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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 that 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.

1. 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 initiation and inhibition of food intake e.g. [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

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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 [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 tissue. 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 aetiology 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 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 worldwide 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 aetiology and management of obesity, and the obesity epidemic, that are difficult for the adipocentric theory to explain.

2. 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 objective 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 does not provide data of sufficient accuracy to be used in assessments of the energy balance budget [31,32].

3. 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 Fig. 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.

4. 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

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