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Role of resting metabolic rate and energy expenditure in hunger and appetite control: a new formulation

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A long-running issue in appetite research concerns the influence of energy expenditure on energy intake. More than 50 years ago, Otto G. Edholm proposed that “the differences between the intakes of food [of individuals] must originate in differences in the expenditure of energy”. However, a relationship between energy expenditure and energy intake within any one day could not be found, although there was a correlation over 2 weeks. This issue was never resolved before interest in integrative biology was replaced by molecular biochemistry. Using a psychobiological approach, we have studied appetite control in an energy balance framework using a multi-level experimental system on a single cohort of overweight and obese human subjects. This has disclosed relationships between variables in the domains of body composition [fat-free mass (FFM), fat mass (FM)], metabolism, gastrointestinal hormones, hunger and energy intake. In this Commentary, we review our own and other data, and discuss a new formulation whereby appetite control and energy intake are regulated by energy expenditure. Specifically, we propose that FFM (the largest contributor to resting metabolic rate), but not body mass index or FM, is closely associated with self-determined meal size and daily energy intake. This formulation has implications for understanding weight regulation and the management of obesity.

Introduction

The control of appetite is complex and involves the coordination of inputs from both physiological and environmental sources. Early theoretical approaches were based on the idea that the control mechanism was dedicated exclusively to signals from glucose metabolism, amino acids or proteins, or adipose tissue. Respectively, these formed the glucostatic (Mayer, 1955), aminostatic (Mellinkoff et al., 1956) and lipostatic (Kennedy, 1953) hypotheses. More recent central nervous system models have emphasised inputs from adipose tissue and the gastrointestinal (GI) tract [along with input from sensory features of food (e.g. Schwartz and Morton, 2001; Keesey and Powley, 2008)]. The major signals include leptin from adipose tissue, and hormones such as ghrelin, PYY, glucagon-like peptide 1 (GLP-1), cholecystokinin (CCK), amylin and insulin from specialised cells in the GI tract or associated organs. Such models are said to account for the

regulation of appetite and, in turn, contribute to the regulation of body weight, through the identification of specific molecular signals carrying information from the periphery to a network of pathways centred on the hypothalamus. Interest in this type of formulation strengthened during the period when molecular biology began to take over from integrative physiology as an explanatory approach in biological sciences.

The major task facing any model of human appetite regulation is to account for the ongoing and recurring drive to eat, together with the intermittent suppression of eating via episodic satiety signalling and tonic inhibition (Halford and Blundell, 2000). In this Commentary, we outline the basis of a new formulation that explains how aspects of body composition and energy expenditure (EE) regulate hunger and appetite. This formulation is based on 15 years of psychobiological research with overweight and obese human subjects, and should help to contribute to understanding the relative impact of biological and environmental cues on body weight.

Energy balance approach to appetite control

An alternative to the molecular approach to appetite control has arisen from the study of energy balance: the inter-relationships between EE and energy intake (EI). In part, this view stems from the statement that any increase in EE will be met with an equivalent increase in EI (Mayer et al., 1956). Indeed, it was proposed that “the differences between the intakes of food [of individuals] must originate in differences in the expenditure of energy” (Edholm et al., 1955). Edholm’s experimental studies, however, revealed no

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correlation between EE and EI in any one single day, but there was a good correlation over 2 weeks. The lack of any relation in a day is perhaps not surprising, because any episode of EE (such as work or exercise) happening towards the end of the day would not leave time for a balancing effect of eating. Moreover, daily EE can fluctuate markedly from day to day according to individual behavioural tendencies. By contrast, resting metabolic rate (RMR) is the largest component of total daily EE and is quite uniform across the day and between days (Johnstone et al., 2005; Johnstone et al., 2006; Ravussin et al., 1982), and can therefore generate a more constant energetic demand. Consequently, activity-based EE and RMR probably have different influences on EI. It is plausible that EE from RMR could provide a tonic signal of energy demand that could act as a driver of daily EI. By contrast, physical activity EE (being of greater intensity and sporadic) would be expected to exert a mechanistically different type of control over appetite.

Impact of exercise on appetite control

Exercise can raise resting values of EE several fold depending on the volume, mode and intensity. In addition, the effect of exercise on various body systems means that it will have numerous physiological effects in addition to an increase in EE. Such effects include an overall increase in heart rate, and changes in the distribution of blood flow, sympathetic nervous system activity, gut hormone activity and in the absorption of nutrients. Therefore, it might be anticipated that there could be a number of separate effects on mechanisms influencing appetite. In addition, it can be presumed that a single acute bout of exercise would have different effects from continued daily sessions of exercise that would exert an increasing cumulative challenge to energy balance. A comprehensive picture therefore requires a comparison between various intensities of exercise over varying periods of time with measurement, wherever possible, of all variables in the energy budget. A central issue underlying the investigation of exercise is to determine [as Mayer proposed (Mayer et al., 1956)] whether or not exercise inevitably induces a compensatory response characterised by an increase in hunger – and in turn food intake – that would lead to an increase in EI that is sufficient to balance the increase in EE generated by exercise.

Over the last 15 years, we have developed an experimental platform based on a psychobiological approach and incorporating a multi-level system (Caudwell et al., 2011). In the last 10 years this has allowed the disclosure of relationships between variables in the domains of body composition [fat free mass (FFM), fat mass (FM)], metabolism (RMR, respiratory quotient, respiratory exchange ratio), GI hormones, food composition, psychological sensations, food behaviour, psychometric traits, nutritional composition and allelic variation in a single cohort of overweight and obese subjects. In summary, we find that acute (single) bouts of exercise do not lead to a consistent increase in the average food intake in the immediate post-exercise period or in the following 24 hours (for reviews see Blundell and King, 1998; Martins et al., 2007). However, there is considerable variability associated with appetite variables (Finlayson et al., 2009). As exercise sessions are repeated over periods varying from 9 to 16 days, a partial compensatory response begins to appear (Stubbs et al., 2004a; Stubbs et al., 2004b). There seems to be little or no compensation through a decrease in non-exercise-related activity (Turner et al., 2010). When exercise was

performed daily over a period of 16 days and total EE was measured using the doubly labelled water method, it was calculated that exercise raised average daily EE by 3.5 MJ and generated a 30% compensation in EI (Whybrow et al., 2008).

Several other studies have measured the impact of different exercise prescriptions over periods of 12 to 32 weeks (Church et al., 2007; Church et al., 2009; Donnelly et al., 2000; Donnelly et al., 2003). A typical 12-week study using overweight and obese men and women showed that exercise caused an average weight loss of 3.3 kg, indicating that the exercise EE was not fully compensated (King et al., 2008), but individual variability was very large [also observed in other studies (Church et al., 2007; Church et al., 2009) using lower intensities of exercise]. A key feature of this study was that exercise sessions (five times per week for 12 weeks) was fully supervised and the EE measured so as to rule out the possibility of the outcome being influenced by lack of compliance. Subsequent investigations indicated a dual action of exercise on appetite control that partly explained the large variation in body weight change. The exercise caused a significant increase in fasting levels of hunger (a compensatory response), but this was highly variable between subjects. However, there was an associated increase in the post-prandial satiety signalling from meals, indicated by a change in the satiety quotient (Green et al., 1997; King et al., 2009; Martins et al., 2010). Consequently, the effect of exercise on appetite comprises two components: one generating a tonic stimulation of appetite and the other a counteractive meal-related episodic inhibition. The second response seems to be related to changes in either the release of, or sensitivity to, GI peptides (Broom et al., 2007; Martins et al., 2010). These effects of exercise-related EE on appetite are likely to be quite different from any effect related to the lower intensity and more uniform tonic action of RMR.

Body composition and appetite

Using the multi-level experimental platform described above (Caudwell et al., 2011), it has been possible to observe the relationships between variables in separate domains (biological, nutritional, behavioural, metabolic), all measured objectively and to similar degrees of accuracy. Importantly, the measurements have been made simultaneously in the same group of overweight and obese people. This has enabled the disclosure of unexpected associations between body composition and appetite. A little more than 10 years ago, the discovery of leptin was decisive in focussing attention on adipose tissue as a major controller of energy balance (EI and EE). Several models of appetite regulation have described the role of leptin (as a signal from adipose tissue) in influencing hypothalamic neuropeptide pathways that control the stimulation and inhibition of food intake (Morton and Schwartz, 2001; Badman and Flier, 2005). With most attention directed to the role of adipose tissue (or FM), it can be considered that FFM has become the 'forgotten variable', even though it is clearly important under some conditions (Dulloo et al., 1997). It is therefore interesting that detailed analysis of body composition and appetite variables using the multi-level platform have demonstrated that FFM, but not FM or body mass index (BMI), is strongly correlated with meal size and daily EI (Blundell et al., 2012). The strong implication of this relationship is that some privileged molecules arising from FFM, or some physiological consequences that reflect the activity of FFM, act as a signal to drive food intake.

RMR as a driver of food intake

Considering total daily EE, it is noticeable that RMR is its largest component (50-70%), of which FFM is the major contributor, accounting for about 60-70%, whereas FM accounts for as little as 5-7%, with gender and age being minor components (Johnstone et al., 2005). Consequently, it is plausible that RMR could act as a mediating variable to reflect the influence of FFM on appetite control. Accordingly, in a series of analyses – based on the multi-level platform described earlier – we have demonstrated that RMR is positively associated with meal size and with daily EE (note that the relationship between RMR and total daily EI mirrors the relationship between FFM and total daily EI, which is shown in Fig. 1A). In addition, RMR is also a predictor of fasting levels of hunger and influences the profile of hunger across the day (illustrated by Fig. 1B, which shows data for the closely correlated parameter of FFM). The strong implication of these relationships is that RMR – as a measure of EE – reflects a physiological demand for energy that acts as a ‘driver’ of food intake. This is plausible and constitutes a demonstration of Edholm’s proposal that differences in food intake must originate in the differences in energy expenditure (Edholm et al., 1955). Although Edholm did not demonstrate a relationship between EI and the (highly variable) total daily EE (within any single day), we have demonstrated a clear relationship with the more stable and uniform factor of RMR. The existence of a relationship (within a single day) between RMR and daily EE would depend on the total volume and intensity of the ‘discretionary’ physical activity component of EE, and upon the relative strengths of the dual processes of appetite control generated by exercise (see above).

A new formulation for appetite control

Most recent models of appetite regulation have drawn attention to the roles for adipose tissue and GI peptides. However, these models are better able to account for the inhibition of eating rather than its initiation. The models embody the view that tonic and episodic inhibitory factors modulate an ‘intrinsic’ orexigenic drive to eat. This endogenous drive is not usually well defined. However, in early theorising about appetite control, equal emphasis was given to the inhibitory and excitatory (drive) features of appetite. The latter was conceptualised as Morgan’s ‘central motive state’ (Morgan, 1943), and in Stellar’s embodiment of this in an excitatory centre in the hypothalamus (Stellar, 1954). One major issue was to explain what gave animals (including humans) the energy and direction that motivated food seeking. In light of knowledge about the physiology of homeostasis, it is plausible that a drive for food arises from the energy used to maintain physiological and metabolic functioning of the body. Consequently, there is a drive for food generated by EE. This resonates with the proposal of Edholm (Edholm et al., 1955), and represents a merging of parallel thinking from psychobiologists working on animal behaviour and physiologists working on human energy balance.

Together with modern (post-leptin) discoveries, it can be suggested that the physiology of appetite regulation comprises three components: a tonic drive for food arising from the physiological demand for energy; a tonic inhibition arising from signals of energy storage (mainly adipose tissue); and episodic signals arising from the mouth and GI tract in response to the periodic consumption of food. This last category is primarily inhibitory – from the classical

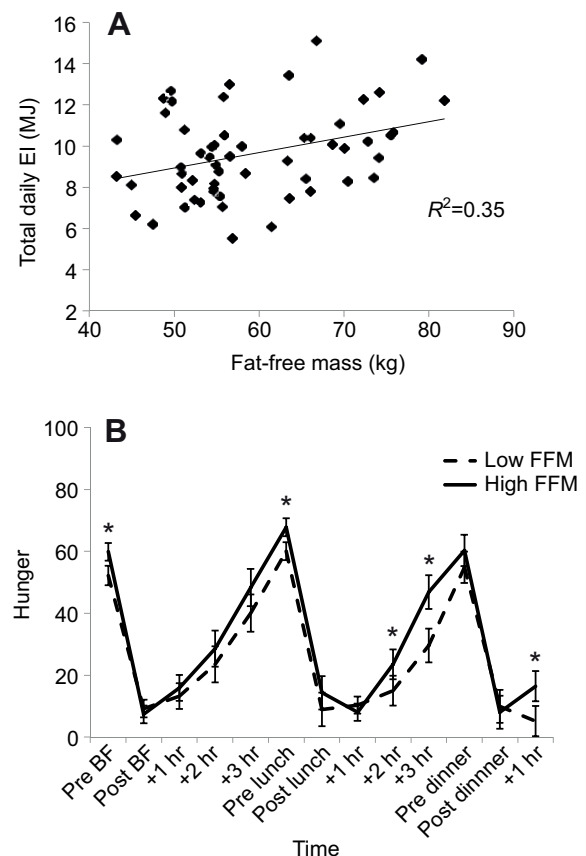


Fig. 1. Relationship between FFM, daily EI and daily profile of hunger.

(A) Scatter plot shows the relationship between FFM and daily EI in a group of 41 overweight or obese men and women. The regression is significant ($P<0.001$). The values represent the average values from objective measures taken at specific probe days at weeks 0, 6 and 12. (B) Daily hunger profiles for individuals with the highest FFMs (eight women and five men) and those with the lowest FFMs (eight women and five men). The groups were formed by dividing the whole sample into tertiles of FFM and comparing the upper and lower tertiles (but keeping similar numbers of men and women in each tertile). The difference between the area under the curve for the two profiles is significant ($P<0.01$); asterisks indicate time points at which the profiles are significantly different. The profiles indicate that hunger in the high FFM group is greater before the onset of a meal and in the period leading up to the meal, but not at the end of the meal. This is consistent with the fact that the high FFM individuals eat a larger meal, which would return hunger to a level appropriate for full satiation. Together, data displayed in A and B indicate that FFM is positively associated with daily EI and with daily hunger levels. Additionally, because RMR is highly and significantly correlated with FFM, the relationships between RMR, EI and hunger very closely match those for FFM shown in the figure. Data derived from studies reported by Blundell et al. (Blundell et al., 2012). BF, breakfast. Hunger is measured in units on a 100 unit scale on the screen of a hand-held PDA.

satiety signals – but also excitatory (signals registering food palatability). This formulation is shown in Fig. 2.

The investigations reviewed here have provided evidence for the physiological drive for food by demonstrating a specific association of FFM, but not FM, with objectively measured food intake variables (Blundell et al., 2012). In turn, this means that the energy required to maintain the body’s lean tissue mass – thus preventing wasting – creates a physiological demand that determines a

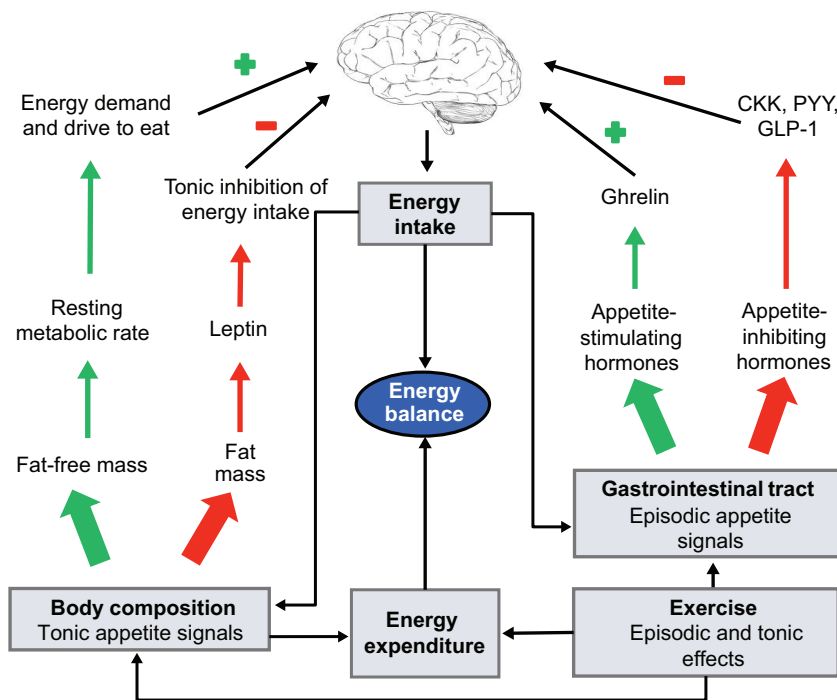


Fig. 2. A new formulation for appetite control. A proposed tonic signal for the drive to eat that reflects the body's demand for energy arises (mainly) from FFM and RMR. In turn, this drive is under tonic inhibition from leptin, whose action reflects the amount of stored energy reserves in the body. As the amount of 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 that are 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 physiological signals. The figure also illustrates the postulated effect of exercise on appetite control. Prolonged exercise displays a dual-process action by stimulating hunger (an effect that is highly variable between individuals) but also by increasing post-prandial satiety signalling (King et al., 2009) through an effect on GI peptides (Martins et al., 2010). See text for further description.

minimal level of EI at meals and over the day. It is worth noting that the relationship between FFM and EI is consistent with the amino-static hypothesis put forward more than 50 years ago by Mellinkoff et al. (Mellinkoff et al., 1956), and with the more detailed proposal of a role for the protein-stat mechanism described by Millward (Millward, 1995).

A further step in the formulation comes from the demonstration that RMR is also strongly correlated with objectively measured self-determined EI (Caudwell et al., 2011). This could be expected from the recognition that FFM is the largest contributor to RMR (accounting for approximately 60% in our studies). It is worth noting that EE arising from FFM receives contributions from the liver (20%), brain (20%), heart (11%), GI tract (9%) and skeletal muscle (20%) (Elia, 1992). Therefore, the physiological demand is created by the need to provide energy to maintain the functioning of the body's vital systems. Moreover, the EE from these organ systems is maintained across the day and is reflected in the relative stability and uniformity of RMR within and between days. Consequently, the proposal that RMR acts as a 'physiological drive' (or is a marker of such a drive) underlying appetite is both parsimonious and plausible. This formulation is quite consistent with those models of appetite regulation that assign major roles to adipose tissue and the GI tract. However, it also draws attention to other aspects of body composition as determinants of appetite.

Combined with other findings, this interpretation provides mechanistic explanations for the link between FFM, RMR and eating behaviour. This formulation can incorporate an extended role for leptin and is in keeping with a widening ergostatic function of additional adipokinetic hormones in energy homeostasis, as envisaged by Frühbeck and Gómez-Ambrosi (Frühbeck and Gómez-Ambrosi, 2001). The idea of FFM creating an orexigenic or ergostatic drive has also been proposed in other descriptions of the appetite regulatory system (Halford and Blundell, 2000). It

should also be recognised that hormones and factors collectively known as 'adipokines' exert effects not only on adipose tissue but also on skeletal muscle (Sáinz et al., 2009), and that differential expression of genes and pathways that are intrinsic to skeletal muscle might also be involved (Wu et al., 2011). Consequently, it can be envisaged that leptin could act as a major tonic inhibitory signal (to dampen the physiological drive) and also as an ergostatic factor through its influence on FFM.

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 the 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 the research and management of obesity. For example, two individuals with similar BMIs (or body mass) might 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). Moreover, in elderly people subject to sarcopenia, the 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 EI 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 (Fig. 1B). The amount of energy that is actually consumed is strongly modulated by the energy density of the food available (Ello-Martin et al., 2005; Rolls, 2000). High energy density of food results in passive overconsumption (Blundell and Macdiarmid, 1997), which has been identified as a major component of the obesogenic environment (Swinburn et al., 2011). 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 EI and to changes in body weight (and body composition). Moreover, we envisage that the system would adapt to progressive changes that occur in body composition over time and could influence energy balance (e.g. Hall et al., 2011). The most likely scenario is that any increase in FFM (and RMR) would increase the drive to eat. This amplifying effect on EI would mean that weight gain becomes part of a positive, rather than a negative, feedback system. Increasing body weight therefore could facilitate further weight gain and increase the difficulty of weight loss or maintenance.

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COMPETING INTERESTS

The authors declare that they do not have any competing or financial interests.

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