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The Biology of Appetite Control: do Resting Metabolic Rate and Fat-Free Mass drive Energy Intake?

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Abstract

The prevailing model of homeostatic appetite control envisages two major inputs; signals from adipose tissue and from peptide hormones in the gastrointestinal tract. This model is based on the presumed major influence of adipose tissue on food intake. However, recent studies have indicated that in obese people fat-free mass (FFM) is strongly positively associated with daily energy intake and with meal size. This effect has been replicated in several independent groups varying in cultural and ethnic backgrounds, and appears to be a robust phenomenon. In contrast fat mass (FM) is weakly, or mildly negatively associated with food intake in obese people. In addition resting metabolic rate (RMR), a major component of total daily energy expenditure, is also associated with food intake. This effect has been replicated in different groups and is robust. This action is consistent with the proposal energy requirements – reflected in RMR (and other aspects of energy expenditure) constitute a biological drive to eat. Consistent with its storage function, FM has a strong inhibitory effect on food intake in lean subjects, but this effect appears to weaken dramatically as adipose tissue increases. This formulation can account for several features of the development and maintenance of obesity and provides an alternative, and transparent, approach to the biology of appetite control.

Background: Current Views on the Biology of Appetite Control

Over the course of 50 years scientific thinking about the mechanisms of appetite control has changed dramatically. In the 1950s and 1960s the hypothalamic 'dual centre' hypothesis was believed to provide a comprehensive account of the intiation and inhibition of food intake e.g. Anand & Brobeck (1951) [1]. Following technological advances in the identification of neurotransmitter pathways in the brain, the 2-centre hypothesis was replaced by a model which was based on catecholaminergic and serotonergic aminergic systems [2]. At the time this approach was understood to provide a modern and powerful explanation of appetite. Later, with the discovery of families of neuropeptides, the peptide hypothesis of central control of appetite replaced the 'somewhat dated' aminergic ideas. Current neural models propose complex networks of transmitter pathways and receptors that receive both stimulatory and inhibitory inputs from the periphery [3]. Important peripheral agents have been incorporated into a recent conceptualisation that has proposed a theory of appetite control based on an interaction between adipose tissue (and prominent adipokines) and peripheral episodic signals from intestinal peptides such as ghrelin,

cholecystokinin (CCK), Insulin, glucagon-like peptide-1 (GLP-1), peptide tyrosine-tyrosine (PYY), amylin and oxyntomodulin [4]. This 2 component approach apparently summarises current thinking. However, the history of the physiology of appetite control illustrates that any model can be improved by new findings and that some models have to be completely replaced following the advent of new knowledge. Commenting on the regulation of body fat in an editorial in American Journal of Physiology (2004) Wade commented that 'a facile explanation has the potential to set back progress in a field by years, because the problem has been thought to have been solved' (when it has not)[5]. Therefore the current conceptualisations should not be regarded as permanent fixtures; they are transient representations of the current state of knowledge.

An important component of the homeostatic approach to appetite and body weight has focussed on the identification of key signals that could inform the brain about the nature of body stores. During the 1950s three basic postulates promoted different signals for 'body weight regulation'; these were the glucostatic [6], aminostatic [7] and lipostatic hypotheses [8]. These simple ideas exerted a mild but pervasive influence on thinking about a complex problem. The discovery of leptin in 1994 by Zhang et al. [9] seemed to provide conclusive proof of the authenticity of the lipostatic hypothesis (which was based on a particular interpretation of the classic rat studies of Kennedy [8]), and leptin was construed as 'the lipostatic signal' that was an essential component required in a negative feedback process for the regulation of adipose tissue. This idea has been incorported into models of appetite control in which leptin is depicted as the major signal (the missing link) that informs the brain about the state of the body's energy stores [4, 10]. Interpretations of this view have positioned adipose tissue at the centre of appetite control [11]. In addition, it has been asserted that adipose tissues are critical integrators of energy balance through the regulation of food intake and energy expenditure [12]. These arguments have contributed to the view that adipose tissue is the main driver of food intake, with day to day food intake controlled in the interests of regulating body weight (and especially adipose tissue); this view appears to have been widely accepted. In addition, leptin is understood to play a key role in the control of appetite by adipose tisssue. Although it is beyond doubt that leptin exerts a critical influence in many biochemical pathways concerning physiological regulation [3, 13] it has been argued that the role of leptin in the etiology of obesity is confined to very rare situations in which there is an absence of a leptin signal [14]. Others have also argued that the role of leptin signalling is not concerned with satiety but is mainly involved in the maintenance of adequate energy stores for survival during periods of energy deficit [15]. This is why leptin may be critical in the resistance to weight loss with dieting. However, it has been noted that the results following exogenous leptin administration in 'typical' obesity have been disappointing [12]. Indeed, neither leptin nor adipose tissue itself has not been shown to exert an influence over

the parameters of hunger and meal size which are key elements in day to day control of appetite in humans.

The second issue that appears to influence thinking is the notion called 'energy homeostasis'. This idea has been proposed to account for the accuracy in which energy balance is maintained over time in normal individuals. For example, some commentaries suggest that for a healthy adult weighing 75 kg who typically consumes approximately one million kcal each year, then a mismatch of just 1% (expending 27 kcal per day fewer than consumed) will yield a body fat increase of 1.1 kg after 1 year [16]. This type of calculation which uses the 1 kg of fat for 7700 kcal rule has recently been shown by Hall [17] and others [18] to be simplistic and to produce implausible predictions. Moreover, given the worldwide epidemic of obesity, and the apparent ease with which many human beings appear to gain weight, it seems implausible that some privileged physiological mechanism is regulating body weight with exquisite precision. If such a mechanism existed it would surely operate to correct weight gain once it began to occur. As Speakman (2014) has pointed out 'If body fatness is under physiological control, then how come we have an obesity epidemic?' [19].

The compelling phenomenon of dietary-induced obesity (DIO) in rats also suggests that physiology can be overcome by a 'weight-inducing' nutritional environment, and that 'energy homeostasis' cannot prevent this. The phenomenon of DIO in rats questions the notion of an all powerful biological regulatory system. Moreover, this experimental 'fact' strongly resonates with the proposal of a human 'obesogenic environment' that promotes weight gain in almost every technologically advanced country on the planet [20]. The analogy with DIO in rats is quite compelling, and is usually not denied.

The argument for body weight stability is not convincing. The existence of world wide obesity suggests that body weight is not tightly regulated. Moreover, overfeeding does not lead to any significant downregulation of energy intake [21, 22]. An alternative view that has been discussed for decades is that regulation is asymmetrical [23]. Whilst the reduction in body weight is strongly defended, physiological compensatory mechanisms do not resist an increase in fat mass [24]. Indeed the physiological system appears to permit fat deposition when nutritional conditions are favourable (such as exposure to a high energy dense diet). This means that the role of culture in determining food selection is critical. In many societies the prevailing ideology of consumerism encourages overconsumption. This applies not only to foods but to all varieties of material goods. The body is not well protected from the behavioural habit of overconsuming food; processes of satiety can be over-ridden to allow the development of a positive energy balance. This has been referred to as 'passive overconsumption' [25, 26] and is regarded as a salient feature of the obesogenic

environment (26). Consequently there are a number of aspects of the etiology and management of obesity, and the obesity epidemic, that are difficult for the adipocentric theory to explain.

An Alternative Approach: Human Energy Balance and Appetite Control

Not since the work done by Edholm [27, 28] and Mayer [29] in the 1950s has thinking about appetite control taken account of evidence in the field of human energy balance research. Therefore it is worth considering whether or not any light can be shed on the expression of human appetite from an energy balance approach. A recent approach to the study of exercise on appetite control within an energy balance framework has used a multi-level experimental platform in obese humans [30]; relationships among body composition, resting metabolism, substrate oxidation, gastrointestinal peptides, sensations of appetite and objectives measures of daily energy intake and meal sizes, have been examined. Such a multi-level approach has not previously been explicitly undertaken. An important feature of the approach is that all variables have been objectively measured and quantified. This is particularly important in the case of daily energy intake for which self-report or self-recall do not provide data of sufficient accuracy to be used in assessments of the energy balance budget [31, 32].

Body Composition and Energy intake

Using a multi-level systems approach [30] in several cohorts of obese (men and women), the relationship between meal sizes, daily energy intakes and aspects of body composition (fat mass [FM] and fat-free mass [FFM]) have been measured simultaneously in the same individuals at different time intervals several months apart [33]. Contrary to what many would have expected, a positive association was observed between FFM and daily energy intake (EI), and also with meal size (see Figure 1). In other words, the greater the amount of FFM in a person, the greater was the daily energy consumed and the larger the individual meal size (in self-determined, objectively measured eating occasions). In order to enhance ecological validity, the study incorporated a schedule of eating opportunities that was representative of real life in the local culture. The relationships between FFM and EI were conserved over time (measures 12 weeks apart) and under quite distinctive dietary challenges (high and low energy dense foods). There was no relationship with body mass index (BMI) nor with the amount of adipose tissue (FM) suggesting that, in a free-running situation (with participants not subject to coercive weight loss or dietary restriction), FM did not exert control over the amount of food selected in a meal, nor consumed over a whole day [33]. This outcome is clearly not consistent with an adipocentric view of appetite control. Moreover the relationships were independent of sex. This means that sex does not explain the association of FFM

with EI. On the contrary FFM can explain the sex effect; men (in general) eat more than women because they have greater amounts of FFM.

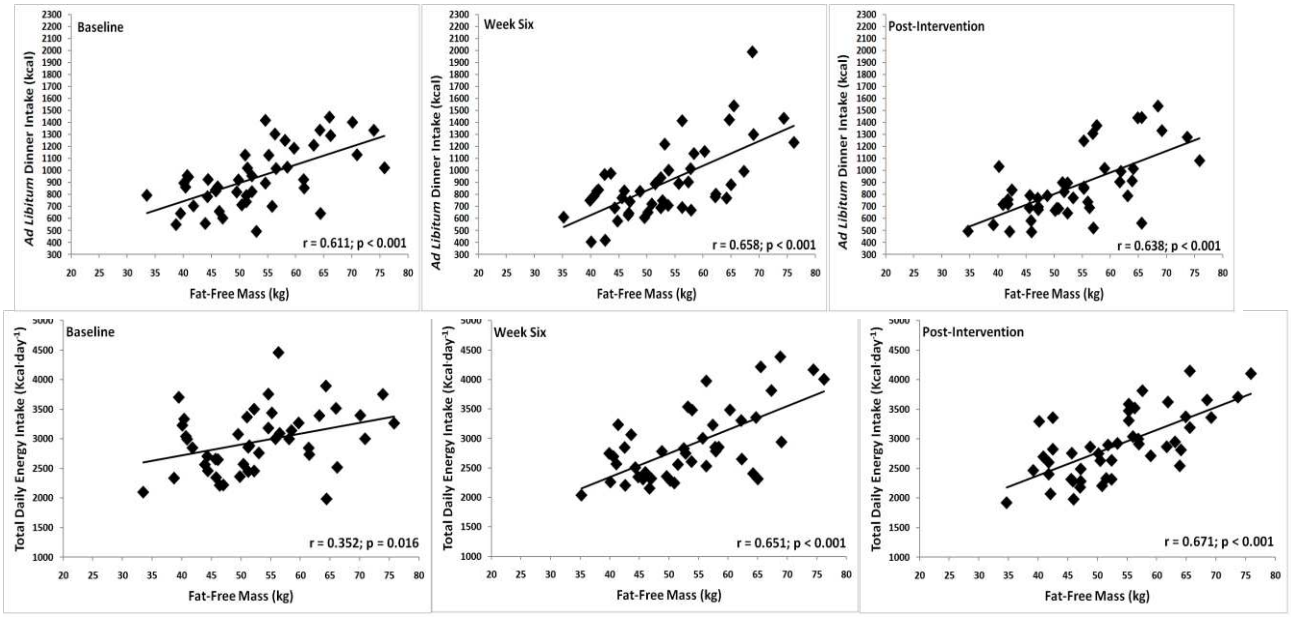

Figure 1

Scatter plot for a group of 46 overweight and obese individuals showing the relationship between fat free mass and self determined total energy intake measured objectively and quantitatively under laboratory conditions for one ad-libitum dinner meal (upper panel) and over the whole day (lower panel). Measurements were made at the beginning, after 6 weeks and at the end (post intervention) of a 12 week programme to improve physical activity. Participants were given 3 ad-libitum meals and one fixed size meal (lunch) at each measurement point, and the daily intakes were averages of days in which participants were offered high energy dense or low energy dense foods. The relationship between FFM and EI is present at individual meals and for the total day energy intake. This positive relationship is quite consistent with the data reported in papers by Lissner et al (1989) and Weise et al (2013).

Confirmation of the Relationship between Body Composition and Energy Intake: The Importance of Replication in Science

One of the most valuable but unpopular aspects of scientific investigations is the importance of replication. With the emphasis in publications on novelty and originality, it is common to find many

findings reported on a single occasion only, with the implication that one demonstration of an effect establishes that effect for ever [34]. Authors are not keen to perform the same study more than once, and grant awarding bodies are not enthusiastic about funding repetitions. However, for any new finding that may run counter to the currently accepted dogma, it is essential that it is replicated in order to demonstrate its robustness.

Interestingly, our attention has recently been drawn to a study published in 1989 that produced results in all aspects similar to those we reported in 2010 and published in 2011. The study by Lissner et al. [35] was designed to investigate whether overweight women might overeat whilst reporting under eating. Participants were observed for periods of 14 to 63 days and all measurements were carried out in a metabolic unit that incorporated measures of body composition using densitometry. Body composition, weight change and energy intake were precisely and objectively measured by the investigators. The outcome showed that the energy requirement for the maintenance of body weight was not correlated with adiposity expressed as a percentage of body fat. In a regression analysis energy requirement was positively associated with lean mass ($p < 0.0001$), whereas fat mass added no predictive value to the model. The authors concluded that 'lean mass was shown to be a significant predictor of energy requirement and fat mass was not' (p 324). A further relevant comment was that 'The emphasis of research that focuses on the relationship between energy intake and obesity is misplaced because energy requirement appears to be a direct function of lean mass rather than adiposity' (p 324).

This article and its outcome appears to have been completely overlooked for over 20 years, possibly because the findings were discordant with the prevailing interest in the lipostatic hypothesis and the role of fat in appetite control. The similarity between figure 2 in the study by Lissner et al [35]- showing a relationship between EI and lean body mass - and figure 1 in our more recent paper [33] is compelling. In addition the relationship of FFM and EI has been more recently demonstrated in a large group of obese ethnically diverse individuals from a quite different geographical and cultural environment [36]. This sample (n = 184) included Asian, African Americans, Caucasians, Hispanics and Native Americans. The main outcome demonstrated that FFM (and the fat-free mass index (FFMI) – FFM divided by height squared) was correlated positively with objectively measured EI. Moreover in this sample there was a weaker but negative association of FM with daily EI. The authors concluded that food intake could be predicted by FFM (and FFMI) and to a lesser extent by FM. As proposed earlier [33, 37] these authors concluded that FFM and FM have opposing effects on energy homeostasis.

Fat-free Mass and Energy Intake – What is the Mechanism?

In order to establish biological explanations for behavior it is first necessary to demonstrate clear and unambiguous relationships between the biological and behavioural variables. This establishes a valid relationship and provides at least *prima facie* evidence that biology is causing the behavior. In turn this poses a question about the mechanism (or mechanisms) that embodies the causal link. Our research has demonstrated that some signal associated with FFM exerts a determining effect over the amount of food consumed. One possibility is that some privileged biochemical molecule associated with skeletal muscle (or some other organ that comprises FFM) could act as a signal to the central nervous system networks controlling EI. This is a possibility but there are many candidate molecules since skeletal muscle tissue produces large numbers of myokines and related entities that could embody signaling properties [38].

However, an alternative hypothesis arises from the known influence of FFM on energy expenditure and energy balance. In our studies, and those of others, FFM is highly correlated with the energy expended in resting metabolism i.e. resting metabolic rate (RMR) (FFM-RMR: r values = 0.51 – 0.85, $p<0.0001$). Consequently one possibility is that the association between FFM and EI is generated by the energy demand from FFM and reflected in RMR. In other words the energy required to maintain the body's lean tissues (including all vital organs) determines a minimum level of EI at meals and over the whole day.

Fat-free Mass, Resting Metabolic Rate and Appetite Control

This association between FFM and eating behaviour has implications for an energy balance approach to appetite control, and for the relationship between energy expenditure and EI as described by Edholm [27, 28]. It is well established that FFM is the primary determinant of RMR, and that RMR is the largest component of total daily energy expenditure [39]. From a homeostatic standpoint, an ongoing and recurring drive to eat arising from the physiological demand for energy (e.g. RMR) appears logical, as this energy demand would remain relatively stable between days and would ensure the maintenance and execution of key biological and behavioural processes. Consequently it might be predicted that RMR, the major component of daily energy expenditure (60 – 70%) could be associated with the quantitative aspect of eating behaviour and with daily EI. When this was examined [40], it was demonstrated that RMR was a significant determinant of the size of a self determined meal, and of daily energy consumed (when measured objectively and quantified). This effect has been demonstrated in several cohorts of obese and lean individuals and is a robust finding (see Figure 2). In addition, RMR was associated with the intensity of hunger objectively rated on

hand held electronic data capture instruments [41]. Consequently, these findings – that are broadly consistent with the early predictions of Edholm – have demonstrated an association between the major components of daily energy expenditure and daily EI. In other words, they demonstrate that appetite control could be a function of energy balance.

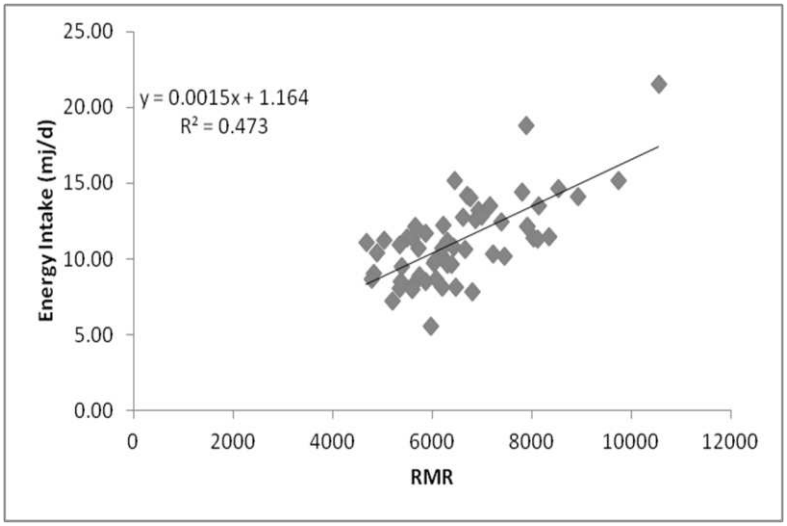

Figure 2

This figure shows a scatter plot of the relationship between daily energy intake and resting metabolic rate (RMR) for a group of 30 normal weight and 29 overweight men and women. The daily self determined food intake was measured objectively for a period of 11 days in a nutrition research unit. Subjects were free to make choices between food items but all items consumed were quantitatively recorded. These data formed part of a study on actual and reported food intakes under energy balance conditions (Stubbs et al, 2014).

Importantly the relationship between RMR and daily EI has been replicated in a completely independent large data set from participants of variable BMIs allowed to freely select their own diet under meticulously controlled semi-free living conditions [42]. This study was actually conducted to assess the degree of dietary under-reporting that would occur under strictly controlled scientific conditions. Significantly, in this investigation, which included measurements of all aspects of body composition and the energy balance budget, RMR emerged as the strongest determinant of daily EI. These reports indicate that the association between RMR and EI is robust and is not restricted to a particular group of people measured in a specific geographical location. Since FFM and RMR are both

strongly associated with EI, the question arises whether or not the effect of FFM on EI is explained by its impact on RMR. We have investigated this issue using mathematical modeling and the outcomes suggest that the influence of FFM on EI can be accounted for by the mediation of RMR.

Effects in Lean Individuals

The studies described above have been carried out mainly on overweight and obese individuals (men and women). The number of lean (and young) individuals was small. However, associations among FFM, FM and EI in obese people may not be typical for people of normal or low body mass. We have therefore measured the relationship between body composition and EI in a group of young lean male and female subjects with an average BMI of 22 kg/m^2 and an average age of 20 years. The outcome was clear but different from the effects seen in obese participants. As shown in Table 1, and in keeping with previous data, FFM and FFMI were strongly positively correlated with meal size and total energy intake (sum of 2 meals). However, in contrast to the finding in obese people, FM and FMI were significantly negatively associated with EI. These associations remained highly significant even after conducting partial correlations controlling for sex (FFMI and EI, r = 0.35; FMI and EI, r = -0.37). This observation that FM is negatively associated with EI implies that in lean individuals with low levels of body fat (average fat mass and % body fat- 10 kg and 14.9%, respectively), the adipose tissue is exerting an inhibitory effect on food intake.

	EI Breakfast	EI Lunch	Total
BMI (kg/m2)	-.005	.015	.009
Body Fat (%)	-.548**	-.509**	-.624**
Fat Mass (kg)	-.483**	-.418**	-.529**
Fat-free Mass (kg)	.541**	.516**	.628**
RMR (kcal/day)	.425**	.436**	.519**
FM-I	-.519**	-.471**	-.583**
FFM-I	.447**	.429**	.522**

Table 1 This table shows the degree of association between the variables of body composition (left hand column) and energy intake (EI) at Breakfast (BFEI), lunch (EI lunch) and the total intake for the two meals. The figures in the body of the table are correlation coefficients (r) for 47 participants (24 male and 23 female) with mean BMI = 22 and age = 20. These participants were lean, healthy active

people who took part in sports. Lean body mass was 60.9 kg and fat mass 10.2 kg. FFM-I = Fat-free Mass Index; FM-I = Fat Mass Index.

** = p< .001. see text for details.

It can be deduced that this observation is in keeping with the role of fat as a store of energy, and adipose tissue as a generator of negative feedback indicating adequate energy reserves in the body. It also suggests that the feedback signals engage with highly sensitive receptor mechanisms. We envisage that both insulin and leptin would operate as feedback signals (but the strength of their effect is mediated by adiposity levels). Since leptin and insulin resistance increase as adiposity increases this implies that the inhibitory action of FM on EI would weaken with increasing FM. In obesity the dampening effect of the large amount of energy stored in adipose tissue would be mild.

A New Formulation for the Biology of Appetite Control

It is often inferred that food intake is a function of energy requirements, but this assumption lacks empirical support, and until recently, it has not been convincingly demonstrated that energy expenditure influences within-day appetite control. Indeed, current theoretical models used to explain appetite control do not incorporate energy expenditure (or metabolic signals relating to fat-free mass or resting metabolic rate) as putative signals of food intake. Rather, appetite is thought to be a function of signals arising from adipose tissue and the gastrointestinal tract. In contrast to the prevailing 'adipocentric' view of appetite control, our data (and that of others) indicate that in addition to signals from adipose tissue and gastrointestinal peptides, there is input from metabolism associated with FFM and the energy requirement associated with RMR. Consequently, the conventional adipocentric model should be revised to allow for an influence of FFM – in addition to FM. The role of FFM in determining food intake can also be interpreted in the light of the re-analysis of the Keys' human starvation studies carried out by Dulloo et al [43]. The post-starvation recovery period has been analysed in detail and indicates that weight is regained until a certain level of FFM has been reached (while there is an overshoot in the restoration of FM). This suggests a relationship between EI and FFM during recovery from a huge weight loss. In addition, the association of FFM and EI is in keeping with the amino-static hypothesis put forward more than 60 years ago by Mellinkoff [7] and the more sophisticated proposal for a protein-stat described by Millward [44].

Our findings do not imply that FM does not play a role in appetite control. Our interpretation is that, under normal weight conditions, FM has an inhibitory influence on food intake but the strength of this tonic inhibition is moderated by insulin and leptin sensitivity [37]. As people overconsume (due to cultural obesogenic influences), FM increases and the consequential increase in leptin and insulin resistance weaken the inhibitory influence of FM on appetite. This amounts to a 'dis-inhibition', so that accumulating FM fails to suppress food intake and permits more eating (over-consumption). Indeed there is good evidence that low insulin sensitivity reduces post-prandial satiety and weakens meal to meal appetite control [45]. Therefore, on the basis of these recent findings we have proposed a conjoint influence of FFM and FM on appetite control [33]. This is set out in Figure 3. This model provides a different theoretical approach to the biology of appetite control, with the influence of FFM and RMR, in addition to signals stemming from adipose tissue and GI peptides, providing a more comprehensive account of appetite.

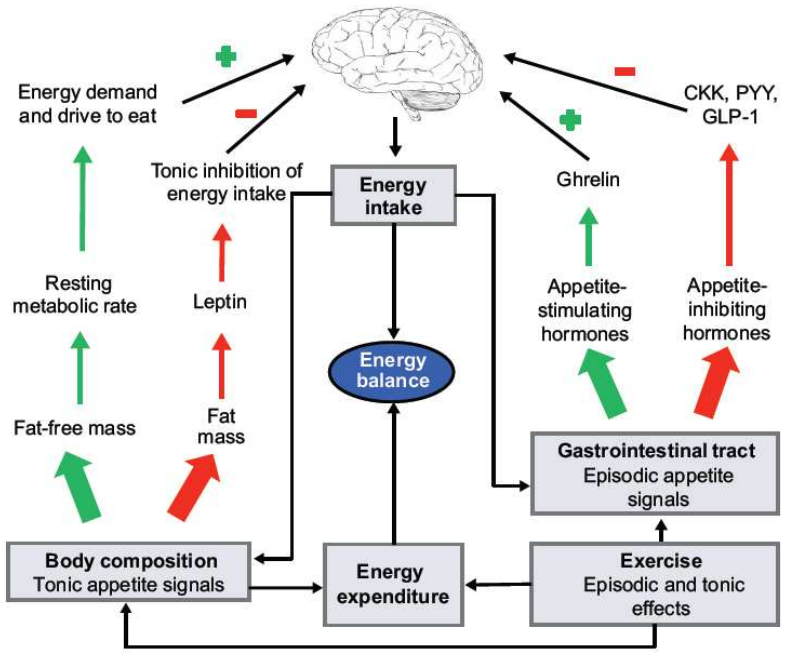

Figure 3

This diagram shows a formulation for appetite control in which a proposed tonic signal for the drive to eat that reflects the body's demand for energy arises (mainly) from fat free mass and RMR. In turn this drive is under tonic inhibition from leptin whose action reflects the amount of stored energy reserves in the body. As adipose tissue increases, leptin insensitivity occurs and this tonic inhibition is reduced. The drive to eat is periodically interrupted and suppressed by episodic signals in the form of peptides released from the GI tract in response to food consumption. The resultant pattern of

eating is a consequence of the interactions among tonic and episodic physiological signals. See text for further description.

It should be noted that the state of energy balance and changes in body composition may alter the relationship between FFM, RMR and EI. Under conditions of significant energy deficit and weight loss other regulatory signals (such as leptin) may feature more predominantly in the control of appetite [46]. Therefore, its needs to be established how FM and FFM operate (independently or conjointly) in the regulation of appetite during periods of significant weight loss. Developing clearer models concerning the relationship between changes in body composition and signalling systems associated with energy balance and imbalance has considerable implications for weight management in both health and disease.

Implications

Do findings set out above, together with the new formula for the basic biology of appetite control, offer any explanations for the puzzling problems that confront the study of weight regulation and obesity? Many accounts of appetite control would benefit from the recognition that there exists a tonic drive for energy that emanates from the continuous demand for energy to match energy expenditure from skeletal tissue and the body's vital organs (heart, liver, gastro-intestinal tract and brain).

One question that is rarely answered, partly because the question is rarely posed, is why obese people continue to feel hungry and are driven to eat in the presence of large amounts of stored energy in the body. Since obese individuals possess not only large amounts of adipose tissue but also additional FFM, it would be expected that obese people would have a persistent drive to eat (from the large FFM and higher RMR) that would be stronger than that of smaller and more lean individuals of the same age. This explanation can also account for people feeling periodically hungry in the absence of any obvious deficit or self deprivation. The uniform demand from RMR would be expected to generate a drive to eat that would be episodically suppressed by the action of the stomach and gastrointestinal (GI) peptides following the consumption of food. Therefore the pattern of eating would arise from an interaction between the tonic drive to eat and episodic inhibitory actions. In contrast to the episodic inhibitory action of most of the GI peptides, adipose tissues are envisaged to exert a tonic inhibition (that depends on receptor sensitivity – see above).

Athletes competing in sports that require a high body mass (field events in athletics, American football, rugby etc) with very high levels of skeletal muscle, would consume large amounts food and

display voracious appetites. In contrast elderly people with sarcopenia often suffer from a loss of appetite. Our explanation would be that the loss of FFM results in a weakening of hunger and a reduced food intake. Management of this condition may need to involve the gentle use of exercise to stimulate lean mass. Such a mechanism may involve the activation of stem cells as proposed by Gutin [47].

A model of appetite control that incorporates separate roles for FFM and FM can also help to explain the inexorable progress of accumulating fatness as people progress from leanness to obesity. As fat is gained the inhibitory effect of fat on appetite weakens (due to increasing receptor insensitivity) whilst at the same time any incremental increase in FFM would augment the drive to eat. Consequently as people become fatter it becomes easier to overeat, not more difficult. It follows that obese people do not get any help from their stored fat to help them to resist the drive to eat; in fact it makes it harder.

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