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The drive to eat in *homo sapiens*: energy expenditure drives energy intake

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Highlights:

- FFM and RMR can be considered as major determinants of energy intake in humans.
- EE generates a drive to eat to support vital physiological functions.
- Activity EE shows high individual variability and creates a more variable drive.
- Appetite control can be conceptualized within an energy balance framework.
- Tonic and episodic processes interact within an appetite control system.

Abstract

The drive to eat is a component of appetite control, independent of the omnivorous habit of humans, and separate from food choice, satiety and food reward. The drive forms part of the tonic component of appetite and arises from biological needs; it is distinct from episodic aspects of appetite which are heavily influenced by culture and the environment (and which reflect the omnivorous habit). It is proposed that the tonic drive to eat reflects a need state generated by metabolic energy expenditure (EE) required to maintain the functioning and integrity of vital organs. Specifically, the tonic drive is quantitatively associated with fat-free mass (FFM) and resting metabolic rate (RMR). A rational proposition is that high metabolic rate organs (such as heart, liver, kidneys, brain) together with skeletal muscle generate a metabolic need which drives energy intake (EI). The basic phenomenon of a relationship between FFM, RMR and EI, first published in 2011, has been substantially replicated and there are at least 12 concordant published studies carried out in 7 different countries (and 3 continents) with various ethnic groups of lean and obese humans. These studies demonstrate that FFM and RMR represent major determinants of the drive to eat, and this is rational from an evolutionary perspective. The EE of bodily movements through skeletal muscle activity (namely physical activity and exercise) represents another driver which is clearly but more weakly associated with an increase in EI. This account of appetite control, developed within an energy balance framework, is consistent with the apparent inexorable escalation of fatness in individual humans, and for the progressive increase in the prevalence of obesity which, among other factors, reflects the difficulty of managing the biological drive to eat.

Keywords: appetite, energy intake, energy expenditure, fat-free mass, resting metabolic rate, drive

The drive to eat within an energy balance framework

Energy balance implies an interplay between energy intake (EI) and energy expenditure (EE). However, early research on appetite (say between 1950 and 1970) envisaged appetite control as self-contained, undergoing regulation in relation to the postulated regulation of body weight. The terms 'food intake regulation' and 'body weight regulation' were widely used as explanatory principles. Taken together, some dysregulation in food intake or body weight was seen as primarily responsible for obesity (together with low metabolic rate and low adaptive thermogenesis). Within this environment, the drive to eat was located in the brain; initially in specific localised centres, later in neurochemical pathways or in clusters of cell bodies of neurotransmitters and synaptic receptors. Throughout this period, in the field of ingestive behaviour, there was little, if any, reference to EE. Operating in parallel, the field of energy balance physiology was concerned with EE (measured through indirect calorimetry) sometimes as a consequence of the effect of fixed energy loads of food. These physiologists had little interest in the measurement or observation of eating behaviour, whilst psychologists and behaviour scientists had little interest in the use of calorimetry. During this period, the study of appetite was heavily influenced by research on laboratory rats which was used as a basis for understanding the actions of humans. Consequently, the study of appetite control was isolated ideologically and methodologically from the study of energy balance.

However more than 60 years ago, two strands of research foresaw the value of simultaneous consideration of EE and EI in humans. On the basis of a study of jute mill workers in Calcutta, Mayer described a simple but insightful scheme in which the amount of food eaten was associated with the sedentary or active nature of the occupational work performed [1]. Under conditions of high EE (heavy work) the high level of food eaten was closely linked to the high level of energy used in work. However, this tight connection was lost in the sedentary state when eating became detached from physiological need and body weight became elevated [2, 3]. A more definite statement describing EI and EE arose from a series of studies of Edholm, Widdowson and others in which simultaneous measures were made of daily EI and physical activity EE in army cadets under closely observed and monitored conditions [4, 5]. Edholm drew explicit conclusions from this body of work with specific implications for appetite. Indeed, Edholm's work was motivated by the 'desire to find out more about the mechanisms which relate intake to expenditure – what regulates appetite, in fact' [4](p 286). However, both of these (now) classic studies were ignored or forgotten for almost half a century.

The first deliberate studies involving simultaneous physiological measurements of EE and objective and quantitative measurement of human eating behaviour began to be carried out about

25 years ago, often for the assessment of the impact of exercise on appetite control [e.g. 6]. These small-scale studies developed into a genuine energy balance framework for investigating appetite control [7-9] and indicated reciprocal relationships between EE and nutritional EI.

Fat-free mass and resting metabolic rate are major determinants of energy intake

Although the work of Edholm focussed on activity EE, it inspired thinking about the role of whole-body EE and metabolic EE (or resting metabolic rate; RMR) in particular. In turn, owing to the relationship between RMR and body composition, this led to hypotheses about the possible relationships of appetite with body fat mass and fat-free mass (FFM). The first deliberate and purposeful investigations of these issues occurred over 10 years ago. The first publication described two separate 12-week interventions in participants with overweight and obesity using a biopsychological systems approach in which near simultaneous measurements were made of body composition, RMR (through indirect calorimetry), quantitative and objective measurement of self-determined daily and meal-time food intake, and ratings of the perception of hunger and other appetite sensations [10, 11].

The outcome of these studies demonstrated that FFM, but not fat mass was positively associated with daily EI and with meal size [10, 11]. This work received rapid confirmation [12]. It is worth noting that these studies served as a test of the widely regarded lipostatic hypothesis of appetite regulation. In fact, fat mass was unrelated or weakly negatively related to EI. Also of interest is the fact that the presentation of these results serendipitously brought to light a much earlier publication which had reported identical conclusions but which were not immediately apparent because the work was investigating a different issue (namely the validity of EI in people with obesity) [13]. These authors reported that *'energy requirement was positively associated with lean mass ($p<0.0001$) whereas fat mass added no predictive value to the model' (p 324); and that 'the emphasis of research that focuses on the relationship between EI and obesity is misplaced because EI appears to be a direct function of lean mass rather than adiposity' (p 324).* These relationships were effectively hidden until re-discovered by the current first author in 2014 (25 years after the original study had been published) during a scientific discussion with David Levitsky (one of the authors of the 1989 work). The association between lean mass (fat-free mass) and EI reported in 1989 anticipated later research and demonstrated a relationship similar to that later demonstrated through the Leeds approach (originally published in 2011) and later in collaboration with Rowett Research Institute, Aberdeen and shown in Figure 1. We recognise that FFM cannot be used interchangeably with lean mass, but for convenience in this review we do not insist on separate definitions.

It is also important to point out that the inter-relationships among body composition variables and EI are statistical associations and not biological pathways (see [14]). Although we do believe that biological processes link these variables, there is insufficient evidence at the moment to be decisive about this. Conceptually we do not believe the relationships are linear (this would be unusual in biology) but we have limited information to determine what type of relationship exists. Our understanding, based largely on the work of Muller and Heymsfield (and previously described in Stubbs et al. [15]), is that as weight is linearly gained fat mass is disproportionately increased relative to FFM. It can be inferred that if two people have similar FFM but very different fat mass then energy expenditure will be different by a (largely) predictable amount. The person with a higher fat mass will need a higher energy intake to maintain their higher total mass. Moreover, a model that accounts for the potential effects of FFM, RMR and fat mass on appetite and EI needs to account for the apparent change of direction in the relationship among these variables during positive and negative energy balances. This issue has recently been discussed in Stubbs et al. [15].

In passing, it is worth drawing attention here to the alignment of the current proposals and the general concept of allometric scaling [16]. Indeed, as physiologists have pointed out: 'size matters'. We recognise the influence on our thinking of the classic studies of Kleiber [17] and the famous 'mouse to elephant curve' of Brody [18].

----------*Figure 1 here*----------

It is now recognised that one of the most important features related to the validity of scientific outputs is that they should be subject to replication [19, 20]. It is therefore important to note that this type of relationship between FFM and EI has been replicated in several separate studies over a period of 8 years and on people in at least 9 different countries: England, USA, Canada, Scotland, Estonia, Ireland, Spain, Singapore and Australia, and in 4 continents [10, 12, 14, 21-31]. Consequently, the relationship is robust and seemingly independent of the culture and the environment. Moreover, the clear positive association of FFM but not fat mass, prompted a line of thinking more closely related to the propositions of Edholm regarding EE and EI. Considering total daily EE, it is widely observed that RMR is the major component (50 – 70%) to which FFM contributes about 60 – 70%, whereas fat mass accounts for as little as 5 – 7% [32]. [However, as a reviewer has pointed out, this statement about fat mass % applies only to certain scenarios. In individuals with a very large amount of adipose tissue, the contribution of fat mass to RMR may be much closer to that of skeletal muscle.] It is nonetheless a reasonable hypothesis that RMR would be associated with EI. This was initially shown in 2013 where RMR was strongly related to both meal size and total daily EI under exposure to high or low energy dense foods [22]. The effect was

142 therefore independent of the food environment and has been replicated in several studies [21, 27,
143 31]. This relationship is shown in Figure 2.

144 ----------*Figure 2 here*----------

145 The publication of the outputs of archived data from the laboratory of Doucet in Ottawa
146 [21], strongly confirming earlier research from the Leeds group, prompted an editorial in AJCN by
147 Lam and Ravussin [33], stating that '*…RMR and FFM are the strongest determinants of energy intake*
148 *– largely confirming previous correlations*..' (p 1169). This relationship is therefore robust and has
149 been replicated on several different populations and ethnic groups from 4 continents.

150 These findings have led to a formal statement of the current theory in which RMR
151 '*represents a physiological source of hunger that drives food intake at a level proportional to basal*
152 *energy requirements. This long-term (tonic) signal of energy demand would help 'tune' energy intake*
153 *to energy expenditure, and help ensure the maintenance and execution of key biological and*
154 *behavioural processes'* [34] (p 1618). It is relevant here to consider how various components of body
155 composition contribute to metabolic activity. As noted by Javed et al [35], FFM is a heterogeneous
156 compartment of body composition of which the constituents have a wide range of metabolic rates.
157 Compared with skeletal muscle with an RMR of 14.5 kcal/kg/day; that of heart and kidneys is 33-fold
158 higher (440 kcal/kg/day), of the brain 18-fold higher (240 kcal/kg/day), and of the liver 15-fold higher
159 (200 kcal/kg/day). In contrast, adipose tissue is 4.5 kcal/kg/day. Collectively, the brain, liver, heart
160 and kidneys account for 60 – 70% of RMR (80% if lungs are included [36]) in adults whereas their
161 combined weight is <6% of total body weight. Skeletal muscle accounts for 20 – 30% of RMR but
162 comprises 40 – 50% of body weight [35](p 907). Consequently, the proposition can be refined to
163 state that the *energetic need generated by high metabolic rate organs such as heart, brain, liver,*
164 *kidneys (and skeletal muscle) is the source of the drive to eat; in turn, this leads to feeding behaviour*
165 *that provides the essential energy for maintaining these organs.*

166 Importantly, the coefficients of metabolic activity of specific organs have been recalculated
167 using the MRI procedure [37, 38]. In order to interpret this metabolic activity for its potential as a
168 biological driver, one of the reviewers of this submitted article suggested calculating the absolute
169 and proportional contributions of specific organ activity to total resting EE. These calculations are set
170 out in Table 1. Notably, a sub-group of the present authors is currently conducting an MRI study to
171 determine the contribution of metabolic activity of specific organs as proportional drivers of EI.

Table 1. Metabolic activity of specific tissues expressed in different ways so as to indicate how the energy expended could be related to EI. The figures have been calculated for a woman weighing 66 kg.

Tissue	Metabolic rate (kcal/kg/day)[1]	Weight (kg)[1]	% body weight	Specific metabolic rate (kcal/day)	% of resting energy expenditure
Adipose tissue	4.5	20.9	31.7	94.1	6.7
Skeletal muscle	13.1	21.4	32.4	280.3	19.9
Brain	241.0	1.27	1.9	306.1	21.7
Liver	201.0	1.27	1.9	255.3	18.1
Kidneys	442.0	0.25	0.4	110.5	7.8
Heart	442.0	0.26	0.4	114.9	8.1
Residual	12.1	20.6	31.2	249.3	17.7
Total	**1355.7**	**65.95**	**100**	**1410.4**	**100**

[1]Data from Wang et al. [38]

Also relevant to the theoretical position established here is the recently developed concept of functional body composition [39-41], which describes relationships among components of body composition and their physiological and metabolic actions. Accordingly, we propose that an appropriate next step in understanding the biological basis of the drive to eat is to extend the analysis if functional body composition into the realm of (eating/feeding) behaviour.

Energy expenditure and energy intake: the role of behavioural activity

The work of Edholm was intended to establish a fundamental relationship between EE and EI as a basis for understanding human appetite [4]. It was further postulated that '*the differences between the intakes of food must originate in the differences in energy expenditure' (*p 297). As summarised above many studies now concord in finding that the energy expressed as RMR is 'a major determinant of energy intake' [33]. However, it can also be surmised that the energy expended in physical activity behaviours could also act as a driver of feeding behaviour. Indeed, the studies of Edholm were on the associations between the energy consumed by daily physical activity and the energy eaten in food. In addition, the scheme proposed by Mayer and others [1] incorporates the

idea that a person with a high workload resulting in greater total daily EE is likely to have a greater EI than a person whose workload resulted in a lower total daily EE.

This relationship can be investigated through various research designs. For example, individuals can be selected initially for habitual high and low levels of physical activity (measured by self-recording e.g. IPAQ or by wearable activity monitoring devices) and their food intake measured [42]. Alternatively, a large group of unselected people can be subjected to simultaneous measurements of physical activity EE and freely selected food intake [23, 43]. A fixed amount of daily exercise can be coercively imposed over several weeks and self-determined food intake measured [e.g. 44, 45]. The appetite response can be measured objectively in response to exercise delivered at high and low levels of energy flux [46]. All of these procedures can reveal whether or not EI responds to a raised level of behavioural EE. However, it must be kept in mind that there are likely to be differing outcomes according to whether the exercise is acute (single episodes) or chronic (habitual).

It should be mentioned at the outset that physical activity behaviours display a high degree of inter-individual variability [42, 43, 47]. In principle therefore, with careful behavioural measurement, it should be quite feasible to demonstrate differences in EI if they exist. The data for a group of individuals showing variations in activity EE is shown in Figure 3 [42, 48], together with the relationship between activity EE and laboratory-measured meal size (Figure 4) [48]. Figure 5 shows the objectively-measured daily EE in a group of 242 individuals showing large variations in their daily behavioural activity EE (measured by the FLEX heart rate procedure) [23].

----------*Figure 3 here*----------

----------*Figure 4 here*----------

----------*Figure 5 here*----------

Consequently, there is good evidence that variations in physical activity EE are positively related to daily EI. This relationship is consistent with the proposition that EE acts as a driver for EI. However, the association is weaker than the relationship of RMR with EI. There are good reasons for this. First RMR represents a 'tonic' driver and is fairly stable from day to day; it therefore exerts a fairly uniform and enduring action. In contrast, activity EE has an episodic character and may vary from day to day, and within any day. Physical activity also varies in intensity and structure, and

therefore in the amount of bodily movement involved. Physical activity is also influenced by the culture and the variability in the lifestyle of people. It is therefore more sporadic and unpredictable. It also normally accounts for a much lower proportion of total daily EE than does RMR. Therefore, the quantitative 'mass action' effect of bodily activity will inevitably be smaller than that of RMR. However, activity EE does, of course, have the potential to exert a very powerful effect on the EI of certain individuals, such as some cyclists and other athletes, operating at extremely high levels of daily energy expenditure [e.g. 49]. However, as noted above, there is unlikely to be any enduring eating behaviour change in response to an acute episode of exercise. Changes in appetite will ensue when the exercise becomes habitual [50].

Building on these demonstrated relationships, a recent review has drawn attention to the potential importance of various aspects of skeletal muscle activity for understanding appetite control [51]. For the moment, it can be deduced that the relationship of bodily skeletal muscle activity (as measured by adjustments in EE) is consistent with the proposal of a role for EE (metabolic and behavioural) as a driver of EI.

Considering more general aspects of appetite research, much less attention has been given to the effects of physical activity and EE than to the effects of nutritional composition, food structure, palatability and contextual factors. As a reviewer of this manuscript pointed out, there is much more to be understood about the interactions between physical activity EE and the behaviour of consumers to select and eat food.

In addition, it is worth questioning here whether any light can be shed on the relationships among body composition, metabolism and EI by considering studies on bed rest or immobilisation. We know from observations in energy and macronutrient intake during prolonged bed rest in a head-down tilt position [52] that body weight declines during bed rest and increases on recovery. EI is affected in the same way. Also, there is a tendency for FFM to decrease slightly and fat mass to increase during bed rest in healthy subjects [53]. Therefore, further study of bed rest/immobilisation could provide an opportunity to disclose body composition/activity EE, and EI relationships.

Is the drive to eat regulated?

It is noticeable that the foregoing account of the relationship of EE and EI is supported by its evolutionary functional value. That is, the need state generates a drive for eating behaviour that ensures that humans ingest – at least – sufficient energy to match energy requirements when operating close to energy balance. [This mechanism may be over-ridden in states of negative energy balance when the functional integrity of tissues and organs are challenged [15]]. This relationship

may acquire the meaning of a type of biological rule; however, it does not require the mediation of any form of regulation. This means that the energy balance approach proposed here is much different from traditional biomedical thinking about appetite control which is predicated on the idea that the purpose of appetite is to achieve the regulation of body weight or body adipose tissue. This principle is incorporated in the lipostatic hypothesis, or the adipocentric theory of appetite often attributed to the work of Kennedy [54]. However, it can be questioned whether the claim for the existence of a regulatory principle is theoretically justified.

One of the dominant explanatory principles in the field of appetite, energy balance and obesity is the concept of biological regulation. This is usually stated as body weight regulation or, more commonly, adipose tissue regulation. These terms are closely linked to a doctrine of energy homeostasis which implies that energy (in and out) is controlled in the interests of a higher objective – namely regulatory control of components of body composition. A comparison is often made with the principle of glucose regulation. These terms give the impression of a precise control mechanism operating within a biological system. It is implied that when these mechanisms go awry the result is obesity which arises from a fault of regulatory or homeostatic principles. However as Speakman [55] has pointed out 'if body weight is under physiological regulation how come we have an obesity epidemic?' (p 88).

Perhaps we should keep in mind that biological regulation of a system is not the only principle through which a system can deal with some perturbation or unpredictability. An evolutionary principle is that a system will have adaptive properties which contribute to biological organisation, but which does not need to incorporate a process of regulation. As argued by Bich et al [56] 'biological systems exhibit a wide range of mechanisms and strategies to ensure their survival under variable conditions' (p 238). These writers point out that there is no agreement on what regulation actually means, and the current use of the concept is ambiguous and mixes fundamentally different biological capacities. Adaptation, feedback, dynamic stability might be principles that could be used as alternatives to regulation and which do not embody the absolute certainty of the attainment of some fixed internal state (body mass, fat mass etc). Some researchers have questioned whether the 'existence of lipostatic regulation of body fatness is an illusion' [57].

These arguments question whether the notion of regulation (for example, of fat) is essential to an understanding of the control of the behaviour of energy intake (food consumption). Much of the justification for the use of terms such as fat regulation, adipostasis and energy homeostasis emanate from studies on laboratory rodents whose uniform laboratory environments and lifestyles are far removed from the ecological and evolutionary pressures that frame an understanding of the

relationship between body fat and food in humans. As eloquently described by Pond [58] and Wells [59] body fat has many functions which differ according to the lifestyle and evolutionary development of the particular species. Also Speakman and others [57] have pointed out with reference to adipose tissue that 'it is likely that different species under different evolutionary scenarios will have evolved systems appropriate to their own circumstances' (p 483). For example, the control of adipose tissue in migratory species or in hibernators cannot be used as a model for humans; the functions of body fat show considerable diversity even amongst mammals. In humans, adipose tissue may have flexible capacity which allows an adaptation to environmental exigencies and unpredictability; such a function does not embody a requirement for fat to be regulated at some fixed value. One likely evolutionary function of human fat is to maximise biological (survival) advantage in the face of environmental uncertainty. Such uncertainty is inherent in the heterogeneous nature of the food environment and the diversity of feeding behaviour.

It is relevant that the reaction of body weight to a perturbation in energy balance is asymmetrical; there is a strong defence against an energy deficit but weak defence against an energy surfeit or positive energy balance. Over the years there has been a strong urge to explain why people can gain weight with apparent ease but – even with strong motivation – fail to maintain hard earned weight loss. If any component of body composition is subject to regulation, it is more likely to be lean mass rather than fat mass. There is persuasive evidence from an analysis of the classic study of starvation by Keys that lean mass, rather than fat mass, may be the key component of body composition driving food intake (together with prior energy deficit) in the recovery from excessive weight loss [60, 61].

This research again implicates lean mass rather than fat mass as a major controller of energy intake. However, it involves men recovering from weight loss, rather than a situation approximating energy balance conditions. Considering more usual situations, it has recently been concluded that 'faced with the present lack of direct evidence for biological control of body weight in humans, […] we should be open to the alternative idea that there is no feedback control of body weight' [39](p 10). This reasoning implies that EI is not a controlled variable in order to achieve regulation of body weight (or adipose tissue).

This discussion about the use of the term 'regulation' in the study of appetite in humans is relevant because the thesis proposed here, that EE drives EI, does not incorporate, nor does it require, the interposition of a regulatory principle. The drive to eat arises from biological signals (related to the utilisation of energy in the body) but there is no direct feedback to this process to maintain it at a fixed level. Therefore, there is no value in declaring that the drive to eat is regulated.

Although the drive to eat is clearly purposeful and ultimately maintains the integrity of the body, this process is independent of direct negative feedback. Indeed, it follows that the greater the size of metabolically active organs, then the greater is the drive to eat and the higher the EI. An increase in body size (or adipose tissue size) does not diminish the drive to eat. This observation has clear implications for the development and maintenance of obesity (see later). Although there is no negative feedback (and no regulated system), there are of course inhibitory as well as excitatory (drive) processes in the expression of food intake. Central to this argument is the distinction between tonic and episodic processes of appetite control. This distinction also incorporates separate effects of FFM and fat mass on appetite, and illustrates why the drive to eat is independent of cultural influences.

Tonic and episodic influences on appetite

Processes that influence the expression of appetite can be separated into tonic and episodic [62]. Tonic processes are rather stable and enduring and change slowly over time. Episodic processes are organised around the occurrence of bouts of eating behaviour (meals, snacks, etc); they occur periodically and are short lived rather than long lasting. These episodes take various forms within any one day and may change from day to day.

The origin of the drive to eat – as described above – is clearly a tonic process and reflects a constant need for energy. In humans this drive is periodically released (or triggered) and leads to episodic outputs of behaviour; the drive itself is not episodic (it is constant). This behaviour includes food seeking, acquisition and eating. The behavioural output is expressed in a particular environment with a specific culture, geographical location and socio-economic circumstances. These external forces shape the behaviour and determine its structure and form; they determine the foods eaten, the way they are consumed, where and with whom they are eaten, their frequency and over which period of time. These episodes of behaviour, and their accompanying sensations, constitute the phenomenon that people recognise as appetite. This episodic appetite behaviour is culturally dependent; the tonic drive to eat is independent of culture and is dependent on biological processes. Only when the drive to eat erupts into the external environment as behaviour does the impact of culture become apparent.

In addition, as a reviewer of this manuscript has pointed out, most attention in research on food intake has focussed upon the nutritional and overtly visible aspects of this behaviour rather than on the drive underlying the behaviour. A consequence of this is that many studies have

focussed on the meal which is an episodic feature heavily influenced by the environment and contextual factors. Perhaps researchers may have paid too little attention to tonic influences?

The drive to eat and the trigger to eat

This analysis describes why knowledge of the drive to eat does not explain the totality of appetite control; it explains an important component. The drive to eat does not explain food choice, satiation or satiety, food reward, consumer behaviour or cognitions about eating. The drive to eat accounts for the energy requirements (need state) that lead to eating. Importantly, the drive to eat has to be triggered (or released) in order to be expressed in behavioural form; it does not happen by accident. These triggering events may arise from signals of acute lack of immediately available nutrients that will meet the long-term needs. These signals include an empty stomach, low blood glucose, low gastro-intestinal activity and other events indicating a lack of recent ingestion. One important trigger involves glucose dynamics. A significant body of evidence in the late 1980-1990s demonstrated that the decline in plasma glucose predicted the onset of eating [63-65]. These signals represent biomarkers of short-term requirements of the need to eat. Although it is feasible that adjustments in plasma glucose constitute triggers for the drive to eat, it must also be considered that a drop in glucose, for example, may constitute a separate form of hunger. Consequently, glucose dynamics may constitute a type of episodically generated hunger (in contrast to the tonic drive generated by FFM and RMR).

However, we also need to allude to the possibility, raised by a reviewer, that our proposal for a glucose trigger could also influence RMR via alterations in liver glycogen metabolism. This suggestion would indicate how the liver could influence the tonic process via RMR but also the episodic processes via glucose dynamics. This would be a way to reconcile the actions of tonic and episodic processes. Although we postulate a conceptual separation between tonic and episodic processes; they may not be so clearly separated at the physiological level.

Since biomarkers may be neural (activity at neural receptors in periphery or brain) or hormonal, it is important to consider the influence of ghrelin, which is known to be closely related to periods of eating and is sometimes known as the 'appetite hormone' [66]. Although recent reviews [67, 68] have indicated that ghrelin is far more than a hunger hormone, its measured oscillations in blood are known to be quite well synchronised with episodes of eating [69]. Typically ghrelin in blood is high preceding a meal but falls during the period of postprandial satiety as food is ingested [e.g. 70]. This proximity of ghrelin to episodes of behaviour suggests that it has the character of a trigger (or releaser) of the drive to eat. However, ghrelin does not embody the drive itself.

One way to conceptualise these actions is to consider that the tonic need state underlying the drive to eat will be triggered (or released) at judicious times relevant to other physiological requirements or environmental contingencies. For example, it would not be appropriate for eating to be triggered during sleep. During waking hours eating would be triggered, for example, by low immediate availability (circulating levels) of nutrients constantly being used for metabolic functions. This combination of a tonic need state and episodic physiological processes can account for the daily pattern of eating events supplying nutrients. However, this explanation does not require any reference to the 'regulation' of appetite. The use of the term regulation would add nothing to the phenomenology of the observed pattern of events. However, it is certainly the case that the apparently cohesive interplay between tonic and episodic processes is 'coordinated' by the brain. This coordination serves an evolutionary purpose in allowing different physiological functions to be served, and to be compatible with the pattern of eating behaviour.

Inhibitors of the drive to eat – tonic and episodic

The drive to eat determined by FFM and RMR is moderated by a tonic inhibitory influence from fat mass [26, 31, 71], and is periodically suppressed by inhibitory processes arising from bouts of eating. The tonic influence is almost certainly mediated via leptin [72]. Although it was argued earlier that there is little justification for an adipocentric theory of appetite, there is no doubt that fat mass does play a significant role in the modulation of eating behaviour. In addition to the evidence from the cases of obesity arising from monogenic mutations of the leptin gene leading to leptin deficiency and obesity [73], there is also evidence that leptin is negatively associated with hunger during weight loss [74]. This body of evidence suggests that leptin is exerting an inhibitory influence on eating. Evidence also arises from studies using a biological systems approach in which we have measured body composition variables, RMR, behavioural EE, objective EI and various other physiological and psychological markers simultaneously in lean, overweight and obese people. In contrast to FFM which is positively associated with EI, fat mass is often negatively associated – more strongly in lean people than in those with obesity [75, 76], possibly partially mediated by eating behaviour traits [31]. In addition, with relatively large samples (n = 240+), linear regression modelling has indicated two separate links between fat mass and EI. First a weak positive association mediated by RMR (as would be expected because of the small positive contribution of fat mass to variance in RMR); and a stronger direct negative relationship with EI [31], indicating that fat mass exerts an inhibitory effect (which can be deduced to weaken as fat mass increases [26]). These actions are illustrated in Figure 6.

----------*Figure 6 here* ----------

The inhibitory effect of fat mass can be perceived as a tonic action which exerts a fairly constant modulation (becoming weaker as fat mass increases) of the drive from FFM/RMR. In contrast there is a very clear and noticeable episodic inhibition arising from the effects of periods of food consumption. It has been argued above that these periods of eating are triggered by physiological signals (together with psychological events). These eating periods can also be inhibited by physiological signals. The act of eating instigates a series of gastrointestinal physiological reactions designed to manage the passage of food through the body and to extract the maximum energy and nutrients. These processes are mediated by physical and mechanical action of the gastrointestinal (GI) tract and by specific hormones (such as insulin, CCK, GLP-1, PYY) with particular roles relating to the digestion and absorption of food. During this post-prandial period of intense GI activity, food intake is suppressed. This suppression is referred to as satiety.

This episodic inhibition of the drive to eat is a temporary suppression which allows time for the GI tract to carry out essential functions free from further ingestion. The bout of eating is initiated by triggers and is terminated, and the inhibition maintained, by a complex series of GI processes. However, the need state which generates the drive (metabolic activity of RMR) is not diminished; it is only prevented from spilling over into behaviour. Eating can be re-initiated (or re-released) once the inhibitory effects of GI activity have dealt with the ingested load of nutrients.

Role of brain mechanisms – integration of drive and inhibition

It is important to put these proposals about the drive to eat into the context of other approaches to appetite. Foremost among these is knowledge about the involvement of brain mechanisms. From the epoch in which hunger and satiety were believed to be enshrined in excitatory and inhibitory centres in the diencephalon [77], the brain activity has been regarded as a source of the drive to eat. More recently the drive has been seen to be encoded in the actions of particular neurotransmitters (such as NPY, DA, orexins, peptides, etc) or their receptors [78, 79]. Networks of neural circuits have been carefully worked out. It is important to point out that the proposal put forward here is not in conflict with research on brain substrates of appetite. The energy requirements of the vital organs (including skeletal muscle for activity) is reflected in intracellular transactions which in turn have necessary representations in brain activity before impacting on the final common pathway for behaviour. Consequently, the drive to eat as described above will undergo transformation into brain neural activity and integration at the CNS level with other systems reflecting other physiological priorities, and involving a complex network of neural processes.

445 At the present time it is easier to contemplate the neural links of tonic inhibition arising from
446 fat mass (see above). This inhibitory effect from a major bodily tissue would appear to be mediated
447 via the leptin – POMC – MC4 pathway described by [80]. This mechanism was uncovered by research
448 following the epic discovery of the hormone leptin and its profound association with adipose tissue
449 and with brain leptin receptors. In contrast, there is currently no similar established biochemical link
450 between FFM and the brain. However, there exist a number of substances such as AMPK, an enzyme
451 involved in sensing the energy status of a cell [81], and irisin, a myokine linked to food intake in
452 humans [82]. These could potentially provide a neural signal or biomarker as a periphery-brain link
453 for FFM [51].

454 **Implications for obesity**

455 Over the last 50 years there has been an inexorable rise in the world-wide prevalence of obesity. For
456 example, in the UK in 1970 the prevalence was approximately 5%, today it is close to 30% [83]. A
457 similar situation is apparent in the US and in most technologically advanced countries; though there
458 is some variation within Europe for example [e.g. 84]. This enormous increase in the number of
459 people with high levels of bodily fat mass has occurred without any obvious provocative biological
460 causal agency. Since the landmark article of Egger and Swinburn [85] identifying an obesogenic
461 environment, it has been argued that the cause is cultural and socio-economic. This could take the
462 form of an economically driven change in consumer behaviour leading to an increase in the
463 frequency of eating episodes [86], or the necessity for continuous economic growth driving
464 purchasing and consumption [87]. These scenarios do not support the idea of a faulty biological
465 system regulating either body fat or appetite.

466 One of the reviewers of this manuscript prompted a consideration of whether the appetite
467 system proposed here invites a reframing of the questions about how obesity arises and how it is
468 treated. Since the drive to eat is a natural response to energy requirements we do not contemplate
469 that this drive is responsible for obesity. Our modelling studies involving physiological and
470 behavioural variables [14, 31] implicates the nature of the diet (and especially its energy density) as
471 a major factor leading to overconsumption, a positive energy balance (not strongly defended) and
472 adipose tissue gain. However, the theoretical position presented in this article certainly illustrates
473 how biology is strongly implicated in the progressive increase in the accumulation of adipose tissue
474 within individuals and, therefore, in the escalation of obesity within populations. We have described
475 how an energy need created by RMR is associated with an elevated EI (and an increased hunger). As
476 a person is induced into a positive energy balance, the resulting increase in adipose tissue will be
477 supported by an increase in FFM (lean tissue), although it should be noted that the increase in FFM

is small compared with the increase in fat mass. Together the overall increase in body tissue will raise RMR with the potential to drive a greater food intake (although sarcopenic obesity may modulate this association). However, in general, as people accumulate adipose tissue, their underlying energy need increases and therefore the drive for food. The biological drive to eat is not pathological, but it is remorseless, and this is one reason why the drive to eat is extremely difficult to sustain at a low level. The drive itself is very difficult to restrain since it constitutes a force that is necessary for the maintenance of life.

The increase in fat mass also has a further unhelpful consequence. Although there is good evidence (cited above) that fat mass exerts a tonic inhibitory effect on EI, this is much stronger in lean individuals than in people with obesity. This appears paradoxical since there is a greater amount of circulating leptin associated with a greater fat mass and therefore the potential for a stronger degree of inhibition. The explanation seems to depend on leptin resistance, which may weaken the inhibitory effect on appetite. A similar effect has been observed with another major hormone – insulin – known to be elevated with adiposity, leading to regional insulin resistance and a consequent weakening of appetite control [88]. Taken together these actions mean the tonic inhibitory effect of fat mass is weakened. Therefore, people with obesity have to cope with two unhelpful biological problems: an increased tonic drive to eat and a weaker tonic inhibition. Given this scenario, together with an aggressive consumer driven environment, it can be understood how the accumulation of adipose tissue, once initiated, has relentless potential for expansion. This means that the obesity epidemic is unlikely to be resolved through biological interventions; though it may be susceptible to serious large scale economic or environmental forces [e.g. 89].

Summary

This article has reviewed a concise but cohesive body of evidence identifying particular sources of the biological drive to eat in humans. This evidence has been summarised in a recent editorial as indicating that 'fat-free mass and resting metabolic rate are major determinants of the drive to eat' [33]. The position statement set out here proposes that the EE of high metabolic rate organs (such as heart, brain, liver, kidneys) constitute an energy demand which forms the basis of a behavioural drive to seek food and eat. This tonic drive to eat can be contrasted with episodic aspects of appetite which are heavily influenced by the culture and environment. These episodic aspects of appetite include the types of foods available, food choices, perceptions of appropriateness, where and how to eat. These aspects of appetite vary enormously from one group of human beings to another. The underlying drive to eat is not influenced by culture and appears to be ubiquitous to all humans. We therefore cautiously feel that it is appropriate to use the term 'drive to eat in *homo sapiens'* since it

511 can be perceived as a fundamental property of humans. In turn this drive to eat is part of a broader
512 framework in which appetite control is understood in relation to EE. This approach provides an
513 alternative way of conceptualising appetite control and suggests roles for tonic and episodic
514 processes in obesity.

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Figure legends

Figure 1. Scatter plot and bivariate correlation coefficients (95% confidence interval) between fat-free mass (air displacement plethysmography) and total daily energy intake in 242 individuals in which energy intake was measured over 6-7 days using a self-reported weighed dietary record method. Data adapted from Hopkins et al [23]. In this paper multiple regression indicated that resting metabolic rate, fat mass and activity energy expenditure were independent predictors of mean daily energy intake after controlling for age and sex. This figure shows that different individuals with the same measured FFM show different EIs. We have inferred that this is due to people varying along other features that also influence the measures of the self-determined amount of food eaten such as the particular mood state, stress level, nutritional composition of foods available or individual preferences for the particular foods offered.

Figure 2. Scatter plot and bivariate correlation coefficients (95% confidence interval) between resting metabolic rate (indirect calorimetry) and total daily energy intake in (A) 59 individuals in which energy intake was objectively and covertly measured during a 14-day stay in a residential feeding behaviour suite [14], and (B) 242 individuals in semi free-living environment in which energy intake was measured over 6-7 days using a self-reported weighed dietary record method [23]. In panel A [14], multiple regression indicated that after controlling for age and sex, both fat-free mass and resting metabolic rate predicted daily energy intake. However, a mediation model using path analysis indicated that the effect of fat-free mass on energy intake was mediated by resting metabolic rate. In panel B [23], multiple regression indicated that resting metabolic rate independently predicted mean daily energy intake alongside fat mass (negative) and activity energy expenditure after controlling for age and sex.

Figure 3. Inter-individual variation in (A) activity energy expenditure (derived by subtracting resting metabolic rate measured by indirect calorimetry from 0.9 × total daily energy expenditure measured by an activity monitor) and (B) activity energy expenditure as a percentage of total daily energy expenditure in 70 individuals ranging in physical activity levels [42, 48].

Figure 4. Scatter plot and bivariate correlation coefficients (95% confidence interval) between (A) activity energy expenditure (derived by subtracting resting metabolic rate measured by indirect calorimetry from 0.9 × total daily energy expenditure measured by an activity monitor) and laboratory-measured meal size, and (B) minutes of moderate-to-vigorous physical activity (activity monitor) and laboratory-measured meal size in 70 individuals [48]. In panel A, multiple regression indicated that the relationship between activity energy expenditure and meal size weakened

(standardized β = 0.245, p=0.096) after controlling for fat-free mass, study, sex, and age. In panel B, multiple regression indicated that the association between minutes of moderate-to-vigorous physical activity and meal size remained significant (standardized β=0.256, p=0.024) after controlling for study, sex and age.

Figure 5. Inter-individual variation in total daily energy expenditure (FLEX heart rate method) and its subcomponents, resting metabolic rate (indirect calorimetry) and activity energy expenditure (total daily energy expenditure minus resting metabolic rate) in 242 individuals [23].

Figure 6. This model illustrates the interplay between tonic and episodic processes for appetite control, together with drive and inhibitory pathways. A major feature of the model is that body composition influences appetite control via both a drive and an inhibitory system. It is proposed that fat-free mass acts via resting metabolic rate reflecting energy needs of vital organs and constitutes a drive to eat. In contrast, fat mass acts as a tonic inhibitory influence on eating. Both of these processes achieve an expression in behaviour through transformation and integration in complex neuronal processes. In turn, these tonic influences on eating are periodically interrupted by episodic biological signals emanating from complex gastrointestinal physiology arising from food consumption. These signals are also represented in neuronal processes. The model illustrates how energy expenditure is related to energy intake. A further feature of this relationship is the contribution from physical activity energy expenditure, which influences both tonic and episodic processes. See text for further details.