Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Physiology

Biopsychology of human appetite — understanding the excitatory and inhibitory mechanisms of homeostatic control

Nuno Casanova[1], Graham Finlayson[2], John E Blundell[2] and Mark Hopkins[1]

Human appetite is a biopsychological phenomenon that reflects the complex interaction of biological, psychological and environmental processes in the overall expression of food intake. As human appetite interacts with, and is affected by, energy expenditure, it is best viewed within an energy balance framework. Defining what drives and inhibits appetite is essential for the aetiology of overconsumption and obesity development in humans. The inhibitory control of appetite is thought to be achieved via an array of adipose and gastrointestinal derived peptides that modulate hunger and satiety on a meal-to-meal (episodic) and day-to-day (tonic) basis. To date, there has been much less attention on the biological origins of the drive to eat. Recent cross-sectional studies report positive associations between fat-free mass and resting metabolic rate with hunger, meal size and daily energy intake in weight stable individuals. These data have been interpreted to suggest that the metabolic activity of fat-free mass creates a functional drive to eat that ensures energy intake meets the basal energy requirements of vital tissues and organs. In this review we discuss the nature and extent of body weight regulation, what drives and inhibits human appetite, and the dynamic relationships between energy expenditure, body composition and energy intake during periods of energy balance and restriction.

Addresses
[1] School of Food Science and Nutrition, Faculty of Mathematics and Physical Sciences, University of Leeds, Leeds, United Kingdom
[2] School of Psychology, Faculty of Medicine and Health, University of Leeds, Leeds, United Kingdom

Corresponding author: Hopkins, Mark (M.Hopkins@Leeds.ac.uk)

Current Opinion in Physiology 2019, **12**:33–38

This review comes from a themed issue on **Obesity**

Edited by **Rui-Ping Xiao**

For a complete overview see the Issue

Available online 18th June 2019

https://doi.org/10.1016/j.cophys.2019.06.007

Introduction—human appetite as an interaction between biology and psychology

The human appetite system comprises a set of processes that influence energy intake (EI) i.e. food consumption and associated motivational drives such as hunger. This system interacts with and is influenced by energy expenditure (EE). Consequently, human appetite is best considered within an energy balance framework. The essence of human appetite is that it links the internal (physiological) and the external (social, cultural, physical and psychological) environments. Therefore, this interplay means that human appetite is an interactive biopsychological phenomenon.

It is of significance that humans are omnivores and therefore able to consume from a huge range of food materials. This capacity confers an evolutionary advantage and has allowed humans to colonise every part of the planet. However, in a technologically advanced food environment, with an abundance of highly processed foods with strong sensory appeal, the omnivorous habit (prioritising food choice) is disadvantageous and generates vulnerability to overconsumption and obesity. Interestingly, food choice is dependent on features such as geography, culture, climate and religion; it is not heavily biologically programmed. One challenge for research is to disclose ways in which the biological components of human appetite can prevent environmentally driven overconsumption and obesity.

This review will focus on aspects that deal with the quantitative aspects of appetite (how much is eaten), usually referred to as the homeostatic component. The work will deal with the origins of the motivational drive to eat and the inhibitory mechanisms arising from the act of eating. This interplay between excitatory and inhibitory processes determines the pattern of eating behaviour and the profile of hunger that can be identified and measured.

The regulation of energy balance

The nature and extent of body weight regulation have long been a topic of debate. Numerous models have been proposed to explain changes in body weight and composition following underfeeding and overfeeding [1]. The 'set point theory' suggests that energy imbalances trigger responses in EI and EE to re-establish body composition homeostasis [2]. This model was challenged since it could not explain the increase in obesity rates [3], and gave rise

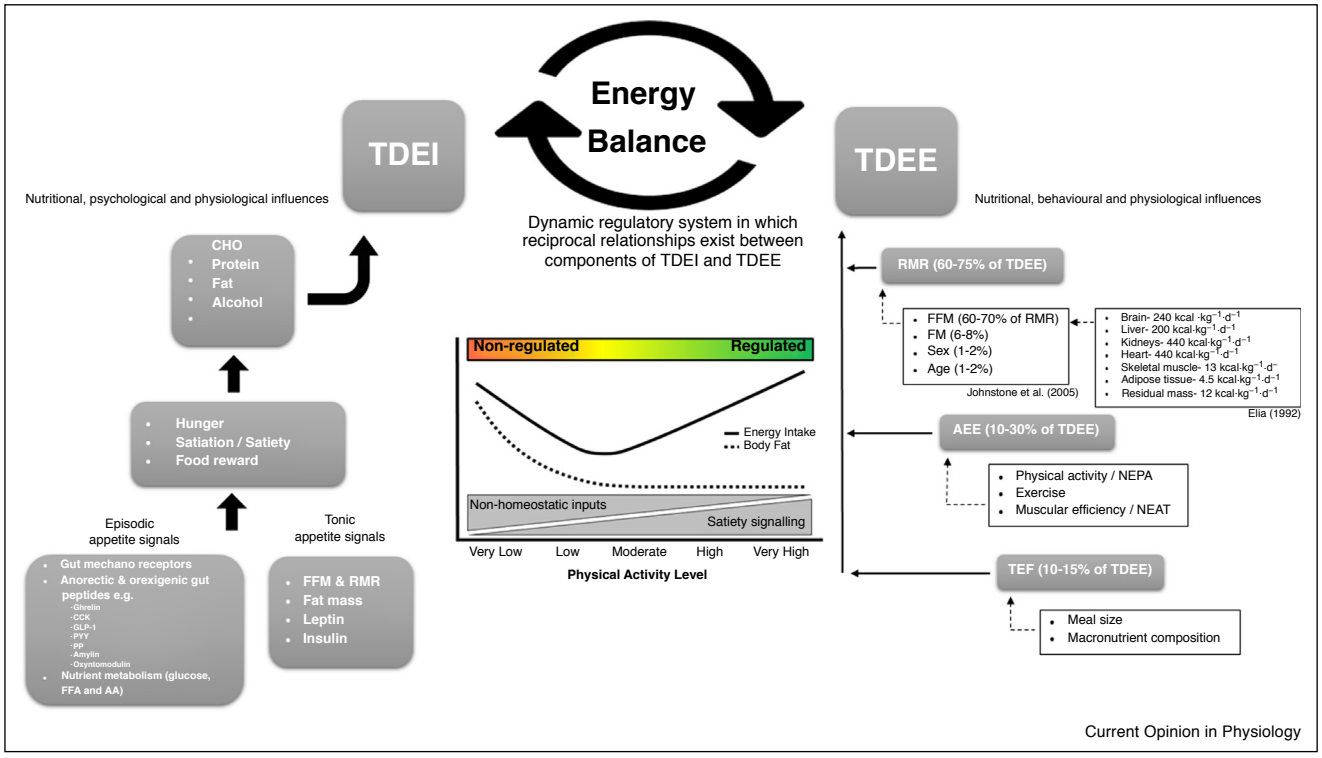
to the notion of a 'settling point', recognising the environment's impact on bodyweight regulation [4]. The dual intervention point model is an alternative attempt to explain bodyweight regulation [5]. Contrary to the previous models, it suggests that there is not a single set point, but lower and upper limits independently regulated, allowing an explanation of the inter-individual differences and asymmetrical compensatory responses to underfeeding (eliciting a strong response) and overfeeding (eliciting a weak response).

In contrast to other physiological processes such as thermoregulation, evidence suggests that appetite and food intake are not subject to tight biological regulation. Large day-to-day deviations in EI are common, but this likely reflects changes in an individual's external environment rather than the influence of biological events. However, this situation may change during weight loss. With an energy deficit, compensatory physiological and behavioural responses occur that attempt to re-establish energy balance [6]. These include a greater than predicted decrease in resting metabolic rate (RMR) i.e. adaptive thermogenesis [7], and increased muscular efficiency [8], appetite [9] and EI [10]. Such compensation appears to be asymmetrical, with stronger forces resisting weight loss than the ones resisting weight gain [11]. This asymmetry may help to explain the apparent ease at which people gain weight but subsequently fail to sustain weight loss over time [12]. While EE changes in a quantifiable manner following energy imbalance, changes in EI appear to have a greater capacity to perturb energy balance and body weight [13••]. Therefore, an understanding of how appetite is regulated may provide insight into the aetiology of weight gain and obesity.

Appetite control in the context of energy balance

The processes through which appetite is controlled are best viewed within an energy balance framework as this allows the integration of biopsychological determinants of EI and EE alongside components of body composition (see Figure 1). Nevertheless, food intake is not controlled solely as an outcome of energy homeostasis [14], with non-homeostatic factors such as food hedonics exerting

Figure 1



Schematic overview of the regulation of energy balance and the nutritional, psychological, behavioural and physiological influences on total daily energy expenditure and energy intake. Reference values for organ and tissue-specific metabolic rate taken from Elia [17], and determinants of RMR taken from Johnstone *et al.* [18]. The relationship between homeostatic regulation and physical activity levels was taken from Beaulieu *et al.* [19••]. TDEI, total daily energy intake; TDEE, total daily energy expenditure; CHO, carbohydrate; NEPA, non-exercise physical activity; NEAT, non-exercise activity thermogenesis; CCK, cholecystokinin; PP, pancreatic polypeptide; PYY, peptide YY; GLP-1, glucagon-like peptide-1; FFA, free-fatty acid; AA, amino acid; FFM, fat-free mass; FM, fat mass; AEE, activity energy expenditure; TEF, thermic effect of food. Adapted from Casanova *et al.* [20].

important influence over eating behaviour [15]. Models of homeostatic appetite regulation embody excitatory and inhibitory feedback signals that reflect acute (episodic) and long-term (tonic) energy availability. Tonic mechanisms exert a stable influence over appetite and provide a link between metabolic requirements, stored energy and day-to-day EI. This feedback has traditionally been centred around the inhibitory action of leptin, but it is now recognised that the EE of metabolically active tissues also provides an enduring signal to eat [16]. Episodic signals respond to the presence or absence of nutrients in the gastrointestinal tract. The classic satiety peptides cholecystokinin, glucagon-like peptide-1 and peptide tyrosine tyrosine, along with the orexigenic peptide ghrelin, supposedly act as physiological cues that influence subjective appetite (e.g. hunger, satiation and satiety) and the timing, type and amount of food consumed [11].

Centrally mediated processes, primarily involving the functionally antagonist neuropeptide Y and agouti-related peptide neurons in the arcuate nucleus of the hypothalamus, co-ordinate acute and long-term signals of energy availability with appropriate efferent feedback responses that alter appetite and EI (and EE) [21]. The central neural systems that underlie homeostatic feeding are closely linked to those underpinning central reward pathways, with hormones such as leptin, insulin and ghrelin postulated to provide a molecular link between hypothalamic (homeostatic) and mesolimbic (reward related) systems [22]. These control mechanisms can be conceptualised via the satiety cascade, which provides a theoretical framework that maps the underlying biological mechanisms of appetite onto the psychological experiences and behavioural events that influence EI [23]. A salient feature of the above appetite-related processes is their inherent inter-individual variability. Large variations in the individual profiles of subjective appetite and appetite-related peptides are seen following nutrient or exercise manipulations [24,25,26•]. This variability may help account for i) the diversity in eating behaviours between individuals, and ii) differences in the susceptibility to weight loss/gain and the marked individual variability in weight loss following lifestyle [27–30], pharmacological [31,32] and surgical [33–35] interventions.

What drives appetite?

Modern theories of human appetite regulation embody the view that adipose and gastrointestinal derived signals inhibit an excitatory drive to eat. However, until recently, the biological origins of this drive to eat have been poorly defined. Recent studies examining components of body composition and EE as putative signals of appetite have demonstrated that FFM and RMR are positively associated with hunger, meal size and total daily EI in weight stable individuals [36–39]. These findings have led to the suggestion that the metabolic activity of FFM creates a functional drive to eat that ensures EI meets the basal energy requirements of tissues and metabolic processes [16,40]. In line with this, the effect of FFM on EI has been shown to be mediated by RMR [41,42••] and total daily EE [43], suggesting that EE *per se* exerts influence on EI. However, the molecular signals that link EE to EI are unknown, and given that skeletal muscle is an endocrine organ [44], specific molecular signals independent of the EE associated with tissues such as skeletal muscle cannot be disregarded. An area that has yet to be studied is the role of specific components of FFM in the regulation of appetite. It is known that high metabolically active organs (e.g. brain, liver, kidneys and heart) represent <6% of total body mass but ~60% of total RMR [45]. Interestingly, Koong observed a strong relationship between liver and gut mass and daily EI in sheep [46], but there has been no attempt to date to integrate organ-specific metabolic rates into regulatory models of homeostatic appetite control in humans.

The relationships described above between body composition, EE and EI pertain to weight stable individuals at or close to energy balance. How these associations change during weight loss or with systematic increases in EE remains a topic of debate [40]. Given the proposed role of FFM and RMR in appetite regulation, it follows that physical activity EE could also influence appetite regulation. Data suggest that habitually high active individuals eat more than less active people and show increased sensitivity in their appetite control system in comparison to inactive individuals. This means that that they have a greater capacity to spontaneously match EI and EE according to their homeostatic signaling [19••,47]. There is also limited evidence to suggest that losses of FFM may act as an orexigenic signal during and after periods of energy deficit. During the Minnesota semi-starvation study [48], 32 healthy men undertook 24 weeks of semi-starvation (25% of weight loss), 12 weeks of controlled refeeding and eight weeks of *ad libitum* refeeding. During the last phase, in which only 12 participants completed, a significant hyperphagic response was present until baseline levels of FFM were restored. This led to an accumulation of fat mass (FM) that surpassed baseline levels (i.e. 'fat-overshoot'), a phenomenon that has been reported after periods of underfeeding in other interventions [49,50]. More recently, after five weeks of very-low calorie diet (500 kcal/d) or 12 weeks of low-calorie diet (1250 kcal/d), Vink [51] observed that losses in FFM were associated with weight regain in the following nine months. While the effect of energy deficit and weight loss on EE have been well studied, little is known about how these changes in EE influence appetite and EI during weight loss. There is limited evidence that adaptive thermogenesis (i.e. a lower than predicted decrease in RMR that cannot be explained by the changes in FFM and FM) [7] is associated with elevated hunger and daily EI following dietary and exercise-induced weight loss [52,53]. However, more focused research is needed to

fully understand the role of FFM and EE as drivers of daily EI during and after weight loss.

What inhibits appetite?

Numerous peripheral adipose and gastrointestinal derived 'satiety signals' are thought to exist that inhibit appetite on a meal-to-meal (episodic) and day-to-day (tonic) basis. Gut peptides such as cholecystokinin, glucagon-like peptide-1 and peptide tyrosine tyrosine, released on the sight and smell of food and the presence of nutrients in the gastrointestinal tract, initiate a cascade of neural and hormonal signals that promote meal termination (satiation) and inhibit the drive to eat following food consumption (satiety) [21]. These 'satiety hormones' act alongside the orexigenic peptide ghrelin, and vagal afferent and metabolic signals, in the episodic regulation of appetite. It is worth noting that while the post-prandial profiles of these hormones appear well placed in time to account for changes in appetite, few studies report direct statistical associations between changes in these peptides and subjective appetite. Furthermore, marked individual variability exists in their post-prandial profiles, and these hormones typically have other physiological functions associated with the delivery and metabolism of nutrients in the gastrointestinal tract. Therefore, any effect on appetite and EI may be a secondary function which provides a modulation rather than a causal inhibition. There appears to be no single unique satiety peptide, with the gut hormones released during feeding acting conjointly to contribute to the inhibition of eating during the post-prandial period.

In bringing satisfaction of long-term energy needs through daily EI, hormones such as leptin exert tonic feedback on appetite and mediate the strength of episodic satiety signals such as cholecystokinin and glucagon-like peptide-1 [21]. Reductions in leptin are thought to promote hunger and EI via a downregulation in proopiomelanocortin and α-Melanocyte-stimulating hormone expression, and an upregulation in neuropeptide Y and agouti-related peptide expression [21]. This has led to the view that leptin is a key regulatory signal in the control of EI, such that EI is controlled in the interests of regulating FM levels via the action of leptin (i.e. 'lipostatic' control). However, evidence demonstrating that FM or leptin exerts strong influence on day-to-day EI in weight stable individuals is inconsistent, with studies reporting no association [36,37] or an inhibitory effect [38,42••,54] of FM on EI. The importance of leptin as an appetite signal may therefore be restricted to periods of energy deficit where adipose tissue reserves are threatened. Furthermore, the inhibitory effect of FM (leptin) on EI seems to be more pronounced in lean individuals compared to obese individuals [54,55], possibly due to changes in leptin sensitivity that diminishes with increased adiposity. Lastly, as with FFM, the relationship between FM and energy intake has been assessed by measuring total fat mass rather than its specific subcomponents. Considering the physiological differences between each component of FM (e.g. visceral versus subcutaneous, and white versus brown adipose tissue), one has to consider that these could have different effects on appetite. For instance, it has been suggested that brown adipose tissue may exert a specific effect on appetite [56]. More data are needed to fully comprehend the role of FM and its specific components in appetite control.

Conclusions

The expression of appetite and food intake in humans reflects the complex interaction between biological, psychological and environmental processes. From a biological perspective, excitatory and inhibitory signals combine to create a homeostatic regulatory system that reflects an integration of acute meal-to-meal signals with long-term nutrient and energy needs. However, homeostatic appetite control does not appear to be under tight regulation, and the biological mechanisms that influence how much we eat appear to be easily overridden by the cognitive, social and environmental factors that influence what we eat (i.e. food choice). Energy deficit and the loss of body tissue appear to alter the strength of homeostatic feedback and elicits compensatory responses that promote increased EI and decreased EE to resist weight loss and undermine weight loss maintenance attempts. Interventions should be targeted specifically at minimising compensatory changes in appetite during weight loss in order to develop more efficacious treatment options.

Conflict of interest statement

Nothing declared.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Speakman JR: **The evolution of body fatness: trading off disease and predation risk**. *J Exp Biol* 2018, **221**:jeb167254.
2. Harris R: **Role of set-point theory in regulation of body weight**. *FASEB J* 1990, **4**:3310.
3. Speakman JR: **If body fatness is under physiological regulation, then how come we have an obesity epidemic?** *Physiology* 2014, **29**:88-98.
4. Wirtshafter D, Davis JD: **Set points, settling points, and the control of body weight**. *Physiol Behav* 1977, **19**:75-78.
5. Speakman JR, Levitsky DA, Allison DB, Bray MS, de Castro JM, Clegg DJ *et al.*: **Set points, settling points and some alternative models: theoretical options to understand how genes and environments combine to regulate body adiposity**. *Dis Models Mech* 2011, **4**:733-745.
6. Melby CL, Paris HL, Foright RM, Peth J: **Attenuating the biologic drive for weight regain following weight loss: must what goes down always go back up?** *Nutrients* 2017, **9**.
7. Leibel RL, Rosenbaum M, Hirsch J: **Changes in energy expenditure resulting from altered body weight**. *N Engl J Med* 1995, **332**:621-628.

8. Rosenbaum M, Vandenborne K, Goldsmith R, Simoneau JA, Heymsfield S, Joanisse DR *et al.*: **Effects of experimental weight perturbation on skeletal muscle work efficiency in human subjects**. *Am J Physiol Regul Integr Comp Physiol* 2003, **285**: R183-R192.

9. Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A *et al.*: **Long-term persistence of hormonal adaptations to weight loss**. *N Engl J Med* 2011, **365**:1597-1604.

10. O'Connor KL, Scisco JL, Smith TJ, Young AJ, Montain SJ, Price LL *et al.*: **Altered appetite-mediating hormone concentrations precede compensatory overeating after severe, short-term energy deprivation in healthy adults**. *J Nutr* 2016, **146**:209-217.

11. Hopkins M, Beaulieu K, Myers A, Gibbons C, Blundell JE: **Mechanisms responsible for homeostatic appetite control: theoretical advances and practical implications**. *Expert Rev Endocrinol Metab* 2017, **12**:401-415.

12. Kelly T, Yang W, Chen CS, Reynolds K, He J: **Global burden of obesity in 2005 and projections to 2030**. *Int J Obes (2005)* 2008, **32**:1431-1437.

13. •• Polidori D, Sanghvi A, Seeley RJ, Hall KD: **How strongly does appetite counter weight loss? Quantification of the feedback control of human energy intake**. *Obesity* 2016, **24**:2289-2295.
The authors observed that the increase in appetite in response to weight loss (~100 kcal/day per kg of lost weight) is larger than the decrease in energy expenditure, helping to explain why long-term weight loss maintenance is difficult.

14. Halford JCG, Blundell JE: **Separate systems for serotonin and leptin in appetite control**. *Ann Med* 2000, **32**:222-232.

15. Finlayson G: **Food addiction and obesity: unnecessary medicalization of hedonic overeating**. *Nat Rev Endocrinol* 2017, **13**:493.

16. Blundell JE, Caudwell P, Gibbons C, Hopkins M, Naslund E, King N *et al.*: **Role of resting metabolic rate and energy expenditure in hunger and appetite control: a new formulation**. *Dis Models Mech* 2012, **5**:608-613.

17. Elia M: **Organ and tissue contribution to metabolic rate**. *Energy Metabolism: Tissue Determinants and Cellular Corollaries*. 1992:19-60.

18. Johnstone AM, Murison SD, Duncan JS, Rance KA, Speakman JR: **Factors influencing variation in basal metabolic rate include fat-free mass, fat mass, age, and circulating thyroxine but not sex, circulating leptin, or triiodothyronine**. *Am J Clin Nutr* 2005, **82**:941-948.

19. •• Beaulieu K, Hopkins M, Blundell J, Finlayson G: **Homeostatic and non-homeostatic appetite control along the spectrum of physical activity levels: an updated perspective**. *Physiol Behav* 2018, **192**:23-29.
The authors describe the relationships between physical activity and energy intake, suggesting that people with higher levels of physical activity are better able to match energy intake to energy expenditure.

20. Casanova N, Beaulieu K, Finlayson G, Hopkins M: **Metabolic adaptations during negative energy balance and their potential impact on appetite and food intake**. *Proc Nutr Soc* 2019:1-11.

21. Schwartz MW, Seeley RJ, Zeltser LM, Drewnowski A, Ravussin E, Redman LM *et al.*: **Obesity pathogenesis: an endocrine society scientific statement**. *Endocrine Reviews*. 2017.

22. Berthoud H-R, Münzberg H, Morrison CD: **Blaming the brain for obesity: integration of hedonic and homeostatic mechanisms**. *Gastroenterology* 2017, **152**:1728-1738.

23. Blundell J: **Pharmacological approaches to appetite suppression**. *Trends Pharmacol Sci* 1991, **12**:147-157.

24. Hopkins M, Blundell JE, King NA: **Individual variability in compensatory eating following acute exercise in overweight and obese women**. *Br J Sports Med* 2013, **48**:1472-1576 http://dx.doi.org/10.1136/bjsports-2012-091721.

25. Goltz FR, Thackray AE, King JA, Dorling JL, Atkinson G, Stensel DJ: **Interindividual responses of appetite to acute exercise: a replicated crossover study**. *Med Sci Sports Exerc* 2018, **50**:758-768.

26. • King JA, Deighton K, Broom DR, Wasse LK, Douglas JA, Burns SF *et al.*: **Individual variation in hunger, energy intake, and ghrelin responses to acute exercise**. *Med Sci Sports Exerc* 2017, **49**:1219-1228.
The authors demonstrated that even though an overall suppression of hunger and acylated ghrelin was observed in response to exercise, large variability between individuals was observed.

27. Yancy WS, Westman EC, McDuffie JR, Grambow SC, Jeffreys AS, Bolton J *et al.*: **A randomized trial of a low-carbohydrate diet vs orlistat plus a low-fat diet for weight loss**. *Arch Intern Med* 2010, **170**:136-145.

28. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ: **Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial**. *JAMA* 2005, **293**:43-53.

29. King NA, Hopkins M, Caudwell P, Stubbs R, Blundell JE: **Individual variability following 12 weeks of supervised exercise: identification and characterization of compensation for exercise-induced weight loss**. *Int J Obes* 2008, **32**:177-184.

30. Church TS, Martin CK, Thompson AM, Earnest CP, Mikus CR, Blair SN: **Changes in weight, waist circumference and compensatory responses with different doses of exercise among sedentary, overweight postmenopausal women**. *PLoS One* 2009, **4**:e4515.

31. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M *et al.*: **A randomized, controlled trial of 3.0 mg of liraglutide in weight management**. *N Engl J Med* 2015, **373**:11-22.

32. Fujioka K, Plodkowski R, O'neil P, Gilder K, Walsh B, Greenway F: **The relationship between early weight loss and weight loss at 1 year with naltrexone ER/bupropion ER combination therapy**. *Int J Obes* 2016, **40**:1369-1375.

33. Still CD, Wood GC, Chu X, Manney C, Strodel W, Petrick A *et al.*: **Clinical factors associated with weight loss outcomes after Roux-en-Y gastric bypass surgery**. *Obesity* 2014, **22**:888-894.

34. Courcoulas AP, Christian NJ, O'Rourke RW, Dakin G, Dellinger EP, Flum DR *et al.*: **Preoperative factors and 3-year weight change in the Longitudinal Assessment of Bariatric Surgery (LABS) consortium**. *Surg Obes Relat Dis* 2015, **11**:1109-1118.

35. Courcoulas AP, Christian NJ, Belle SH, Berk PD, Flum DR, Garcia L *et al.*: **Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity**. *JAMA* 2013, **310**:2416-2425.

36. Caudwell P, Finlayson G, Gibbons C, Hopkins M, King N, Naslund E *et al.*: **Resting metabolic rate is associated with hunger, self-determined meal size, and daily energy intake and may represent a marker for appetite**. *Am J Clin Nutr* 2013, **97**:7-14.

37. Blundell J, Caudwell P, Gibbons C, Hopkins M, Naslund E, King N *et al.*: **Body composition and appetite: fat-free mass (but not fat-mass or BMI) is positively associated with self-determined meal size and daily energy intake in humans**. *Br J Nutr* 2012, **107**:445-459.

38. Weise C, Hohenadel M, Krakoff J, Votruba S: **Body composition and energy expenditure predict ad-libitum food and macronutrient intake in humans**. *Int J Obes (2005)* 2014, **38**:243-251.

39. McNeil J, Lamothe G, Cameron JD, Riou M-È, Cadieux S, Lafrenière J *et al.*: **Investigating predictors of eating: is resting metabolic rate really the strongest proxy of energy intake?** *Am J Clin Nutr* 2017:ajcn153718.

40. Stubbs RJ, Hopkins M, Finlayson G, Duarte C, Gibbons C, Blundell J: **Potential effects of fat mass and fat-free mass on energy intake in different states of energy balance**. *Eur J Clin Nutr* 2018, **72**:698.

41. Hopkins M, Finlayson G, Duarte C, Whybrow S, Horgan GW, Blundell J *et al.*: **Modelling the associations between fat-free mass, resting metabolic rate and energy intake in the context of total energy balance**. *Int J Obes* 2015, **40**:312-318.

42. •• Hopkins M, Finlayson G, Duarte C, Gibbons C, Johnstone A, Whybrow S *et al.*: **Biological and psychological mediators of the relationships between fat mass, fat-free mass and energy intake**. *Int J Obes* 2018, **43**:233-242.

This study shows that the excitatory effect of fat-free mass and fat mass on energy intake is mediated by resting metabolic rate. Additionally, fat mass also presents a inhibitory effect mediated via cognitive restraint.

43. Piaggi P, Thearle MS, Krakoff J, Votruba SB: **Higher daily energy expenditure and respiratory quotient, rather than fat free mass, independently determine greater ad libitum overeating**. *J Clin Endocrinol Metab* 2015, **100**:3011-3012 http://dx.doi.org/10.1210/jc.2015-2164.

44. Pedersen BK, Febbraio MA: **Muscles, exercise and obesity: skeletal muscle as a secretory organ**. *Nat Rev Endocrinol* 2012, **8**:457-465.

45. Gallagher D, Belmonte D, Deurenberg P, Wang Z, Krasnow N, Pi-Sunyer FX *et al.*: **Organ-tissue mass measurement allows modeling of REE and metabolically active tissue mass**. *Am J Physiol* 1998, **275**:E249-E258.

46. Koong LJ, Ferrell CL, Nienaber JA: **Assessment of interrelationships among levels of intake and production, organ size and fasting heat production in growing animals**. *J Nutr* 1985, **115**:1383-1390.

47. Beaulieu K, Hopkins M, Long C, Blundell J, Finlayson G: **High habitual physical activity improves acute energy compensation in nonobese adults**. *Med Sci Sports Exerc* 2017, **49**:2268-2275.

48. Keys A: *The Biology of Human Starvation*. Minneapolis, London: University of Minnesota Press; Oxford U.P; 1950.

49. Nindl BC, Friedl KE, Frykman PN, Marchitelli LJ, Shippee RL, Patton JF: **Physical performance and metabolic recovery among lean, healthy men following a prolonged energy deficit**. *Int J Sports Med* 1997, **18**:317-324.

50. Friedl KE, Moore RJ, Hoyt RW, Marchitelli LJ, Martinez-Lopez LE, Askew EW: **Endocrine markers of semistarvation in healthy lean men in a multistressor environment**. *J Appl Physiol (Bethesda, Md.: 1985)* 2000, **88**:1820-1830.

51. Vink RG, Roumans NJ, Arkenbosch LA, Mariman EC, van Baak MA: **The effect of rate of weight loss on long-term weight regain in adults with overweight and obesity**. *Obesity (Silver Spring, Md.)* 2016, **24**:321-327.

52. Hopkins M, Gibbons C, Caudwell P, Hellström PM, Näslund E, King N *et al.*: **The adaptive metabolic response to exercise-induced weight loss influences both energy expenditure and energy intake**. *Eur J Clin Nutr* 2014, **68**:581-586.

53. Tremblay A, Royer M, Chaput J, Doucet E: **Adaptive thermogenesis can make a difference in the ability of obese individuals to lose body weight**. *Int J Obes* 2013, **37**:759-764.

54. Cugini P, Salandri A, Cilli M, Ceccotti P, Di Marzo A, Rodio A *et al.*: **Daily hunger sensation and body composition: I. Their relationships in clinically healthy subjects**. *Eat Weight Disord* 1998, **3**:168-172.

55. Cugini P, Salandri A, Cilli M, Ceccotti P, Di Marzo A, Rodio A *et al.*: **Daily hunger sensation and body compartments: II. Their relationships in obese patients**. *Eat Weight Disord* 1999, **4**:81-88.

56. Chondronikola M, Porter C, Malagaris I, Nella AA, Sidossis LS: **Brown adipose tissue is associated with systemic concentrations of peptides secreted from the gastrointestinal system and involved in appetite regulation**. *Eur J Endocrinol* 2017, **177**:33-40.