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The importance of fat-free mass and constituent tissue-organs in the control of human appetite

Mark Hopkins^a and John E Blundell^b

^aSchool of Food Science and Nutrition, Faculty of Environment, University of Leeds, Leeds, United Kingdom. ^bAppetite and Energy Balance Research Group, School of Psychology, Faculty of Medicine and Health, University of Leeds, Leeds, United Kingdom.

Corresponding Author:

Dr. Mark Hopkins,
School of Food Science & Nutrition,
Faculty of Environment
University of Leeds,
Leeds,
United Kingdom.

Email: M.Hopkins@Leeds.ac.uk

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ORCID:

Dr. Mark Hopkins <https://orcid.org/0000-0002-7655-0215>

Professor. John E Blundell <https://orcid.org/0000-0002-7085-9596>

ABSTRACT

Purpose. Traditional models of human appetite focus on the contribution of adipose tissue and the gastro-intestinal tract, both of which exert mainly inhibitory influences. The purpose of this review is to consider the biological factors that influence the drive to eat.

Recent Findings. Fat-free mass is positively associated with objectively measured meal size and daily energy intake. These findings have been replicated in multiple populations across the life-course in laboratory and free-living studies. Studies have shown that the effect of fat-free mass is statistically mediated by resting metabolic rate, suggesting that energy expenditure *per se* may influence energy intake. A recent magnetic resonance imaging study has reported that fasting hunger was associated with high metabolic rate organ (heart, liver, brain, kidneys) and skeletal muscle mass. Integrating measures of body composition at the tissue-organ level and markers of their metabolic function with appetitive measures could provide novel insight into the mechanisms that influence appetite.

Summary. These recent findings suggest that fat-free mass and resting metabolic rate are determinants of energy intake. Consideration of fat-free mass and energy expenditure as physiological sources of appetitive signals helps reconcile the mechanisms underpinning the inhibition of eating with those that drive eating.

Key words: Fat-free mass, resting metabolic rate, appetite, energy Intake.

53 KEY POINTS

54

55 • The energetic demands of fat-free mass and its constituent tissue-organs may represent a
56 physiological source of hunger that promotes energy intake at a level proportional to basal
57 energy requirements.

58

59 • Loss of fat-free mass during weight loss may also act as an orexigenic signal that promotes
60 increased appetite and weight regain, but given the limited fat-free mass loss seen following
61 lifestyle interventions its effect appears modest.

62

63 • Studies examining how the signals through which body's energy needs are sensed, integrated
64 and translated into eating behaviors are a priority for future studies.

65 1.0 INTRODUCTION

66 Traditional models of appetite control have assigned prominent roles to signals arising from adipose
67 tissue (e.g., leptin) and the gastro-intestinal tract (e.g., GLP-1, CCK, PYY) (1*). These signals may help
68 account for the physiological mechanisms underpinning post-ingestive satiety (episodic signalling)
69 and the longer-term inhibition of eating (tonic signalling), but they do not adequately explain the
70 biological signals that underly the motivation to eat. Since appetite and food intake will reflect the
71 balance between episodic and tonic drive and inhibitory processes, it is important to identify factors
72 that drive as well as suppress eating. Ghrelin is primarily regarded as an orexigenic hormone involved
73 in the episodic control of appetite that promote hunger and meal initiation, but gene knockout
74 studies have demonstrated that feeding remains unabated when ghrelin signalling is inhibited (2).
75 Indeed, hunger and the drive to eat appear to be highly conserved sensations that mediate between
76 biological energy requirements and their nutritional satisfaction (3). Tonic appetite signals such as
77 leptin can influence day-to-day food intake by altering central sensitivity to peripheral
78 gastrointestinal hormone concentrations, particularly when energy stores (e.g., adipose tissue) are
79 perturbed with weight loss. However, adipose tissue is an 'energy reservoir' that does not contribute
80 significantly to daily energy requirements (with tissue specific metabolic rates ranging from 200 to
81 $440 \text{ kcal}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ for the liver, brain, heart, and kidneys rather than $4.5 \text{ kcal}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ adipose tissue;
82 (4)), which are primarily a consequence of the energetic demands of high metabolic rate organs and
83 the energy expended through physical and non-physical activity. This positions fat-free mass (FFM)
84 and energy expenditure as key feature of appetite, but until recently they have not been explicitly
85 considered as sources of physiological signals that influence human appetite.

86 2.0 THE ROLE OF FAT-FREE MASS AND RESTING METABOLIC IN THE CONTROL OF APPETITE

87 In a series of human studies over the last 15 years we have demonstrated that i) FFM, but not fat
88 mass (FM), is associated with objectively measured meal size and energy intake (EI), ii) the effect of

FFM on EI is mediated statistically by resting metabolic rate (RMR); and iii) FM weakens the strength of association between FFM and RMR with EI (see Blundell et al., (5) for a detailed review of evidence). Our findings suggest that FFM represents a tonic physiological source of hunger that drives EI at a level proportional to basal energy requirements, and helps to 'tune' EI to EE to ensure the maintenance of key biological processes (5). These processes would act alongside other tonic signals (e.g., leptin) in providing slow modulation of appetite to reflect both energetic demands of metabolically active tissues and longer-term energy storage. Our findings have been independently replicated. For example, McNeil et al., (6) reported that FFM, leptin, dietary restraint, and self-reported physical activity were associated with self-reported EI in 244 young adults, with FFM remaining as the only predictor after removal of under-reporters. Findings have also been replicated across the life course, with Wells et al., (7) reporting that milk intake and EI in 12-week infants was associated with FFM (but not FM), while at the other end of the spectrum, Hopkins et al. (8) reported that FFM and total daily energy expenditure (doubly labelled water) predicted self-reported EI in 590 older adults (63.1 ± 5.9 years).

The findings of McNeil et al., (6) that leptin was negatively associated with EI are interesting in that previous studies have reported inconsistent findings between FM and EI, with negative associations reported in lean individuals but no association or weak positive associations seen in those with obesity (see Blundell et al., (5)). To examine this issue further, Casanova et al., (9) recently investigated the associations between body composition, energy expenditure and EI (*ad libitum* test meal and free-living 24-hour EI) in healthy weight ($n = 45$) and individuals with overweight or obesity ($n = 48$). FM was negatively associated with test meal EI in the lean individuals, but no associations were seen in those with overweight or obesity. It has also been suggested that excess FM may weaken the association FFM and EI. For example, Grannell et al. found a positive association between FFM and *ad libitum* test meal EI in 43 individuals with severe obesity, but the strength of this association was weaker in those with a higher BMI (10). These findings are supported by

Casanova et al., (9), who reported that percentage body fat moderated the associations between RMR and total daily energy expenditure with free-living 24-hour EI. Weaker associations in those with obesity are in line with the notion of leptin resistance (11), and suggests that the relationship between FM and EI is more variable than with FFM and may be differ depending on the level of adiposity.

2.1 Examining the Drive to Eat at the Tissue-Organ Level

Our work suggests that the biological origins of the tonic drive to eat are rooted in the energetic demands of metabolically active tissues rather than adipose or gastrointestinal signals. Multi-organ predictive models of RMR have been shown to explain greater between-subject variance in RMR compared to models using FFM as a homogenous body compartment (approximately 5% of additional variance) (12). However, integrated physiological models of human appetite that consider FFM and its constituent tissue-organs alongside adipose and gastrointestinal derived feedback are lacking, with studies examining the associations between FFM and appetite have typically employed 2-compartmental models of body composition. In contrast, using whole-body magnetic resonance imaging, Casanova et al., (13*) demonstrated in 21 young healthy males ($BMI = 23.4 \pm 2.1 \text{ kg/m}^2$) that the association between the combined masses of the high-metabolic rate organs (brain, liver, heart and kidneys) and fasting hunger ($r = 0.58$; $p = 0.01$) was stronger than with FFM ($r = 0.39$; $p = 0.09$). In particular, liver ($r = 0.51$; $p = 0.02$) and skeletal muscle mass ($r = 0.57$; $p = 0.04$) were associated with fasting hunger. These associations may reflect the significant contribution of these two tissue-organs to RMR (~17% and ~21%, respectively, in these data), and suggest that metabolically active tissue may create a 'mass-dependent' tonic drive to eat that reflects the body's energy needs (see Figure 1). This notion is supported by studies employing statistical mediation models which show the effect of FFM on EI is mediated by RMR (14, 15) or TDEE (16). Taken together these data suggest that energy expenditure *per se* may influence EI, but it should be noted that the liver and skeletal muscle secrete numerous cytokine and myokine signals involved in inter-

organ crosstalk and communication between the periphery and the brain (17). It cannot therefore be ruled out that specific endocrine signals secreted by such organs mediate the observed associations between FFM (or individual components of FFM) and EI. Interestingly, Casanova et al., (13) also reported lower brain-to-body energy allocation was associated with higher fasting hunger, suggesting that greater peripheral glucose demand may stimulate increased hunger and EI to ensure sufficient glucose provision to the brain. As such, integrating measures of body composition at the tissue-organ level alongside markers of their metabolic function with appetitive measures could provide novel insight into the biological mechanisms and structure-function relationships that influence appetite and EI.

Figure 1 here

2.2 Fat-free Mass as Orexigenic Signal during Weight Loss

An increased motivation to eat following intentional weight loss is thought to be a critical reason for weight regain, but changes in subjective hunger and appetite-related hormones following weight loss are inconsistent (18-20). These discrepancies may in part relate to the method of energy restriction used, with attenuated compensatory changes in appetite seen following ketogenic and very-low calorie diets for example (21). Much less attention has been given to how the composition of weight loss, a function of initial body fat and the rate and extent of weight loss (22), influences compensatory changes in EI. Using data from the DiOGenes study, Turicchi et al., (23) reported that greater percentage FFM loss (%FFML) was associated with increased hunger following 8% weight loss in men (but not women). Including changes in FFM alongside FM in predictive models of weight regain has also been shown to better explain weight regain than body weight or FM alone (24). These findings have recently been supported by Martins et al., (25), who reported that greater %FFML was associated with greater weight regain ($r = -0.216$, $P = 0.01$) in 141 women with obesity one year post weight loss achieved via diet or diet plus either resistance or aerobic exercise. However, in a separate study the same authors reported that %FFML (or absolute FFM loss) was not associated with weight regain at 1 year following 8 weeks of a very low-energy diet in 70 individuals

with obesity (26). This discrepancy may relate to the fact that participants only regained 1.6 kg of body weight at 1 year despite 17.1 kg of weight loss. It should also be noted that the variance in post-weight loss appetite or weight regain explained by %FFML in these studies is small (typically explaining 3-5% of between-subject variance). This may reflect the limited losses in FFM typically seen following diet or exercise weight loss interventions (27). Whether FFM loss following bariatric surgery (28) or the use of gut peptide agonists (e.g., GLP-1 receptor agonists or GLP-1/GIP dual agonists) (29), where greater weight and therefore FFM losses are seen, explains greater variance in compensatory changes in appetite or weight regain is unknown. Where extreme energy deficits have been employed in lean men via semi-starvation or military training, FFM loss has again been shown to promote hyperphagia (see (30)). Interestingly, Flack et al., (31) has also reported that a greater increase in the reinforcing value of food was associated with greater FFM loss following 12-weeks of aerobic exercise. While there has been interest in how FM and leptin influence hedonic aspects of appetite, the role of FFM in food reward remains largely unknown.

It has been suggested that FFM loss may act as an orexigenic signal to preserve the functional integrity of its constituent tissue-organs (32). The composition of FFM (and FM) compartments is altered during weight loss, with muscle loss shown to make up the majority of lean tissue loss (17.5% of total tissue loss) during 24-months of calorie restriction (with a small reduction in liver mass and non-significant reductions in brain, spleen, and kidney mass also seen) (33). However, studies examining changes in body composition at tissue-organ level during weight loss are limited and have not included concurrent measurement of appetite.

3.0 POTENTIAL MECHANISMS LINKING FAT-FREE MASS TO EATING BEHAVIOUR

The mechanisms through which FFM or individual components of FFM are translated into changes in motivated eating behaviors are unknown. Using positron emission tomography Weise et al., reported that the association between FFM and hunger was mediated by periaqueductal gray

regional cerebral blood flow (34), suggesting that neural activity here could form part of a system that translates FFM-induced energy demand into motivated eating behaviour. Inverse associations have been reported between FFM and total or unacylated ghrelin (35), but whether this association has any functional relevance for the control of appetite is unclear as it is the acylated form traditionally thought to play a role in appetite control. There is increasing interest in the gut-brain-muscle axis in the control of energy homeostasis (36). Cytokines and myokines such as IL-6 and myostatin can influence EI via effects on the hypothalamus (37*, 38) or indirectly via effects on satiety hormones such as GLP-1 (39), but their role as candidate signals linking FFM to appetite has yet to be clearly established. The mechanisms linking FFM and EE to EI under conditions to energy balance may also differ to prolonged energy deficit where tissue loss occurs. Grannell et al., (38) has recently suggested that skeletal muscle loss may elicit compensatory changes in EI alongside counter-regulatory responses in protein synthesis to limit muscle atrophy. They suggest that reductions in myostatin concentrations may elicit increases in muscle-derived ghrelin and hepatic insulin-like growth factor-1 concentrations, which act on the hypothalamus to increase EI (38). However, whether this pathway provides a causal explanation for any increase in orexigenic drive with FFM loss has yet to be demonstrated.

4.0 CLINICAL IMPLICATIONS

There is increasing recognition of the importance of targeting lean mass in successful weight loss and its maintenance (40*), with the recently developed pharmaceutical agent bimagrumab (which targets the activin type 2 receptor to block muscle atrophy) showing promise as a weight loss agent in a phase 2 clinical trial where FM loss occurred alongside gains in lean mass for example (41). Such findings emphasise the importance of considering FFM in the study of energy balance and associated physiological feedback models.

A model of human appetite that considers FFM and energy expenditure as key tonic features of homeostatic appetite may have a number of clinically relevant implications. For example, it offers a plausible explanation for the gradual escalation of body fat via positive feedback. As weight is gained, both FM and FFM expand (albeit at differing rates). This implies that a higher FFM and associated RMR would increase the background tonic drive to eat. This would occur simultaneously with FM expansion and accompanying insulin and leptin resistance, such that as an individual gains weight this stronger drive to eat would occur alongside weakening inhibition. Furthermore, if FFM loss acts as an orexigenic signal during weight loss then strategies that attenuate FFM loss may help counter any compensatory changes in appetite. The composition of weight loss is modifiable via the inclusion of exercise alongside dietary energy restriction (42), and to a lesser extent, high-protein energy restricted diets (43). However, to date no study has examined whether minimising FFM loss during weight loss alters appetite-related outcomes. Given the changes in body composition and energy expenditure seen with aging, there has also been recent interest in how FFM influences appetite and EI in older adults. Based on a secondary analysis of the Interactive Diet and Activity Tracking Study, Hopkins et al., (44) reported that FFM and total daily energy expenditure were associated with self-reported EI in 590 older adults (63.1 ± 5.9 years). Age moderated these associations, such that these associations were weaker in older age quintiles (44). Johnson et al. (45) has also examined the effects of increasing FFM on appetite and EI in healthy older adults (66 ± 4 years) following 12-weeks of resistance training and protein supplementation. The change in FFM (+1.2 kg) was associated with the change in EI during an *ad libitum* test meal ($r = 0.53$), with 54% of the change in *ad libitum* EI attributed to the increase in FFM. Future research should examine the potential for a bi-directional relationship between FFM loss and appetite impairment with aging, and the potential benefit of preserving or increasing FFM on appetite in older adults.

5.0 CONCLUSION

242 Despite historic focus on the signalling pathways from adipose tissue and the gastro-intestinal tract,
243 functionally relevant associations exist between FFM and the expression of appetite. Consideration
244 of FFM and energy expenditure as physiological sources of tonic appetitive signals helps reconcile
245 the mechanisms that underpin the inhibition of eating with the mechanisms that drive eating.
246 Integrated models of appetite that include FFM and energy expenditure as tonic signals of appetite
247 alongside inputs from adipose tissue and the gastrointestinal tract may provide new insight into how
248 differences in energy requirements and functional demands over time (e.g., growth, weight
249 loss/gain, changes in physical activity) are met via daily food intake. Studies examining how the
250 body's energy needs are sensed, integrated and translated into eating behaviors are a priority.

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255 **Conflicts of interest**

256 None.

257 **6.0 REFERENCES**

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401 **Figure Label**

402 Figure 1: Conceptual diagram of the episodic and tonic physiological processes that influence the
403 inhibition and drive to eat. Particular focus is given to the role of fat-free mass in the tonic drive to
404 eat, in which it is proposed that fat-free mass acts via resting metabolic rate to reflect the energy
405 needs of metabolically active tissues (e.g., high metabolic rate organs) in daily food intake. This drive
406 is countered by tonic inhibitory processes, in which it is thought the adipokine leptin plays a role.
407 These tonic processes are periodically interrupted by episodic signals stemming from the complex
408 gastrointestinal physiology arising from food consumption. Together, these processes are expressed
409 in eating behaviour via central integration of peripheral feedback and subsequent changes in
410 neuronal expression in specific brain regions known to influence feeding. FFM, fat-free mass. GLP-1,
411 glucagon-like peptide-1. PYY, peptide tyrosine tyrosine. CCK, Cholecystokinin. AgRP, Agouti-related
412 protein. NPY, neuropeptide Y. POMC, pro-opiomelanocortin. CART, cocaine- and amphetamine-
413 regulated transcript.
414