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Biology of the drive to eat[1]

Implications for understanding human appetite and obesity

John Blundell

Abstract

Understanding the drive to eat is a fundamental issue that can throw light on the aetiology of obesity and the inexorable surge of the obesity epidemic. It is proposed here that energy expenditure (EE) is a driver of energy intake (EI). Surprisingly this is a neglected area of thinking in this field. Theoretical writings about obesity often focus on the idea of 'regulation' and refer casually to a matching of energy intake and energy expenditure as if this happens automatically and there is nothing to explain. However, biological processes do not happen by accident, and the way in which EE is related to EI requires a justification and an explanation. It is frequently written that nothing in biology makes sense without the theory of evolution; the processes linking EE and EI are based on an evolutionary perspective. It is proposed that the energy required to maintain vital organs (heart, liver, brain, kidneys, skeletal muscle) represents an irresistible metabolic drive for food (the drive to eat). Much attention in this field has been directed to the inhibition of eating (or lack of it), with formulations lacking a mechanism for driving food behaviour. The evidence that fat free mass and resting metabolic rate constitute major determinants of energy intake has implications for understanding the aetiology and management of obesity.

Keywords: appetite, obesity, energy balance, food selection

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Food selection and the drive to eat

It is a key feature of appetite control that food selection and the drive to eat are quite separate processes which are influenced by distinct clusters of socio-cultural and biological factors.

One of the most salient features of appetite in humans depends on the fact that humans are omnivores. Unlike herbivores or carnivores whose feeding habits are biologically programmed for restricted types of foods, omnivores have a much greater range of potentially edible items. One consequence of this has been to enable humans to colonise and exploit many different types of environments sustaining quite distinctive nutritional repertoires. It follows that, for humans, the type of food that is put into the mouth is not heavily programmed biologically but depends on the local culture, geography, climate, religion, ethnic principle and social forces. This means that the processes of food intake control have to be geared to a variety of dietary scenarios and the control mechanisms have to be sufficiently adaptable to deal with a huge range of food types.

Although food is basically comprised of fats, proteins and carbohydrates (CHOs), it is put into the mouth in a large number of forms and associated with a multitude of tastes and textures. The behavioural act of putting a selected type of food into the mouth is a precursor of eating. This means that food choice depends on the environment. In certain environments rational food choice can be undermined by an environment in which nutritional value (and therefore biological value) of specific food items can be concealed or confused. This can easily happen in technologically advanced societies in which synthetic foods can be readily manufactured and which contain arbitrary and unlikely combinations of composition, textures and tastes. This can lead to quantitatively and qualitatively inappropriate eating habits.

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Appetite varies from species to species

An equally important feature, often overlooked, is that the motivation to eat is one of the strongest psychological experiences and is based in biological processes. This drive is clearly of evolutionary significance and it is extremely difficult to control. This drive is common to all living organisms but the strength, timing and direction of the drive vary from species to species, and there is considerable variability within species. In humans the strength of the drive to eat cannot be denied except under special cultural or pathological conditions. The strength of the drive obliges an engagement with the environment which is the source of food. The power of the drive and its unrelenting presence suggests the operation of important biological processes.

Because of its undeniable existence, the drive to eat – and the foods on which it is targeted – have been incorporated into social patterns and have attained cultural values. Hence the biological origins are often masked, or overlooked, in favour of socio-cultural explanations for why people eat. However, it should be kept in mind that the drive to eat has evolved to ensure evolutionary success in a variety of habitats and geophysical situations – and in the face of a huge diversity of potential foods.

The drive to eat is now embraced (in many parts of the planet) by an environment of abundance together with an aggressive political ideology where success is based in economics rather than biology. The strength of the drive to eat, together with the omnivorous habit (plus considerable brain power), have contributed to the evolutionary success of humans but now they are the cause of considerable disadvantage. Is there any escape from the current predicament of energy imbalance and obesity?

In the study of appetite control, much interest has focussed on the inhibition of the drive to eat (satiety) and relatively little on the origins of the drive itself. However, explanations for this unremitting drive are important for understanding the nature of obesity and other states. This paper describes recent investigations of the biological basis of the drive to eat.

What drives the regulation of food intake?

Over 50 years ago animal research gave rise to the idea that the drive to eat originated in an excitatory centre of the hypothalamus. This idea generated considerable research activity but made the source of the drive to eat rather inaccessible – particularly for dealing with human food intake.

Leptin: adipocentric concept

More recently two notions have dominated the field; the first of these is the adipocentric concept of appetite control i.e. 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 specifically, adipose tissue).

The discovery of leptin in 1994 by Zhang et al. [1] seemed to provide conclusive proof of the authenticity of the lipostatic hypothesis (which was based on interpretations of the classic rat studies of Kennedy [2]), 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 incorporated 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 [3, 4]. In turn a forceful interpretation of this view has positioned adipose tissue at the centre of appetite control. Indeed it has been stated by Woods and Ramsay [5] that *"There is compelling evidence that total body fat is regulated (...) when it is decreased reflexes restore it to normal (...) when it is increased reflexes (...) elicit weight loss. These processes account for the relatively stable maintenance of body weight over long periods"*; and that *"food intake is an effector or response mechanism that can be recruited or turned off in the regulation of body fat"* (Woods and Ramsay, 2011, p. 109). This view has been incorporated into general thinking about the control of appetite and appears to have been widely accepted.

In addition, leptin is understood to play a key role in the control of appetite by adipose tissue. Although it is beyond doubt that leptin exerts a critical influence in many biochemical pathways concerning physiological regulation [6, 7] it has been argued that the role of leptin in the aetiology of obesity is confined to very rare situations in which there is an absence of a leptin signal [8]. Others have also argued that the role of leptin signalling is mainly involved in the maintenance of adequate energy stores for survival during periods of energy deficit [9]. This is why leptin may be critical in the resistance to weight loss with dieting. More importantly for this review, there is little evidence for a role for leptin in day to day appetite control. In addition, the impact of 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.

Concept of energy homeostasis

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. A recent commentary has argued that *"for a healthy adult weighing 75kg typically consuming 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"* [10]. This type of calculation which uses the 1 kg of fat for 8,000 kcal rule has recently been shown by HALL [11] and others [12] to be simplistic and to produce implausible predictions.

However, 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. 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 [13]. As Speakman has pointed out *"If body fatness is under physiological regulation, how come we have an obesity epidemic?"* [14].

The argument for body weight stability is not compelling. The existence of worldwide obesity suggests that body weight is not tightly regulated.

Asymmetrical regulation

An alternative view that has been discussed for decades is that regulation is asymmetrical [15]. Whilst the reduction in body weight is strongly defended, physiology does not resist an increase in fat mass [16]. 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' [17, 18] and is regarded as a salient feature of the obesogenic environment [19].

Updating the formula for appetite control: an energy balance approach

Over the course of 50 years, scientific thinking about the mechanisms of appetite control has changed dramatically. A recent conceptualisation has proposed a theory of appetite control based on an interaction between adipose tissue (and prominent adipokines) and peripheral episodic signals from intestinal peptides [3]. This 2-component approach apparently summarises current thinking and incorporates a belief in the adipocentric theory of appetite control. 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.

Not since the work done by EDHOLM [20, 21] and MAYER [22] 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.

Fat-free mass and energy intake

Within the last 10 years an approach to the study of appetite control and energy balance has used a multi-level experimental platform in obese humans [23]; relationships among body composition, resting metabolism, substrate oxidation, gastrointestinal peptides, sensations of appetite and objective measures of daily energy intake and meal sizes, have been examined. Such an explicit multi-level approach has not previously been 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.**

Using this system 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 [24]. Contrary to what many would have expected, a positive association was observed between FFM and daily energy intake (EI), and also with meal size. In other words, the greater the amount of FFM in

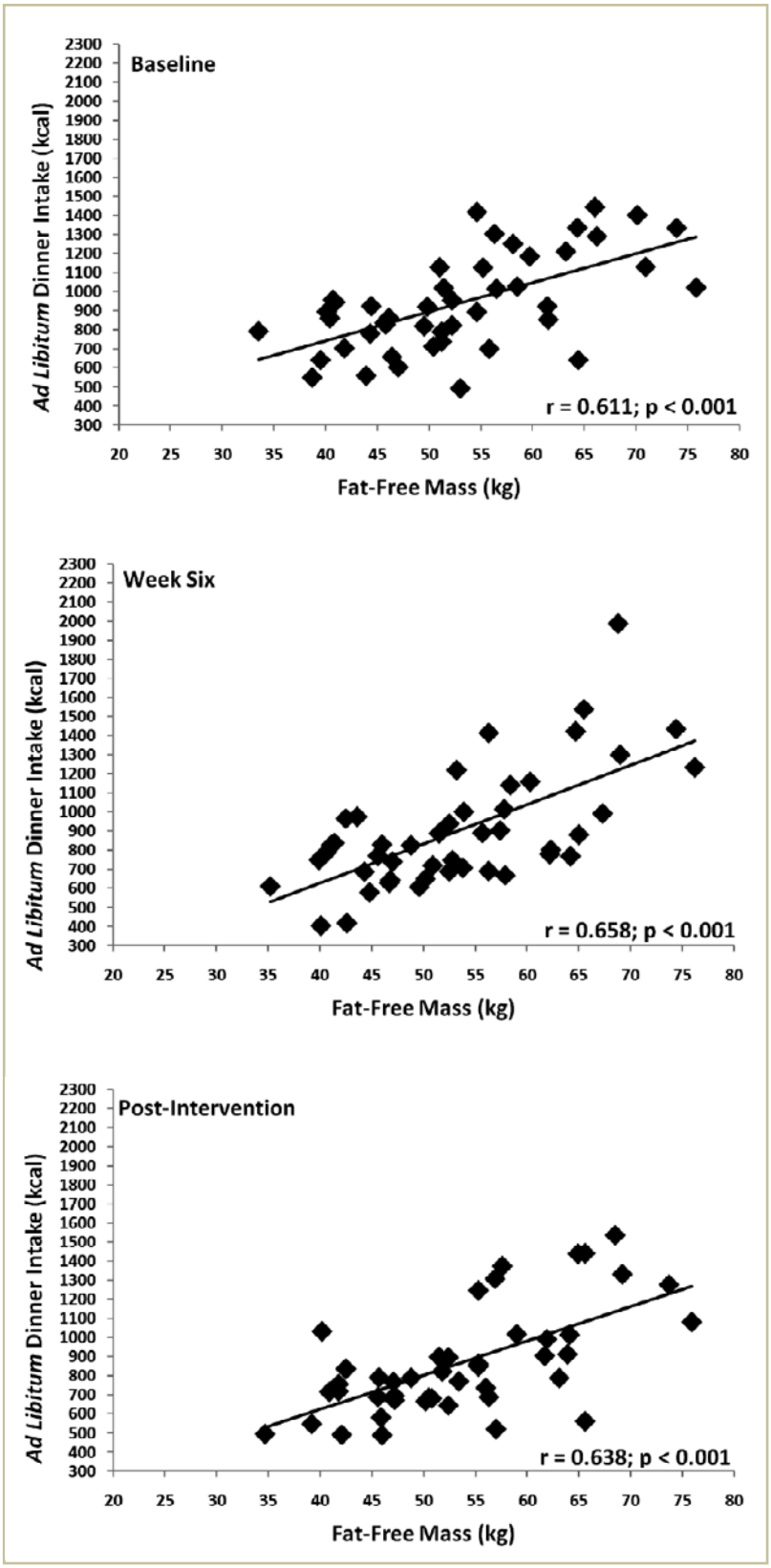

Abb. 1: **Relationship between fat-free mass and an objectively measured meal intake at 3 time points during a 12 week study** (adapted from BLUNDELL et al., 2015 [43])
Particpants (n = 46) are people with obesity.

a person, the greater was the daily energy consumed and the larger the individual meal size (in a self-determined objectively measured eating opportunity; ◆ Figure 1).

There was no relationship with 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 does not exert control over the amount of food selected in a meal, nor consumed over a whole day.

This outcome is clearly not consistent with an adipocentric view of appetite control. Moreover, the relationships were independent of gender. This means that gender does not explain the association of FFM with EI. On the contrary FFM can explain the gender effect; men (in general) eat more than women because they have greater amounts of FFM.

This association between FFM and eating behaviour has implications for an energy balance approach to appetite control, and for the relationship between energy expenditure (EE) and EI as described by Edholm [20, 21]. It is well established that FFM is the primary determinant of resting metabolic rate (RMR), and that RMR is the largest component of total daily energy expenditure [25]. 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 EE (60–70%) could be associated with the quantitative aspect of eating behaviour and with daily EI.

When this was examined [26], it was demonstrated that RMR was a significant determinant of the size of

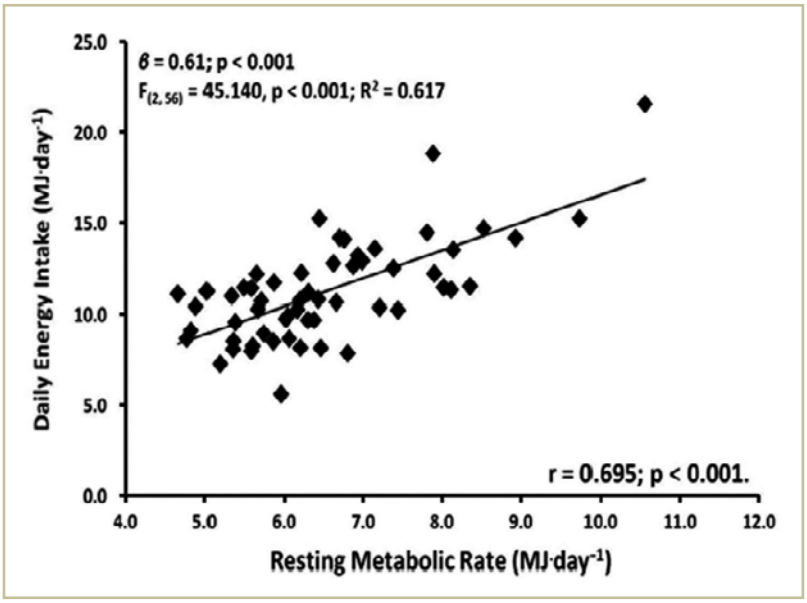

Fig. 2: **Relationship between resting metabolic rate (RMR) and total daily energy intake quantified through objective self-weighed food intakes** (taken from BLUNDELL et al., 2015 [43])

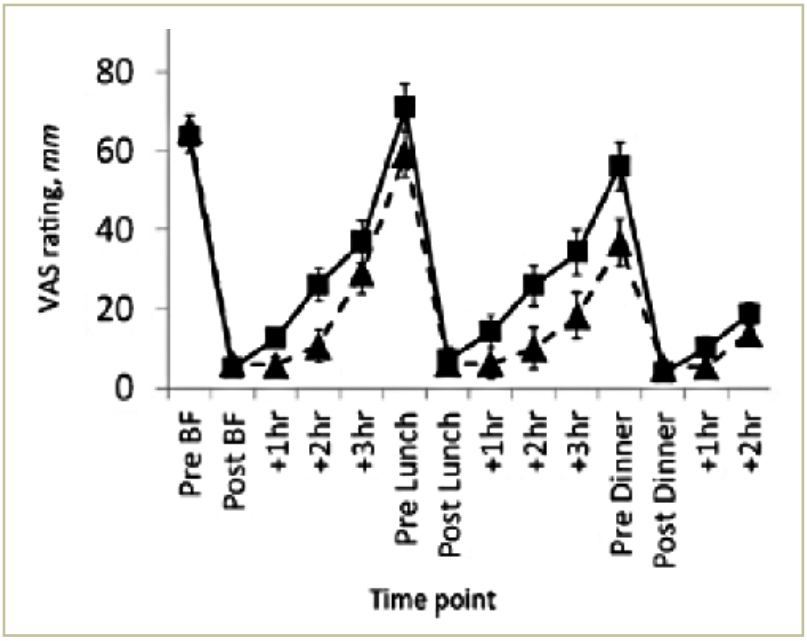

Fig. 3: **Profiles of ratings of hunger over the course of a day in people with high and low resting metabolic rates** (adapted from BLUNDELL et al. 2013 [43])
The dashed line represents individuals in the bottom tertile of RMR, and the solid line subjects from the top tertile of RMR. The time points are periods across the course of 10 hours across the day. Participants are overweight and obese adults (n = 41).
RMR = resting metabolic rate; VAS = visual analogue scale

a self-determined meal, and of daily energy consumed (when measured objectively and quantified; ◆ Figure 2). In addition, RMR was associated with the intensity of hunger objectively rated on hand held electronic data capture instruments [27]; ◆ Figure 3).

Consequently, these findings – that are broadly consistent with the early predictions of EDHOLM – have demonstrated an association between the major components of daily EE and daily EI. In other words, they demonstrate that appetite control could be a function of energy balance.

Importantly the major findings have been replicated in completely independent large data sets that included participants from different ethnic groups showing a huge range of energy intakes [28], and from participants of variable BMIs allowed to freely select their own diet under meticulously controlled semi-free living conditions [29].

Further confirmation of the relationship between body composition and appetite have been shown even with self-recorded daily food intakes [30], with changes in weight of young children [31] and in adolescents [32] These confirmatory reports suggest that the associations are robust and are not restricted to a particular group of people measured in a specific geographical location. Moreover the fundamental relationship of RMR and meal energy intake has been disclosed in the analysis of archived data of energy balance studies [33] This publication was followed by an editorial in the American Journal of Clinical Nutrition (AJCN) declaring that RMR and FFM are the major determinants of energy intake [34].

Considering the strength of the associations, these findings have implications for the role of FFM and RMR in appetite control. They suggest that the conventional adipo-

centric model should be revised to allow for an influence of FFM – in addition to FM. The adipocentric feature of the conventional model would be lessened. 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 [35]. As people overconsume (due to cultural obesogenic influences), fat mass increases and the consequential increase in leptin and insulin resistance weaken the inhibitory influence of fat mass on appetite. This amounts to a 'dis-inhibition', so that accumulating fat mass 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 [36]. In addition, clear positive associations of FFM and EI, and negative associations of FM and EI, have been demonstrated – but overlooked – in a comprehensive analysis carried out by Lissner et al. [37] more than 25 years ago. Therefore, on the basis of these recent findings a con-joint influence of FFM and FM on appetite control has been proposed[38]. This is set out in ◆ Figure 4. What are the implications of this formulation for the relationship between exercise and appetite control?

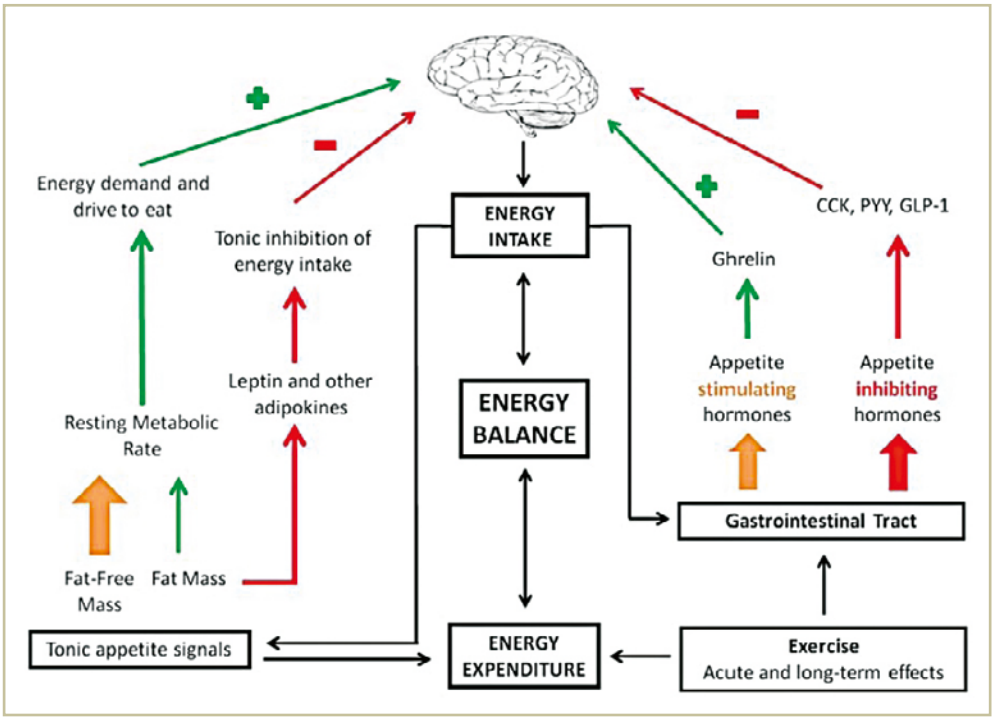

Fig. 4: **Formulation of appetite control**
In this formulation of appetite control there is a separation of tonic and episodic signals. Evidence suggests that a tonic signal reflecting the body's demand for energy is generated by FFM acting primarily through RMR. An inhibitory tonic effect is exerted through fat mass. As fat mass increases incrementally, this inhibitory input is weakened – through lowering of insulin and leptin sensitivity. The drive to eat is periodically interrupted by episodic signals in the form of peptides released from the GI tract in response to food consumption. The resulting pattern of eating is a consequence of the interactions between tonic and episodic processes.
FFM = fat-free mass; GI = gastrointestinal; RMR = resting metabolic rate

Implications for weight management

The proposal that FFM and RMR contribute to a physiological demand for energy that influences appetite is plausible and has implications.

First, it is one further reason to be dissatisfied with the use of measures of body weight (or BMI) in research and management of obesity. The recognition that FFM and FM have different functional properties in relation to appetite is a strong reason to use body composition (rather than the coarse variable of body weight) in both research and management of obesity.

For example, two individuals with similar BMIs (or body mass) may have quite different proportions of FFM and FM, and this would confer different properties on their physiological and behavioural responses. Those people with a high FFM should have a proportionately higher orexigenic drive to maintain a greater minimal meal intake (i.e. they should eat more) than people with less lean tissues and organs.

This means that obese people (with a greater lean mass in support of a large amount of adipose tissue), and people carrying a large muscle mass (field athletes, rugby players, swimmers etc) should have a stronger tendency to consume larger meals than smaller people. It follows that such people would have greater difficulty in tolerating dietary restriction (because the more energetically active lean mass would sustain a drive for a minimal amount of food).

This formulation explains why people with obesity who carry large stores of energy in their bodies continue to feel hungry and to eat even as they gain more weight. As FFM increases the drive to eat becomes stronger; at the same time the increase in FM would diminish the inhibition of appetite (a dis-inhibition) due to a combination of increasing

insulin and leptin insensitivity. Moreover, in elderly people subject to sarcopenia, a reduced lean mass would result in a diminished appetite.

However, it should not be inferred that the influence of FFM and RMR upon food intake is a cause of weight gain or obesity. This mechanism is a physiological way of achieving energy balance (ensuring that energy intake does not fall below the energy demand of the body). As such this is a mechanism for preserving body weight. The mechanism influences the strength of the drive to eat (feeding behaviour) and determines the level of hunger at the beginning of a meal (◆ Figure 1).

The amount of energy that is actually consumed is strongly modulated by the energy density of the food available [39]. When energy density is high this results in passive overconsumption [18] which has been identified as a major component of the obesogenic environment [19]. Consequently, a high RMR could influence weight gain by maintaining a high level of hunger, but a positive energy balance would depend on the energy density and palatability of the diet.

This is an example of a physiological regulatory process being undermined by the nature of the modern diet in many technologically advanced countries. In turn, the formulation proposed here can help to promote research to clarify the relative strength of biological and environmental variables that contribute to energy intake and to changes in body weight (and body composition).

Postscript

For over 20 years problems in the control of food intake have been interpreted against the background of the regulation of body fat. This view has been supported by the discovery and presence of a 'signal' (leptin), but has overlooked the complex adaptive capacity and functions of adiposity in humans [40]. In addition the much earlier proposals of Edholm, Widdowson and others were ignored until recent studies targeted that role of energy expenditure in influencing energy intake [41, 42]. The proposition that EE plays a central role in the drive to eat focuses attention on motivation, and positions appetite control within the framework of energy balance. EE and EI do not operate in separate domains of biological activity; they interact. It is proposed here that appetite control can best be understood against a background of EE. The components of EE – metabolic and behavioural – generate powerful energetic demands and exert clear effects on the drive to eat.

Prof. John Blundell
Chair of PsychoBiology
Faculty of Medicine and Health
University of Leeds
J.E.Blundell@leeds.ac.uk

Conflict of Interest
The authors declare no conflict of interest.

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