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Biopsychology of Human Appetite- Understanding the Excitatory and Inhibitory Mechanisms of Homeostatic Control

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Abstract

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.

Key words

Body composition, energy expenditure, fat-free mass, resting metabolic rate, appetite, energy intake.

Abbreviations

EI, energy intake; EE, energy expenditure; FFM, Fat-free mass; Fat mass; RMR, resting metabolic rate.

1. 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.

2. The Regulation of Energy Balance

The nature and extent of body weight regulation has long been a topic of debate. Numerous models have been proposed to explain changes in body weight and composition following under- and over-feeding⁽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 is 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.

3. 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 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⁾.

Figure 1 here

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)⁽¹⁷⁾. 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⁽¹⁸⁾. 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⁽¹⁹⁾. 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⁽²⁰⁻²²⁾. 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⁽²³⁻²⁶⁾, pharmacological^(27, 28) and surgical⁽²⁹⁻³¹⁾ interventions.

4. 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⁽³²⁻³⁵⁾. 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, 36). In line with this, the effect of FFM on EI has been shown to be mediated by RMR^(37, 38) and total daily EE⁽³⁹⁾, 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⁽⁴⁰⁾, 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⁽⁴¹⁾. Interestingly, Koong observed a strong relationship between liver and gut mass and daily EI in sheep⁽⁴²⁾, 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⁽³⁶⁾. Given the proposed role of FFM and RMR in appetite regulation, it follows that physical activity EE could also influence appetite regulation. Data suggests 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 they have a greater capacity to spontaneously match EI and EE according to their homeostatic signalling^(43, 44). 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⁽⁴⁵⁾, 32 healthy men undertook 24-weeks of semi-starvation (25% of weight loss), 12 weeks of controlled refeeding and 8 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^(46, 47). More recently, after 5 weeks of very-low calorie diet (500kcal/d) or 12 weeks of low-calorie diet (1250kcal/d), Vink⁽⁴⁸⁾ observed that losses in FFM were associated with weight regain in the following 9 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^(49, 50). 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.

5. 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 (satiety) and inhibit the drive to eat following food consumption (satiety)⁽¹⁷⁾. 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 whilst 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⁽¹⁷⁾. Reductions in leptin are thought to promote hunger and EI via a down-regulation in proopiomelanocortin and α -Melanocyte-stimulating hormone expression, and an up-regulation in neuropeptide Y and agouti-related peptide expression⁽¹⁷⁾. 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^(32, 33) or an inhibitory effect^(34, 38, 51) 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^(51, 52), possibly due to changes in leptin sensitivity that diminishes with increased adiposity.

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 appears 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.

Highlights

- Human appetite is affected by the internal and external environment.
- The metabolic activity of fat-free mass creates a functional drive to eat.
- Adipose and gastrointestinal peptides that modulate hunger and satiety.
- Appetite does not appear to be under tight homeostatic control.
- Energy deficit and weight loss may alter the strength of homeostatic feedback.

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