fatness. There is no reason to imagine why such a signal would grow in strength as people become fatter, as this would suggest a positive feedback form of appetite dysregulation. It is more likely that other factors drive EI during very significant weight gain such as diet composition and hedonic responses to food.

These circumstantial lines of evidence would support the notion of a metabolic drive to eat associated with FFM,

RMR or both, that creates a tonic hunger signal(s). Although this drive is not likely to drive body weight up in the first place, i.e. promote initial weight gain, it is not inconsistent with maintenance of a higher body weight once this is achieved by other means. Thus, it may be that RMR is associated with EI at or close to EB, but that RMR (and its primary determinant FFM) become dissociated from the process of hyperphagia during significant weight gain as the signal(s) becomes 'overwhelmed' by other stimuli, such as food availability, sensory variety, dietary energy density and food reward, likely to be important in driving weight gain.

Body composition, energy expenditure and appetite during negative energy balance

The Leeds model suggests that FFM and the associated metabolic turnover (RMR) represent a tonic drive to eat. How does this fit with the asymmetry of EB control, i.e. that humans are more tolerant of positive than negative EBs [70, 73]?

1. Marked weight loss is associated with an increased drive to eat (hunger) [53, 74], and increased liking and or wanting for foods. Parenthetically, although low-energy dense foods have been recommended for control of appetite during weight loss attempts it is possible that the physiological effects of decreasing FM and FFM may specifically increase appetite for more energy dense foods. People who suffer enforced malnutrition become markedly hyperphagic on restoration of ad libitum access to food [48, 53].
2. Weight loss is primarily composed of FM (~75%) and FFM (~25%) although the specific ratio of FM:FFM varies under a number of conditions (see below) [75].
3. The decreases in FFM associated with weight loss lead to a decrease in RMR. There is also some (5–10%) decrease in RMR over and above that attributable to changes in FFM per se [35].

Current evidence suggests that FFM is associated through energy requirements with EI. FFM during weight gain may be similarly associated with the maintenance of higher EIs but there is no direct evidence to suggest that increases in FFM during obesity development drive EIs upwards. The best evidence in human adults for the relationship between changes in body composition, appetite and EI come from longitudinal studies where weight loss is induced.

Semi-starvation studies

One seminal study, the Key's Minnesota semi-starvation study [53], has enabled the relationship between tissue loss and subsequent feeding behaviour to be determined. The results have been re-analysed in detail by Dulloo [47, 76, 77]. During the Minnesota study a group of lean men where underfed (~40% of their normal EI) for 24 weeks, during which they lost ~70% of their FM and ~18–20% of their FFM. For the next 12 weeks they were incrementally refed, but by the end of this period they were still in a deficit of ~25% for FM and 12–15% for FFM. During the final 8 weeks subjects had ad libitum access to a range of foods, with EI initially increasing to 160% of requirements and gradually subsiding to pre-weight loss levels. However, although FFM had returned to pre-weight loss levels by this time, FM had reached 170% of pre-weight loss values [46–48]. Importantly, the cessation of post-weight loss hyperphagia coincided with a massive overshoot of FM, and repletion of FFM compared to baseline levels. The analysis by Dulloo suggested that both prior depletion of FM and of FFM were independently associated with the subsequent hyperphagic response [47]. This is important because it suggests that FM:FFM relationships during extreme energy deficits may impact subsequent appetite and EI.

Therapeutic weight loss

Weight loss-induced decreases in FM influence hormone cascades that promote physiological and behavioural compensation, which favour subsequent weight regain [78–80]. Decreases in weight and FFM can also reduce spontaneous physical activity EE [53, 81], RMR and total daily energy expenditure [27, 31, 32, 82], and potentially, increase muscular efficiency [83]. The adaptations may persist for 12 months after weight loss and contribute to weight regain [84]. Energy deficits also affect appetite control. Doucet and Cameron [74] noted that energy deficits of ~25% are accompanied by both decreased EE and increased appetite. Simuthran et al. [85] showed that 8% weight loss, induced by very low calorie diets and its maintenance lead to persistent changes in circulating appetite-related hormones and increased hunger 12 months after weight loss.

Although the above evidence indicates that physiological responses to weight loss can affect EB behaviours, whether losses of FFM promote compensatory changes in appetite and EI during therapeutic weight loss has received little attention. Vink et al. [86] recently showed that FFM loss during 9% weight loss predicted subsequent weight regain 9 months later. However, there is a need for further studies that examine the functional impact of FFM losses on appetite and EI during therapeutic weight loss. Taken together, semi-starvation and therapeautic weight loss studies appear to suggest that physiological changes related to decreases in FM and FFM are associated with compensatory decreases in components of EE and increases in appetite and EI. During situations of energy deficit where FFM is threatened, it is plausible to suggest that FFM losses

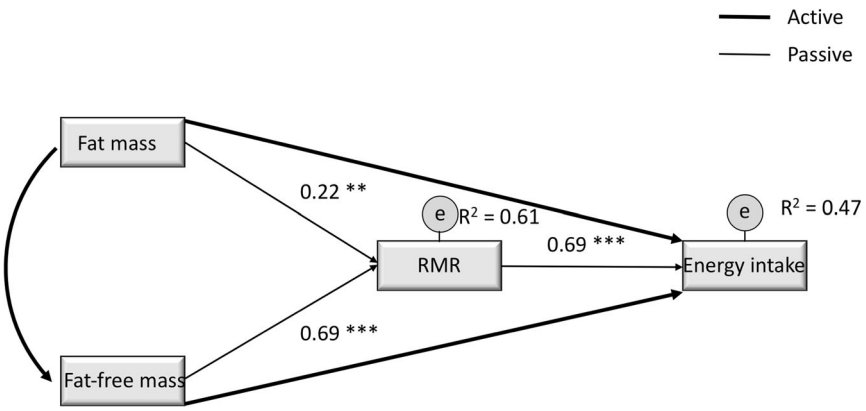

Fig. 5 Hypothetical path diagram illustrating how during weight loss the direct effects of fat mass (FM) and fat-free mass (FFM) on appetite and energy intake (EI), may supplement or over-ride the indirect passive or tonic effect of FM and FFM on EI mediated by resting metabolic rate (RMR), that is apparent in humans at or close to energy balance. Under conditions where FFM is in deficit (e.g. due to an acute inhibition of growth or due to an energy deficit that threatens FFM), the direct paths between FM and FFM may become significant and represent an 'active drive' that overrides the passive or tonic drive to eat that FFM exerts on EI through RMR (diagram derived from [14])

act as an orexigenic signal that actively drives EI to help preserve FFM.

Passive vs active drives

The above observations create an apparent problem for the model proposed by Blundell and colleagues. If increased energy turnover is associated with increases in appetite and EI [14, 15, 61, 67], how is it that during weight loss, decreases in FM, FFM and RMR are also associated with increases in appetite and EI? These scenarios are depicted in Fig. 4b. A model that accounts for the potential effects of FFM, RMR and FM on appetite and EI, it needs to account for the apparent change of direction in the relationship between FM and FFM and appetite during positive and negative energy balances.

As noted by Dulloo et al. [48], one potential explanation is that FM and FFM exert 'passive' and 'active' drives on appetite under situations of differing energy balance. At or near to EB, FFM (and to a lesser extent, FM) may have a relatively passive role in driving EI i.e. the FFM (and FM)-related energy demands associated with these tissue compartments creates a 'passive' or tonic pull on EI to meet the long-term energetic demands of metabolically active tissue and processes [48]. However, during energy deficit where FFM is threatened, dynamic losses of FFM may act as an 'active' orexigenic signal that stimulates increased EI (hunger and/or hyperphagia) in order to preserve FFM. This distinction between passive and active roles of FFM may enable us to explain the roles of FFM in appetite control at different levels of energy balance. However, direct evidence examining how the associations between FFM, RMR and EI change under conditions of energy surfeit and deficit is currently lacking.

We hypothesise that the tonic drive to eat we have inferred from our associations and mediation analysis (Fig. 1) represents Dulloo's 'passive drive' that translate FFM-induced energy needs into EI. However, under conditions where FFM is in deficit (e.g. due to an acute inhibition of growth or due to an energy deficit that threatens FFM), the direct paths between FM and FFM would become significant and represent an 'active drive' that overrides the passive or tonic drive to eat that FFM exerts on EI through RMR (Fig. 5). This may help explain the apparent mediating effect of RMR on the relationship between FFM and EI. It is not perhaps RMR per se that creates a tonic pull on EI at or close to EB, but the potential energy deficit that it can produce. This is perhaps distinct from the active drive on EI (over and above energostatic control of EI) associated with repletion of previously depleted FFM or with protein accretion along the growth trajectory of FFM (see sections Insights from catch-up growth, pregnancy… and Insights from animal models—food intake and nutrient…) [45, 54]. The extent to which an energy deficit can compromise the functional integrity of FFM is related to the FFM:FM ratio of weight lost, which is itself influenced by both body composition and extent of energy deficit. This prompts a consideration of when and to what extent changes in FFM may influence appetite and EB.

Fat and fat-free mass inter-relationships

As this review has focused primarily on the role of FFM so far, it is important to note that FM and FFM are inter-related. As Forbes notes, FM and FFM are 'in a sense companions' because dietary alterations that change EB induce changes in both FM and FFM compartments [41].

As body weight accumulates, both FM and FFM increase, but the proportion of weight gain due to FM relative to FFM increases. As weight is lost, FM is preferentially mobilised to spare FFM [30, 41, 75]. These relationships between FFM:FM or protein: energy relationships (p-ratio) were established by Forbes, and subsequently elaborated by Hall [30], and suggest that (i) FFM gain/loss is a function of FM, (ii) larger weight losses result in greater predicted proportional loss of FFM and (iii) higher initial FM leads to a lower proportion of FFM gained and as weight gain proceeds a lower proportion of weight gain is due to increases in FFM [30].

An important question to ask is how this FM:FFM interrelationship impacts on appetite control. If FFM is associated with a tonic drive to eat (Fig. 2), then a higher absolute FFM will be associated with a higher EI. As weight is gained, FFM increases more slowly than FM, pulling EI upwards (Fig. 4a). As weight is lost, FM is the buffer that protects the integrity of FFM (Fig. 4b). For people with a high initial FM, larger amounts of weight can be lost without greatly decreasing FFM than for people with a low FM. Therefore, it could be argued that the changes in EE and appetite that occur during extreme, and to a lesser extent the therapeutic range of weight loss, could operate to defend the functional integrity of FFM.

The above arguments suggest that rate of weight loss and the initial body composition at the point of weight loss may interact through FFM:FM relationships to affect appetite. Thus, more rapid weight loss in leaner subjects would create a stronger drive to replete FFM than slower weight loss in obese subjects. To our knowledge direct comparisons are currently unavailable. However, Dulloo has documented weight regain and fat overshoot in relatively lean people subject to energy deficits after total fasting, semi-starvation, caloric restriction (biosphere), training-induced weight loss of US army Rangers and recovery from famine and disease cachexia [49]. He also highlights a phenomenon in which weight loss in the non-obese appears to lead to weight regain and fat overshoot, which he suggests is a function of 'collateral' fattening [46, 49, 75]. It can therefore be hypothesised that from the perspective of energy deficits and FFM, the obese are less likely to experience a drive to regain weight from FFM than are the lean (although other factors may well drive weight regain subsequent to weight loss in the obese).

Insights from catch-up growth, pregnancy and lactation

There is an interesting parallel situation to the Minnesota study regarding deficits in FFM and subsequent hyperphagia. Millward [54] notes that in undernourished children 'catch-up growth' in weight occurs before catch-up growth in height can be detected, and this phenomenon is accompanied by 'a marked stimulation of appetite and food intake and growth proceeds at a rate limited only by food intake until normal body weight for height is achieved. At this time there is a dramatic reduction in appetite and food intake so that growth slows to be subsequently limited by height growth (pp. 102–103)' [54]. Millward convincingly argued that catch-up growth involves a stimulation of appetite 'when amino acids net flow from the free pool into skeletal muscle protein is greater than that of entry from food intake, satiety can be inhibited and hunger induced by some mechanism sensing an apparent body deficit of amino acids' (pp. 114–115) [54]. It is not clear if such a hypothetical mechanism would account for the relationships between FFM:FM changes during weight loss and subsequent appetite in adult humans, but in growing animals and humans it does appear that a prior period of energy deficit leads to the well-recognised phenomenon of catch-up growth [1, 45, 54, 87, 88].

Pregnancy is associated with a marked increase in weight, FM, FFM and importantly, appetite. In rats there is a 100% increase in EI during pregnancy and up to 450% in lactation [89]. In humans the increase in EI is more modest: ~10–15% during pregnancy and 20–25% during lactation [90]. It is reasonable to hypothesise that the marked anabolic increase in FFM associated with gestation may have some role to have in driving appetite and as with collateral fattening and 'preferential catch-up fat' that can predispose the pregnant women to subsequent (post-partum) weight gain.

Insights from animal models—food intake and nutrient partitioning during growth

In a review of food intake and nutrient partitioning during animal growth, Webster [45] concluded that (i) protein accretion is regulated with high precision, (ii) food intake is adjusted to allow maximum protein accretion to meet the needs of growth, and (iii) fat accretion is far less well-regulated. Although this model is constrained primarily to farm animals and rats consuming a limited choice of feeds, it demonstrates across species a circumstance where FFM drives ad libitum EI. Webster suggested that 'The nutrient requirements of a growing animal are determined principally by its impetus for lean tissue growth and the partition of nutrients between protein, fat and heat become thereafter inevitable consequences of its physiological state and the availability of different nutrients' (p. 71) [45].

Evidence from animal studies also suggests that when a variety of species have ad libitum access to a diet (feed) of fixed composition that is insufficient in protein content to meet their genetically programmed growth curve, they become hyperphagic and gain significant amounts of

adipose tissue to satisfy the dietary requirements for lean tissue (FFM) growth [45, 54]. Provision of a low protein diet to growing animals will lead to fat overshoot during normal growth for apparently the same reason [45, 54, 88]. When offered a choice of feeds high or low in protein, growing pigs are capable of selecting a diet that is adequate for FFM and FM growth. When offered a choice of feeds they will select a balanced amino acid mixtures over imbalanced mixtures and they will select low protein feeds over imbalanced amino acid mixtures. A similar capacity to select adequate protein: energy ratios are evident in growing chicks, laying hens and growing lambs (perhaps more accurately than adult sheep) [88], and this again illustrates the interactive nature of FFM:FM relationships [45]. The drive for genetically programmed growth in FFM overrides any drive to maintain energy balance except under conditions where dietary energy is insufficient or extremely low protein diets. There is some evidence that higher protein diets lead to reduced drive to eat and some sparing of FFM during weight loss in adult humans [91].

Conclusions

We hypothesise that at or close to energy balance the tonic drive to eat inferred from associations between body composition and EI represent a passive energy sensing mechanism that translates FFM-induced energy needs into EI. During weight gain, there is an increase in FFM (and potentially an associated 'passive' or tonic increase in EI)—although this is not sufficient to account for the development of obesity in itself, it may however be important in defending an elevated body weight. During energy deficits or when growth is retarded, there may be an 'active' drive exerted by FM and FFM on EI under conditions where FFM is in deficit and its functional integrity is threatened. We hypothesise that this drive would over-ride the tonic or passive drive to eat and is responsible for the hyperphagia that is seen during alterations of diet composition in growing animals, catch-up growth in children and after significant weight loss in adults. Thus, although FFM may exert a tonic background pull on appetite and EI under conditions of EB or weight gain, integrated changes in body composition that impact on the functional integrity of FFM appear to drive appetite and EI in an attempt to preserve the functional integrity of metabolically active tissues.

This hypothetical model would help understanding of the relationship between body structure, function and behaviour at different levels of EB. These relationships should be tested in prospective studies that examine the relationship between body structure, function and behaviour during chronic periods of altered EB. At present, there is a clear need to identify putative signals linking FFM to appetite and EI during EB and energy imbalances. Understanding how integrated changes in FM and FFM during prolonged energy deficits generate peripheral signals that cue eating behaviour may help identify intervention targets that lead to better management of appetite and EI during significant weight loss for therapeutic purposes. Such studies may have relevance for weight loss and maintenance strategies and the nutritional management of malnutrition across the life course.

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Compliance with ethical standards

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References

1. Blaxter K. Energy metabolism in animals and man. Cambridge: Cambridge University Press; 1989.
2. Mayer J. Regulation of energy intake and the body weight: the glucostatic theory and the lipostatic hypothesis. Ann N Y Acad Sci. 1955;63:15–43.
3. James WPT. From SDA to DIT to TEF. In: Kinney JM, Tucker HN, editors. Energy matabolism: tissue determinants and cellular corrolaries. New York: Raven Press; 1992; pp. 163–86.
4. Hall KD. Predicting metabolic adaptation, body weight change, and energy intake in humans. Am J Physiol Endocrinol Metab. 2010;298:449–66.
5. Newsholme EA. Sounding board. A possible metabolic basis for the control of body weight. N Engl J Med. 1980;302:400–5.
6. Rothwell NJ, Stock MJ. Luxuskonsumption, diet-induced thermogenesis and brown fat: the case in favour. Clin Sci. 1983;64:19–23.
7. Flatt JP. 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. 1987;499:104–23.
8. Stubbs J, Ferres S, Horgan G. Energy density of foods: effects on energy intake. Crit Rev Food Sci Nutr. 2000;40:481–515.
9. Wurtman RJ, Wurtman JJ. Do carbohydrates affect food intake via neurotransmitter activity? Appetite. 1988;11(Suppl 1):42–47.
10. Le Magnen J. Hunger. Cambridge, United Kingdom: Cambridge University Press; 1985.
11. Spitzer L, Rodin J. Human eating behaviour: a critical review of studies in normal weight and overweight individuals. Appetite. 1981;2:293–329.
12. Schwartz MW, Woods SC, Seeley RJ, Barsh GS, Baskin DG, Leibel RL. Is the energy homeostasis system inherently biased toward weight gain? Diabetes. 2003;52:232–8.
13. Keesey RE, Powley TL. Body energy homeostasis. Appetite. 2008;51:442–5.

14. Hopkins M, Finlayson G, Duarte C, Whybrow S, Ritz P, Horgan GW, et al. Modelling the associations between fat-free mass, resting metabolic rate and energy intake in the context of total energy balance. Int J Obes. 2016;40:312–8.
15. Blundell JE, Caudwell P, Gibbons C, Hopkins M, Naslund E, King N, et al. Role of resting metabolic rate and energy expenditure in hunger and appetite control: a new formulation. Dis Model Mech. 2012;5:608–13.
16. Muller MJ, Baracos V, Bosy-Westphal A, Dulloo AG, Eckel J, Fearon KC, et al. Functional body composition and related aspects in research on obesity and cachexia: report on the 12th Stock Conference held on 6 and 7 September 2013 in Hamburg, Germany. Obes Rev. 2014;15:640–56.
17. Muller MJ, Bosy-Westphal A, Later W, Haas V, Heller M. Functional body composition: Insights into the regulation of energy metabolism and some clinical applications. Eur J Clin Nutr. 2009;63:1045–56.
18. Ravussin E, Burnand B, Schutz Y, Jequier E. Twenty-four-hour energy expenditure and resting metabolic rate in obese, moderately obese, and control subjects. Am J Clin Nutr. 1982;35:566–73.
19. Widdowson EM, Mc CR. Individual dietary surveys. Proc Nutr Soc. 1945;3:110–6.
20. Prentice AM, Black AE, Murgatroyd PR, Goldberg G, Coward WA. Metabolism or appetite: questions of energy balance with particular reference to obesity. J Human Nutr Diet. 1989;2:95–104.
21. Jequier E. Calorie balance versus nutrient balance. In: Kinney JM, Tucker HN, editors. Energy metabolism: tissue determinants and cellular corollaries. New York: Raven Press; 1992.
22. Forbes GB. Lean body mass-body fat inter-relationships in humans. Nutr Rev. 1987;45:225–31.
23. Forbes GB. Body fat content influences the body composition response to nutrition and exercise. Ann N Y Acad Sci. 2000;904:359–65.
24. Weinsier RL, Bracco D, Schutz Y. Predicted effects of small decreases in energy expenditure on weight gain in adult women. Int J Obes Relat Metab Disord. 1993;17:693–700.
25. Deriaz O, Tremblay A, Bouchard C. Non linear weight gain with long term overfeeding in man. Obes Res. 1993;1:179–85.
26. Diaz EO, Prentice AM, Goldberg GR, Murgatroyd PR, Coward WA. Metabolic response to experimental overfeeding in lean and overweight healthy volunteers. Am J Clin Nutr. 1992;56:641–55.
27. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. N Engl J Med. 1995;332:621–8.
28. Webb P, Annis JF. Adaptation to overeating in lean and overweight men and women. Hum Nutr Clin Nutr. 1983;37:117–31.
29. Joosen AM, Westerterp KR. Energy expenditure during overfeeding. Nutr Metab. 2006;3:25.
30. Hall KD. Body fat and fat-free mass inter-relationships: Forbes's theory revisited. Br J Nutr. 2007;97:1059–63.
31. Hall KD. Modeling metabolic adaptations and energy regulation in humans. Annu Rev Nutr. 2012;32:35–54.
32. Martin CK, Heilbronn LK, de Jonge L, DeLany JP, Volaufova J, Anton SD, et al. Effect of calorie restriction on resting metabolic rate and spontaneous physical activity. Obesity. 2007;15:2964–73.
33. Schwartz A, Kuk JL, Lamothe G, Doucet E. Greater than predicted decrease in resting energy expenditure and weight loss: results from a systematic review. Obesity. 2012;20:2307–10.
34. Weinsier RL, Nagy TR, Hunter GR, Darnell BE, Hensrud DD, Weiss HL. Do adaptive changes in metabolic rate favor weight regain in weight-reduced individuals? An examination of the set-point theory. Am J Clin Nutr. 2000;72:1088–94.
35. Westerterp KR. Metabolic adaptations to over—and underfeeding—still a matter of debate? Eur J Clin Nutr. 2013;67:443–5.
36. Polidori D, Sanghvi A, Seeley RJ, Hall KD. How strongly does appetite counter weight loss? Quantification of the feedback control of human energy intake. Obesity. 2016;24:2289–95.
37. Stubbs RJ, Elia M. Macronutrients and appetite control with implications for the nutritional management of the malnourished. Clin Nutr. 2001;20:129–39.
38. Prentice AM, Poppitt SD. Importance of energy density and macronutrients in the regulation of energy intake. Int J Obes Relat Metab Disord. 1996;20(Suppl 2):S18–23.
39. Stubbs RJ. Nutrition Society Medal Lecture. Appetite, feeding behaviour and energy balance in human subjects. Proc Nutr Soc. 1998;57:341–56.
40. Elia M, Stubbs RJ, Henry CJK. Differences in fat, carbohydrate, and protein metabolism between lean and obese subjects undergoing total starvation. Obes Res. 1999;7:597–604.
41. Forbes GB. The companionship of lean and fat. Basic Life Sci. 1993;60:1–14.
42. de Onis M, Monteiro C, Akré J, Clugston G. The worldwide magnitude of protein–energy malnutrition: an overview from the WHO Global Database on Child Growth. Bull World Health Organ. 1993;71:703–12.
43. Uauy R, Alvear J. Effects of protein–energy interactions on growth. In: Schurch B, Scrimshaw NS, editors. Protein–energy interactions. Lausanne, Switzerland: IDECG; 1992. pp. 151–82.
44. Garza C, Motil KJ. Protein–energy relationships in pregnancy and lactation. In: Scrimshaw NS, Schurch B, editors. Protein–energy interactions. Lausanne, Switzerland: IDECG; 1992.
45. Webster AJ. Energy partitioning, tissue growth and appetite control. Proc Nutr Soc. 1993;52:69–76.
46. Dulloo AG. Collateral fattening: When a deficit in lean body mass drives overeating. Obesity. 2017;25:277–9.
47. Dulloo AG, Jacquet J, Girardier L. Poststarvation hyperphagia and body fat overshooting in humans: a role for feedback signals from lean and fat tissues. Am J Clin Nutr. 1997;65:717–23.
48. Dulloo AG, Jacquet J, Miles-Chan JL, Schutz Y. Passive and active roles of fat-free mass in the control of energy intake and body composition regulation. Eur J Clin Nutr. 2017;71:353–7.
49. Dulloo AG, Jacquet J, Montani JP, Schutz Y. How dieting makes the lean fatter: from a perspective of body composition autoregulation through adipostats and proteinstats awaiting discovery. Obes Rev. 2015;16(Suppl 1):25–35.
50. Dulloo AG, Montani JP. Pathways from dieting to weight regain, to obesity and to the metabolic syndrome: an overview. Obes Rev. 2015;16(Suppl 1):1–6.
51. Elia M. Effect of starvation and very low calorie diets on protein–energy inter-relationships and nutrtional needs. In: Scrimshaw NS, Schurch B, editors. Protein–energy interactions. Lausanne, Switzerland: IDECG; 1992.
52. Scrimshaw NS, Bistrian BR, Brunser O, Elia M, Jackson AA, Jiang JM, et al. Effects of disease on desirable protein/energy ratios. In: Scrimshaw NS, Schürch B, editors. Protein–energy interactions. Lausanne, Switzerland: IDECG; 1992. pp. 385–98.
53. Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. The biology of human starvation. Oxford: University of Minnesota Press; 1950.
54. Millward DJ. A protein-stat mechanism for regulation of growth and maintenance of the lean body mass. Nutr Res Rev. 1995;8:93–120.
55. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homolog. Nature. 1994;372:425–32.
56. Kennedy GC. The role of depot fat in the hypothalamic control of food intake in the rat. Proc R Soc B. 1953;140:578–92.
57. Jequier E. Leptin signaling, adiposity, and energy balance. Ann N Y Acad Sci. 2002;967:379–88.

58. Morton G, Cummings D, Baskin D, Barsh G, Schwartz M. Central nervous system control of food intake and body weight. Nature. 2006;443:289–95.
59. Woods SC, Ramsay DS. Food intake, metabolism and homeostasis. Physiol Behav. 2011;104:4–7.
60. Blundell J, Caudwell P, Gibbons C, Hopkins M, Naslund E, King N, et al. Body composition and appetite: fat-free mass (but not fat-mass or BMI) is positively associated with self-determined meal size and daily energy intake in humans. Br J Nutr. 2012;107:445–59.
61. Blundell JE, Finlayson G, Gibbons C, Caudwell P, Hopkins M. The biology of appetite control: do resting metabolic rate and fat-free mass drive energy intake? Physiol Behav. 2015;152(Pt B):473–8.
62. Lissner L, Habicht J-P, Strupp BJ, Levitsky D, Haas JD, Roe D. Body composition and energy intake: do overweight women overeat and underreport? Am J Clin Nutr. 1989;49:320–5.
63. Weise CM, Hohenadel MG, Krakoff J, Votruba SB. Body composition and energy expenditure predict ad libitum food and macronutrient intake in humans. Int J Obes. 2014;38:243–51.
64. Piaggi P, Thearle MS, Krakoff J, Votruba SB. Higher daily energy expenditure and respiratory quotient, rather than fat-free mass, independently determine greater ad libitum overeating. J Clin Endocrinol Metab. 2015;100:3011–20.
65. Cameron JD, Sigal RJ, Kenny GP, Alberga AS, Prud'homme D, Phillips P, et al. Body composition and energy intake - skeletal muscle mass is the strongest predictor of food intake in obese adolescents: The HEARTY trial. Appl Physiol Nutr Metab. 2016;41:611–7.
66. Cugini P, Salandri A, Cilli M, Ceccotti P, Di Marzo A, Rodio A, et al. Daily hunger sensation and body composition: I. Their relationships in clinically healthy subjects. Eat Weight Disord. 1998;3:168–72.
67. Hopkins M, Blundell JE. Energy balance, body composition, sedentariness and appetite regulation: pathways to obesity. Clin Sci. 2016;130:1615–28.
68. Prentice AM, Black AE, Coward WA, Davies HL, Goldberg GR, Murgatroyd PR, et al. High levels of energy expenditure in obese women. Br Med J. 1986;292:983–7.
69. Elia M. Organ and tissue contribution to metabolic rate. In: Kinney JM, HNT, editors. Energy metabolism: tissue determinants and cellular corrolaries. New York: Raven Press; 1992; pp. 61–80.
70. Stubbs RJ, Tolkamp BJ. Control of energy balance in relation to energy intake and energy expenditure in animals and man: an ecological perspective. Br J Nutr. 2006;95:657–76.
71. Forbes GB. Human body composition: growth, ageing, nutrition and activity. New York: Springer Verlag; 1987.
72. Owen OE, Smalley KJ, Jungas RL. Starvation. Comprehensive physiology. Supplement 21: Handbook of physiology, the endocrine system, the endocrine pancreas and regulation of metabolism. New York: Wiley; 2011; pp. 1199–225.
73. Blundell JE, Stubbs RJ. Diet composition and the control of food intake in humans. In: Bray GE, Bouchard C, James WPT, editors. Handbook of obesity. New York: Marcel Dekker; 1998; pp. 243–72.
74. Doucet E, Cameron J. Appetite control after weight loss: what is the role of bloodborne peptides? Appl Physiol Nutr Metab. 2007;32:523–32.
75. Heymsfield SB, Gonzalez MC, Shen W, Redman L, Thomas D. Weight loss composition is one-fourth fat-free mass: a critical review and critique of this widely cited rule. Obes Rev. 2014;15:310–21.
76. Dulloo AG. Regulation of body composition during weight recovery: integrating the control of energy partitioning and thermogenesis. Clin Nutr. 1997;16(Suppl 1):25–35.
77. Dulloo AG. Human pattern of food intake and fuel-partitioning during weight recovery after starvation: a theory of autoregulation of body composition. Proc Nutr Soc. 1997;56:25–40.
78. Crujeiras AB, Goyenechea E, Abete I, Lage M, Carreira MC, Martinez JA, et al. Weight regain after a diet-induced loss is predicted by higher baseline leptin and lower ghrelin plasma levels. J Clin Endocrinol Metab. 2010;95:5037–44.
79. Kotidis EV, Koliakos GG, Baltzopoulos VG, Ioannidis KN, Yovos JG, Papavramidis ST. Serum ghrelin, leptin and adiponectin levels before and after weight loss: comparison of three methods of treatment—a prospective study. Obes Surg. 2006;16:1425–32.
80. Pardina E, Lopez-Tejero MD, Llamas R, Catalan R, Galard R, Allende H, et al. Ghrelin and apolipoprotein AIV levels show opposite trends to leptin levels during weight loss in morbidly obese patients. Obes Surg. 2009;19:1414–23.
81. Redman LM, Heilbronn LK, Martin CK, de Jonge L, Williamson DA, Delany JP, et al. Metabolic and behavioral compensations in response to caloric restriction: implications for the maintenance of weight loss. PLoS ONE. 2009;4:e4377.
82. Hall KD, Chow CC. Estimating the quantitative relation between food energy intake and changes in body weight. Am J Clin Nutr. 2010;91:816–7.
83. Goldsmith R, Joanisse DR, Gallagher D, Pavlovich K, Shamoon E, Leibel RL, et al. Effects of experimental weight perturbation on skeletal muscle work efficiency, fuel utilization, and biochemistry in human subjects. Am J Physiol Regul Integr Comp Physiol. 2010;298:79–88.
84. Rosenbaum M, Hirsch J, Gallagher DA, Leibel RL. Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight. Am J Clin Nutr. 2008;88:906–12.
85. Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, et al. Long-term persistence of hormonal adaptations to weight loss. N Engl J Med. 2011;365:1597–604.
86. Vink RG, Roumans NJ, Arkenbosch LA, Mariman EC, van Baak MA. The effect of rate of weight loss on long-term weight regain in adults with overweight andobesity. Obesity. 2016;24:321–7.
87. Waterlow JC. Protein–energy inter-relationships during rapid growth. In: Scrimshaw NS, Schürch B, editors. Protein–energy interactions. Lausanne, Switzerland: IDECG; 1992. pp. 183–90.
88. Forbes J. Voluntary food intake and diet selection in farm animals. Wallingford, Oxfordshire: CAB International; 1995. pp. 305–31.
89. Cripps AW, Williams VJ. The effect of pregnancy and lactation on food intake, gastrointestinal anatomy and the absorptive capacity of the small intestine in the albino rat. Br J Nutr. 1975;33:17–32.
90. Forsum E, Kabir N, Sadurskis A, Westerterp K. Total energy expenditure of healthy Swedish women during pregnancy and lactation. Am J Clin Nutr. 1992;56:334–42.
91. Soenen S, Martens EA, Hochstenbach-Waelen A, Lemmens SG, Westerterp-Plantenga MS. Normal protein intake is required for body weight loss and weight maintenance, and elevated protein intake for additional preservation of resting energy expenditure and fat-free mass. J Nutr. 2013;143:591–6.