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theoretical advances and practical implications**

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Mechanisms Responsible for Homeostatic Appetite Control: Theoretical Advances and Practical Implications.

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ABSTRACT

INTRODUCTION: Homeostatic appetite control is part of a psychobiological system that has evolved to maintain an adequate supply of nutrients for growth and maintenance. The system links the physiological needs for energy with the behaviour that satisfies these needs (feeding), and is shaped by excitatory and inhibitory signals. Owing to rapid shifts in the food environment, homeostatic appetite control is not well adapted for modern-day human functioning.

AREAS COVERED: Homeostatic appetite control has two divisions. Tonic processes exert stable and enduring influences, with signals arising from bodily tissues and metabolism. Episodic processes fluctuate rapidly and are related to nutrient ingestion and the composition of foods consumed. Research in these areas incorporates potent endocrine signals that can influence behaviour.

EXPERT COMMENTARY: The regulation of adipose tissue, and its impact on appetite (energy) homeostasis, has been heavily researched. More recently however, it has been demonstrated that fat-free mass has the potential to act as a tonic driver of food intake. A challenging issue is to determine how the post-prandial action of episodic satiety hormones and gastrointestinal mechanisms can effectively brake the metabolic drive to eat in order to keep food intake under control and prevent a positive energy balance and fat accumulation.

1.0 INTRODUCTION – ENERGY HOMEOSTASIS AND THE ADIPOCENTRIC CONTROL OF APPETITE

The term homeostatic appetite control has been used for over 50 years to indicate how appetite may be part of a regulated system based on Claude Bernard's concept of homeostasis [1], and implies that food intake is controlled in the interests of maintaining physiological functioning. The idea of behavioural regulation or homeostasis of internal states was subsequently developed by Richter [2]. Appetite and food intake were viewed as a vehicle for energy supply, and this supply was modulated by a metabolic drive generated in response to energy requirements [2]. The concept was fully developed during the 1950s when physiological regulation was being reviewed alongside cybernetic concepts of feedback and communication [3]. This led to the proposal that food intake was part of a system through which body weight was regulated via the detection of certain key signals; namely blood glucose (glucostatic hypothesis), body temperature (thermostatic hypothesis), amino acids (amino static hypothesis) or lipids (lipostatic or adipostatic hypothesis). The discovery of leptin [4] appeared to confirm that fat mass (FM) was a regulated variable, with leptin acting as a key signal between FM and the central control of food intake.

While there is no doubt that certain physiological processes are under tight homeostatic control, evidence suggests that food intake is not a strictly controlled variable or subject to tight regulation. Further, homeostatic appetite control mechanisms appear to operate asymmetrically; excess energy intake is readily tolerated, whereas energy deficit is strongly opposed. Whether body weight (or FM) is tightly regulated has also been long debated [5], and numerous explanations concerning its regulation have been proposed based on 'set', 'settling' and 'dual intervention points' [6]. However, the worldwide prevalence of obesity would appear to testify against the strong regulation of body weight and FM [6]. Despite an increase in our understanding of the putative signals of appetite control and energy balance, strategies that elicit long-term weight loss and weight loss maintenance remain elusive. For these reasons, the status of appetite control and energy homeostasis are currently being reconsidered, and in particular, the role of body composition and energy expenditure as excitatory features of homeostatic appetite control are being re-examined.

The aim of this narrative review is to provide an up-to-date account of how peripheral episodic and tonic inhibitory signals are integrated with the motivational drive(s) stemming from the functional requirements of metabolically active tissue in the overall expression of appetite and food intake. This review also highlights how an understanding of appetite control can help explain some of the salient features of weight loss, weight gain and weight loss maintenance; namely, individual variability and biological and behavioural compensation to energy imbalance. In the interests of brevity, this review is limited to homeostatic appetite control, but it is acknowledged that hedonic,

psychosocial and environmental factors also influence appetite control. Similarly, a discussion of the central mechanisms of appetite regulation, and the gut-brain axis, can be found elsewhere [7].

2.0 AN ENERGY BALANCE APPROACH TO APPETITE AND FOOD INTAKE

Over the last 10 years evidence has emerged that homeostatic appetite control is best viewed within an energy balance framework, as this allows the integration of physiological and behavioural determinants of intake and expenditure alongside functional changes in body tissue. That said, while the control of appetite fits into an energy balance framework, it is not necessary for appetite and food intake to be controlled solely as an outcome of energy (im)balance [8]. Indeed, there is growing recognition that 'non-homeostatic' factors play an important role in determining the marked differences in feeding behaviours between individuals. Historical antecedents of this approach arise from the proposals of Edholm and others [9,10], who noted that "the differences in intakes of food must originate in the differences in energy expenditure" [9]. This idea is based on the recognition that the energy requirements of the body constitute a metabolic drive for food (to maintain the functionality of organs and metabolic processes). Recently, this has led to a new formulation of the biology of appetite control, in which fat-free mass (FFM) and resting metabolic rate (RMR) are viewed as key excitatory features of homeostatic appetite control that help explain day-to-day feeding patterns in those at or close to energy balance [11,12]. This concept has now been incorporated into more extensive theoretical models of appetite control that attempt to explain the putative appetite signals seen during energy deficit and weight loss [13,14]. Evidence is accumulating in support of these models.

2.1 What is Homeostatic Appetite Control?

Homeostatic appetite control embodies both excitatory and inhibitory signals that influence appetite and food intake via co-ordinated tonic (long-term) and episodic (short-term) control mechanisms. Tonic mechanisms are those with an enduring and stable influence over appetite and food intake, and do not fluctuate significantly between or within day. These tonic control mechanisms have traditionally centred around the inhibitory action of insulin and leptin, but it now appears that the energy expenditure of metabolically active tissue [15] also provides an enduring signal to eat [11]. Episodic influences co-vary with the consumption of food across the day, and respond acutely to the presence (or absence) of nutrients in the gastrointestinal (GI) tract. The classic satiety peptides cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1) and peptide tyrosine tyrosine (PYY), along with the orexigenic peptide ghrelin, are thought to acutely influence the timing, type and amount of food consumed across the day [16]. Recent attention has begun to focus on the impact of meal

frequency and timing on appetite and food intake, but the reader is directed elsewhere for details of this [17].

Evidence in humans suggests that the metabolism or storage of specific macronutrients fails to exert powerful negative feedback on energy intake [18]. However, due to the intermittent nature of food consumption (and physical activity), the energy state of the body is constantly fluctuating between periods of positive and negative energy imbalance during the day [19]. While this suggests that there is no within-day energy balance regulation, a state of approximate energy balance is thought to be achieved over longer periods (e.g. one week [10]). This emphasises the need to understand the biological mechanisms that link energy intake to energy expenditure. This should not be assumed to be a passive process that 'just happens' - if intake and expenditure are linked as part of a biologically regulated system, a mechanism must exist that 'tunes' food intake to the rate of energy expenditure. However, little attention to date has been given to how the demand for energy is translated into motivated behaviour (i.e. food intake), and potential signals linking energy intake and energy expenditure have been discussed elsewhere [20].

Specific methodological procedures that quantify specific aspects of appetite and food intake have been developed (and these are discussed elsewhere [21,22]). Briefly, subjective hunger is regarded as a sensation that reflects a conscious motivation to eat [22], and can be traced back to physical sensations in the body (e.g. stomach) and underlying putative signals [22]. Satiation represents the within-meal events that promote meal termination, and is a determinant of meal size [22]. While satiety is influenced by a sequence of physiological events triggered by the sight, smell and consumption of food, it is also influenced by the properties of food consumed (e.g. palatability) and cognitive and environmental cues [23]. Satiety is defined as the suppression of hunger following a meal and delays the further consumption of food during the post-prandial period [22]. Together, hunger, satiety and satiation can be conceptualised via the satiety cascade (see Figure 1), which provides a theoretical framework that maps the underlying biological mechanisms of appetite onto the psychological experiences and behavioural events that influence food intake [24].

An inability to recognise and respond to internal sensations of hunger [25], or a weakened satiety response to food consumption [26,27], are thought to be risk factors for overconsumption and weight gain in susceptible individuals. Changes in subjective hunger during energy restriction are also predictive of successful long-term weight loss [26] and weight loss maintenance [28]. While a recent systematic review concluded that changes in subjective appetite are not predictive of subsequent food intake [29], direct statistical associations between subjective appetite and food intake were not examined. Rather, studies were 'scored' as demonstrating a 'link' or 'no link'

between appetite and food intake based on the direction of change in these parameters. Moreover, the context and/or environment in which subjective appetite and food intake were measured was not considered (despite the known influence of hedonic, psychological and environmental factors on appetite and food intake).

Figure 1 here.....

3.0 MODELS OF HOMEOSTATIC APPETITE CONTROL

3.1 Episodic Control of Appetite

There is considerable evidence that gut peptides, released during periods of fasting, on the sight and smell of food, and the presence of nutrients in GI tract, constitute signals to initiate, terminate and then inhibit the drive to eat following food consumption. This review will focus on CCK, GLP-1, PYY and ghrelin only, but a growing number of gut peptides have been proposed as unique candidates for hunger and satiety signalling (and more complete overviews can be found elsewhere [30]).

However, not all of these peptides have a close association with the rhythms of hunger and fullness [16]. Although the post-prandial profiles of these hormones initially appear well placed in time to account for changes in appetite, it is likely that their influence is synergistic, with changes in eating behaviour reflecting the conjoint action of multiple hormonal and metabolic stimuli [31]. The importance of gastric emptying in the control of appetite should also be noted, as an integrative relationship between gut peptides and gastric emptying/distension is likely [32]. Marked individual variability is also seen in the profile of GI hormones after food consumption (Figure 2), and many of the GI hormones are pleiotropic and have other physiological functions associated with the delivery and metabolism of nutrients in the GI tract. For example, CCK is involved in the secretion of bile acid from the gall bladder [33], GLP-1 influences intestinal transit time particularly through gastric emptying rate [34], while PYY also influences intestinal transit time (with the highest concentrations of PYY actually found in the rectum rather than small intestine [35]). Therefore, any effect on food intake (satiation or satiety) may be a secondary function which provides a modulation rather than a causal inhibition. The peak concentration of these peptides usually occurs 30-60 minutes after the consumption of food, whereas hunger and fullness peak 10 minutes post-ingestion.

Figure 2 here....

3.1.2 Ghrelin

Ghrelin is a 28-amino acid peptide that stimulates the release of growth hormone from the pituitary [36]. It is primarily secreted from the stomach, but is also known to be synthesised and secreted in many other tissues [37,38]. Ghrelin was the first orexigenic peptide identified in the periphery and is

known to act upon the hypothalamic arcuate nucleus [36,39,40]. The composition of ghrelin is uniquely modified by the addition of an octanoyl group to the serine residue at position three. The enzyme responsible for the ghrelin octanoylation has been reported as ghrelin *O*-acyltransferase (GOAT) [41,42]. Some studies suggest this acylation is crucial for ghrelin to bind to the growth hormone-secretagogue receptor (GHS-R) and cross the blood-brain barrier [43]. The effects of ghrelin on food intake are mediated by neuropeptide Y (NPY) and agouti-related protein (AgRP) in the central nervous system [44]. Plasma ghrelin concentrations have been shown to increase before meals and decrease in the post-prandial state, thus suggesting a physiological role in meal initiation [45]. Intravenous infusion or subcutaneous injection of ghrelin in humans increases both subjective hunger and food intake [43,46], and promotes weight gain in rodents [46]. Whilst obese individuals have lower fasting ghrelin levels, food intake increases after ghrelin infusion in both lean and obese individuals [47]. However, while ghrelin levels in obese individuals fall after food consumption, this fall is attenuated in comparison to lean individuals [48].

3.1.3 Glucagon-like peptide 1

Glucagon-like peptide 1 exists in several forms, the most common being GLP-1_{7-36amide}. GLP-1 is secreted from the same gut endocrine cells that synthesise PYY in the distal small and large intestine and as such, is released into circulation after a meal [43]. The anorectic effects of GLP-1 may involve both vagal and direct input to the central nervous system as GLP-1 is also produced by brainstem neurons projecting to the hindbrain and hypothalamus [30]. GLP-1 is a potent incretin (i.e. stimulator of insulin release) and peripheral administration of GLP-1 inhibits appetite in animals and humans [49]. Studies have shown reduced postprandial GLP-1 response in severely obese individuals and that this normalises with weight loss [50], but others have failed to replicate these findings [51].

3.1.4 Peptide YY

Peptide YY is a 36-amino acid closely related to NPY since both have the PP fold and exert their effects on the Y receptors. Most circulating PYY is in the shortened form PYY₃₋₃₆ which binds to the Y2 receptor [43]. PYY is mainly synthesised in the L-cells of the distal small and large intestine and is known to act upon the hypothalamus and hindbrain regions [52]. PYY is released into the circulation after a meal and is reduced during fasting. Peripheral administration of PYY₃₋₃₆ has been shown to decrease food intake in both rodents [53-55] and humans [56,57]. Circulating PYY₃₋₃₆ levels rise in response to food consumption, particularly in response to the energy content of food [58].

3.1.5 Cholecystokinin

CCK is released post-prandially from the small intestine and decreases food intake via CCK1 receptors present on the vagal nerve. Studies in humans and rodents have shown that CCK1 receptor antagonists can stimulate/prolong food intake during a meal [43]. CCK1 receptors are also expressed in the hindbrain and hypothalamus indicating that CCK might relay satiation signals to the brain both directly and indirectly [59]. Intravenously infused CCK within a physiological range has been shown to significantly decrease food intake in both lean and obese individuals [60]. The inhibitory effect of CCK on food intake is short-lived, that is, CCK inhibits intake by reducing meal size and duration, but does not affect the onset of the following meal [61]. Fat intake specifically has been shown to significantly stimulate [62,63], and has longer lasting effects on [64], CCK release. However, it has been noted previously that constant high fat feeding does result in a reduction of CCK induced satiety, possibly due to a down-regulation of vagal CCK1R [64].

3.2 The Relationship between Subjective Appetite Ratings and Appetite-Related Peptides

It is clear that ghrelin concentrations rise during periods of fasting and declines following food consumption, mirroring the pattern of change in subjective hunger. The other episodic hormones show the opposite pattern, falling during periods of fasting but rising in response to food consumption (mirroring fullness or satiety). The infusion of ghrelin has been shown to increase hunger and energy intake in humans [46], whilst GLP-1, PYY and CCK infusion increases satiety [53,61,65,66]. However, the infusion of these peptides has often been at ultra-physiological levels, and therefore fail to reflect the 'normal' endogenous hormonal milieu that occurs around periods of eating. Furthermore, despite a wealth of studies measuring subjective appetite and appetite-related hormones, and the apparent similarity in post-prandial profiles of subjective appetite and hormones such as ghrelin, GLP-1, PYY and CCK [67], few studies actually report statistical associations between them. A study in 2011 attempted to examine the relationship between hunger and ghrelin, finding that changes in ghrelin concentrations lagged 10-30 minutes behind changes in hunger [68], potentially indicating that hunger and ghrelin respond to different stimuli; hunger may respond to the presence or the amount of food in the stomach whereas ghrelin may be more indicative of the body's digestion processes of energy and macronutrient availability.

One difficulty in finding associations is the large individual variability in peptide levels (see Figure 2) [45], and until recently, studies have typically measured a single or a small number of hormones in response to food intake. Gibbons et al. [16,69] recently investigated the simultaneous response of ghrelin, GLP-1, PYY and CCK to two macronutrient feeding conditions (high-carbohydrate and high-fat). Ghrelin was positively associated with hunger during the early and late phases of satiety, while

GLP-1 was negatively associated with hunger after both high-carbohydrate and high-fat meals but only in the late satiety period (60-180 minutes). Neither CCK nor PYY were related to measures of subjective appetite.

There is evidence that dietary macronutrient composition can alter peptide release following food consumption. For example, CCK responses are heightened following fat and protein ingestion compared to carbohydrate [70,71], whereas the role of GLP-1 as an incretin is consistent with a greater response to ingested carbohydrate [72]. The effect of dietary macronutrients on PYY is unclear, with some studies showing fat causing the largest rise in postprandial PYY [35] and others demonstrating carbohydrates [73] or protein [58]. Studies investigating the effects of macronutrient content on ghrelin levels show that carbohydrates have the strongest suppressive action [74]. However, protein and fat have also been shown to lower ghrelin levels, with the effect of fat intake causing a slower recovery of ghrelin levels compared to a high-carbohydrate meal [75,76]. For all these studies however, methodological differences make it difficult to interpret the effect of macronutrient composition on peptide release (particularly when only a single hormone is measured in response to food intake).

3.3 Tonic Signalling and Appetite Control

In addition to the acute episodic signals involved in homeostatic appetite control, a mechanism that translates the body's energy needs (based on metabolic requirements and stored energy) into day-to-day feeding is needed. Traditionally, this was thought to be achieved via the inhibitory action of FM and leptin (based on an adipocentric view of appetite control). However, it is now being recognised that the energetic demand of metabolically active tissue [15] creates a functional excitatory drive to eat. These excitatory and inhibitory tonic processes will in turn be modulated by acute episodic signalling, with centrally-mediated processes (primarily involving the functionally antagonist NPY and AgRP neurons in the arcuate nucleus of the hypothalamus) acting to co-ordinate peripheral and neural signals of nutrient and energy availability with appropriate efferent feedback responses that alter food intake and energy expenditure [77]. The interaction of excitatory and inhibitory tonic and episodic signals is shown in Figure 3, and this figure illustrates how the homeostatic control of appetite is incorporated into an energy balance framework that links energy intake and expenditure (see section 3.3.2).

Figure 3 here...

3.3.1 A Role for Leptin in the Tonic Control of Appetite?

While leptin is discussed here, it is important to also acknowledge the role of insulin as another potential tonic signal of appetite control [78]. Animal and in vitro studies have indicated that a reduction in leptin promotes hunger and food intake via a down-regulation in the expression of pro-opiomelanocortin (POMC) and α -melanocyte-stimulating hormone (α -MSH), and an up-regulation in the expression of NPY and AgRP [77]. This has led to the view that leptin is a key central regulatory signal in the neural control of food intake [77]. However, while the importance of leptin signalling in the hypothalamus and other areas of the brain is not in question, there is little evidence that peripheral leptin concentrations exert strong regulatory control over day-to-day food intake (when at or close to energy balance), or that increases in leptin concentrations with weight gain exert strong negative feedback on food intake.

Leptin deficiency in humans results in profound hyperphagia [79] which is abated with exogenous leptin administration [80]. In those free from congenital leptin deficiency however, administration of physiologically-relevant doses of leptin has been shown to have little or no effect on food intake or body weight [81]. Rather, the effect of leptin on appetite and energy homeostasis (in those free from congenital leptin deficiency) appears to be closely coupled to the body's short-and-long-term energy status. Acute and short-term (2-7 days) energy restriction results in significant reductions in circulating leptin concentrations (which are disproportionately greater than the associated changes in FM [82-87]), but these changes in circulating leptin are not typically associated with any subsequent changes in appetite or food intake [82,83,85].

The importance of leptin as an appetite signal may therefore be restricted to periods of prolonged energy deficit where adipose tissue reserves are threatened. In line with this, studies have found associations between changes in fasting leptin and subjective appetite during long-term dietary restriction [88-90]. Additionally, in the weight-reduced state exogenous leptin administration reverses the adaptive suppression of multiple metabolic, autonomic and neuroendocrine functions [91], and potentially improves satiety [92]. Therefore, it appears that a sustained loss of leptin is of biological importance [93], with leptin acting as a 'starvation signal' involved in the defence of body weight rather than a satiation or satiety signal involved primarily in day-to-day food intake in weight stable individuals in energy balance [94,95].

3.3.2 An Energetic Demand from Metabolically Active Tissue

Current models of appetite control focus on integrating acute GI signals with the tonic modulating effect of adipose tissue [77]. While our understanding of the putative signals of appetite control has grown significantly, scientific attention appears to have focused more toward the termination of feeding rather than the mechanisms that drive feeding. Indeed, despite the identification of a large

number of inhibitory GI hormones, the only known peripherally derived orexigenic hormone is ghrelin. Given the multiple redundant pathways known to promote satiety, it seems unlikely that a regulatory system would evolve to rely solely on one hormone to promote feeding. There has previously been a strong emphasis on the excitatory features of homeostatic appetite control, with work focusing on the motivation to seek food in animals and humans. This was embodied in Morgan's theory of a 'central motive state' [96] and Stellar's attempts to locate this drive within the hypothalamus [97].

A conceptual model detailing the drive to eat based on energy needs has previously been proposed [98], but only now are studies beginning to recognise energy expenditure (and body composition as a determinant of energy expenditure) as important excitatory features of homeostatic appetite control. Recent studies (re)examining the specific roles of FM, FFM and energy expenditure in appetite control indicate that FFM and RMR are strongly associated with food intake under conditions at or close to energy balance [99-106]. Based on studies measuring food intake under controlled laboratory conditions, our research group [99-101] and others [102,103] have demonstrated that FFM is a strong predictor of hunger and *ad libitum* energy intake. The effect of FFM on energy intake appears to reflect the energetic demands of metabolically active tissue, with the associations between FFM and energy intake reported to be mediated by RMR [101] and 24-hour energy expenditure [104]. However, given recent advances in our understanding of skeletal muscle as an endocrine organ [107], a direct molecular pathway (independent of energy expenditure) from tissue such as skeletal muscle should not be dismissed [105,106].

These data have led to the formulation of a revised model of homeostatic appetite control that reflects an excitatory drive to eat from FFM and RMR [11]. This model, which is discussed in depth elsewhere [11,12,20,108], attempts to integrate the energetic demand of metabolically active tissue and metabolic processes with the known tonic and episodic signals from FM and GI tract, respectively. This model was specifically designed to help explain the tonic signals that influence day-to-day food intake under conditions of weight stability and energy balance [11,12], but it may also have potential in explaining the putative appetite signals seen during energy deficit or surfeit [13,14]. However, its application to periods of energy imbalance remain largely theoretical to date. Importantly, the influence of FFM and RMR on food intake does not preclude a role for FM in appetite control. Rather, there is likely a conjoint action of FFM and FM on appetite and food intake. The influence of FFM and RMR, and signals arising from adipose tissue and GI peptides provide a plausible account of the role of whole-body peripheral signals involved in human appetite control (see Figure 3).

While FFM has consistently been shown to be positively associated with food intake, studies have reported either a negative association [102,109] or no association [99,100,103,105] between FM and food intake. The influence of FM on food intake may vary with adiposity, with Cugini et al. [109,110] reporting a negative association between FM and hunger in lean but not obese individuals. It is also worth noting that adiposity also influences psychometric eating behaviours, with positive associations seen between FM and dietary restraint or disinhibition, for example [111]. However, the influence of such factors on relationships between body composition, energy expenditure and food intake has yet to be established.

3.4 Hedonic Control: Is there a True Separation of Homeostatic and Hedonic Processes?

While the hedonic control of appetite has traditionally been viewed separately to homeostatic appetite control, this distinction is arbitrary as significant overlap and reciprocal feedback is seen between the putative signals of reward-driven and homeostatic feeding. Based on research exploring the neural basis of palatability and addictive behaviour [112], theoretical constructs have been developed to distinguish between feeding behaviours that are either affective (rewarding) or motivational (driving) [113]. Experimental methods have been developed that aim to distinguish between food 'liking' and 'wanting' using functional MRI [114] or behavioural laboratory tasks using the reinforcing value of food [115] or time-critical forced choice paradigms [113,116]. In this context, food 'liking' reflects the perceived pleasurable sensory properties of food, while wanting reflects the attraction towards a specific food over available alternatives [116]. Food 'liking' and 'wanting' have distinct underlying neural pathways (located primarily in the cortico-limbic structures), with dopaminergic signalling mediating 'wanting' while the opiate and cannabinoid systems have been linked to 'liking' [117]. However, the neural systems that underlie homeostatic and hedonic feeding are closely linked [117], with hormones such as leptin, insulin and ghrelin postulated to provide a molecular link between hypothalamic (homeostatic) and mesolimbic (reward related) systems [118].

Food reward has been shown to influence eating behaviour, and can help distinguish those susceptible to overconsumption. Elevated 'liking' and 'wanting' for palatable foods has been reported in obese individuals compared to their lean counterparts [119], while obese individuals with binge eating disorder displayed stronger 'liking' and 'wanting'- especially for sweet and high fat foods- compared to obese individuals without binge eating [120]. The reward value of food has also been shown to increase during short-term energy deficit [121]. Despite a paucity of data on the role of 'liking' and 'wanting' during long-term weight loss and weight loss maintenance, changes in food 'liking' and 'wanting' have been shown to differentiate between those susceptible and resistant to

exercise-induced weight loss [122], and eight weeks of dietary energy restriction has been shown to increase 'liking' [123] in obese adults.

4.0 PRACTICAL IMPLICATIONS FOR MANAGING OBESITY

4.1 Individual Variability in Treatment Response- A 'Biological Norm'

Lifestyle and pharmacological treatments that aim to reduce food intake and body weight have in the main been unsuccessful in producing sustained weight loss and weight loss maintenance. This in part reflects the redundancy in the homeostatic mechanisms that regulate short-and-long-term appetite and food intake. However, it is becoming increasingly clear that marked heterogeneity exists in the biological and behavioural responses to lifestyle, pharmacological and surgical treatments designed to promote weight loss. This heterogeneity has traditionally been masked by a focus on the statistical mean and/or attributed to differences in intervention adherence. As noted by Blastland and Dilnot [124] however, science is often weakened by subscribing to the "tyranny of the average".

Figure 4 here...

Individual variability is inherent to the key processes of appetite control (Figures 3 & 4), and this variability may help explain the diversity in eating behaviours seen between individuals. In line with previous studies [125-127], King et al. [128] report marked variability in hunger, acylated ghrelin and *ad libitum* energy intake in response to a bout of aerobic exercise in young healthy adult males. Importantly, this variability echoes that seen in response to long-term dietary [129-131], exercise [132-135], pharmacological [136,137] and surgical [138-140] weight loss interventions. Given the complexity of human eating behaviour, and the external environment that this system now operates in, this individual variability in treatment response is not surprising. However, it is pertinent to note such variability has also been observed following calorie restriction in mice [141], which are presumably free from the social and environmental 'contamination' that influences studies of human behaviour in today's obesogenic environment. Consequently, the heterogeneity in appetite and body weight responses to lifestyle, pharmacological and surgical interventions should be regarded as a 'biological norm' rather than an exception.

Examination of the individual rather than group response indicates that despite often modest mean weight loss, lifestyle and pharmacological intervention are actually very effective for some individuals, but for others, minimal losses in body weight are seen (and some may gain weight). Thus, the mean response is a poor representation of how a treatment actually influences its intended target population. Recent recognition of this variability represents an important step in the

development of more efficacious and personalised obesity treatments, but to achieve this, predictors of treatment 'responsiveness' need to be established. To date, identification of reliable predictors of treatment variability has been limited. An emerging area of interest is the role that genetic variation plays in the heterogeneity seen in appetite and body weight. Potential candidate genes and gene loci that influence appetite and food intake are currently being examined, and a number of genetic variants relating to the FTO and MC4R genes have been found to be associated with appetite-related processes and energy intake [142-146]. Interactions between common genetic variants and the environment are also likely to play a role in influencing response variability in eating behaviour following weight-loss interventions [147,148]. There is also interest in the role of the gut microbiome in appetite control and weight gain; however, evidence indicating that the microbiome acts as a putative signal in human appetite control, or is a causal factor in human obesity development, is not clear [149].

4.3 Compensatory Responses to Energy Deficit

While significant weight loss recidivism is seen following lifestyle interventions, it is important to acknowledge that attempts to lose weight are undermined by potent neuroendocrine, metabolic and behavioural responses to weight loss. As noted by MacLean et al. [14], these factors combine to create a 'biological pressure' that promotes weight regain. Compensatory responses in appetite control appear to be asymmetrical, responding more strongly to energy deficit rather than surfeit [150], and can occur following as little as two days of energy restriction (and without concomitant reductions in body weight) [82,84,85]. While some common physiological or behavioural responses to weight loss *per se* may exist, there will undoubtedly be some mode specific weight loss adaptations (e.g. differences between diet or exercise interventions). Consequently, an understanding of how these specific methods perturb appetite control and body weight is fundamental to our understanding of weight loss recidivism.

4.3.1 Are there Common Compensatory Responses to Energy Deficit?

As discussed elsewhere [151], a number of biological and behavioural responses have been identified that attenuate the prescribed energy deficit during weight loss, and act to undermine attempts to maintain a new level of (reduced) body weight. Following both dietary [88,90] and exercise-induced weight loss [152,153], fasting hunger has been shown to be elevated. Some evidence also exists to suggest that this increase in orexigenic drive may persist in the weight reduced state, and reflect persistent changes in appetite-related hormones [154]. Adaptive changes in energy expenditure (i.e. adaptive thermogenesis) have also been noted with weight loss [155,156], and again may persist in the weight-reduced state [91]. For example, Leibel et al. [157]

reported that daily energy expenditure was approximately 300 kcal·d⁻¹ lower (15%) than expected in non-obese and obese individuals who lost 10% of their initial body weight through energy restriction. This was brought about by an increased efficiency in skeletal muscle activity. Interestingly, a greater compensatory decline in RMR has also been associated with greater increases in hunger [155] and food intake [158] following weight loss, suggestive of a co-ordinated adaptive response in susceptible individuals that influences both sides of the energy balance equation that promotes the defence of body weight rather than its loss.

4.3.2 Compensatory Changes in Hunger: Diet vs Exercise

The observation that both dietary-and-exercise induced weight loss leads to compensatory changes in appetite has led some to examine whether the strength of compensation differs between weight loss modes. Recent evidence suggests that for a given short-term energy deficit, exercise may produce more favourable changes in appetite than dietary restriction [159-161]. Following three days of either exercise-or-dietary induced isoenergetic calorie deficits (25% reduction of energy needs), Cameron et al. [161] reported greater increases in appetite and compensatory eating following dietary-induced energy deficit than that induced by exercise. The reason behind these differences remain to be elucidated, but King et al. [160] noted differing responses in acylated ghrelin and PYY₃₋₃₆ following isoenergetic energy deficits induced by diet and exercise. Compared with the exercise energy deficit, the diet energy deficit resulted in overall higher ghrelin concentrations and lower PYY₃₋₃₆ concentrations. This was accompanied by overall higher subjective ratings of hunger and lower ratings of fullness in the diet relative to the exercise condition [160]. Beneficial effects of exercise compared to dietary-induced deficits have not always been reported though [162], and whether differences in appetite exist following long-term isoenergetic energy deficits induced by diet or exercise remains unclear. It should also be noted that exercise will perturb blood flow to the GI tract during (and immediately following) exercise, and this change in circulation may alter digestive processes and the release of GI hormones. These changes should be taken into account when making inferences about the acute effects of exercise on appetite-related processes. Such findings suggest that exercise (or physical activity) may mediate the strength of homeostatic appetite control. Cross-sectional studies have reported that habitually active individuals are able to better compensate for high-energy preloads during subsequent feeding episodes than their inactive counterparts [163-165]. Similarly, previously inactive individuals were able to better distinguish and adjust subsequent intake following high and low energy pre-loads after six weeks of aerobic exercise [166]. Twelve weeks of aerobic exercise has also been shown to increase post-prandial satiety in overweight and obese individuals [152,153], with this increase in satiety acting to offset a

concomitant increase in fasting hunger. This improvement may again reflect favourable changes in GI satiety hormones [153]. Thus, exercise appears to exert a dual effect on appetite control through an increase in excitatory drive but also in meal-induced satiety [152]. The idea that exercise or physical activity can sensitise (or indeed, dysregulate at low levels) homeostatic appetite control is not new, with Henry Taylor noting over 50 years ago that 'at low levels of physical activity appetite signals go awry and the body does not recognise that it is being overfed' [167]. However, only now is research beginning to examine how appetite control varies across the physical activity spectrum, and how differences in habitual activity can help explain differences in key appetite-related processes such as hunger, satiation and satiety [168].

4.4 Sedentariness Weakens Homeostatic Appetite Control

Due to the often modest reductions in body weight seen following exercise-based weight loss interventions [169], it is often stated that exercise is ineffective as a treatment for obesity [170]. However, notwithstanding the numerous beneficial health effects of exercise that are independent of body weight [171], studies indicate that high habitual physical activity is associated with lower FM [172], and physical activity is known to be a strong predictor of successful weight loss maintenance [173]. Evidence is also beginning to accumulate to suggest that there is more accurate coupling between energy intake and energy expenditure in active individuals compared to inactive individuals.

Evidence for a relationship between physical activity and energy intake was initially demonstrated by Mayer et al. in their study of Bengali jute mill workers [174], in which daily occupational physical activity and energy intake were closely matched at higher levels of expenditure. However, this coupling was lost in those performing low levels of occupational physical activity, such that daily energy intake exceeded expenditure in those performing 'sedentary' or 'light' work. More recently, Shook et al. [175] reported evidence of appetite dysregulation with low levels of habitual physical activity during a one year observational study, with those in the lowest quintile of physical activity exhibiting greater disinhibition, cravings for savoury foods and weight gain during the one year observation period compared to those in the highest quintile of physical activity. Furthermore, Myers et al. [172] reported that the percentage of time spent sedentary was positively associated with increased adiposity. Furthermore, the proposed J-shaped relationship between physical activity level and energy intake has been confirmed in a recent systematic review that plotted the standardized energy intake scores from 10 cross-sectional studies that measured energy intake across different levels of physical activity [176].

Such findings have led Blundell et al. [177] to amend the J-shaped relationship between physical activity and food intake found by Mayer et al. [174]. In the model presented by Blundell et al. [177], high levels of sedentariness and low levels of physical activity are representative of an 'unregulated zone' of appetite in which energy intake and energy expenditure are loosely coupled as a result of weak homeostatic regulation. In contrast, a 'regulated zone' of appetite exists at higher levels of physical activity where energy intake more closely matches energy expenditure (albeit at higher levels of absolute intake and expenditure) [177]. Whether this reflects an effect of exercise training rather than high levels of physical activity (accumulated over a range of physical activity thresholds) is unclear.

5.0 CONCLUSIONS

The homeostatic mechanisms that control appetite are described in an energy balance framework in which body weight and FM are loosely regulated. This regulatory control must be located in the central nervous system where there is integration of short-term and long-term excitatory and inhibitory signals of nutrient and energy availability and energy turnover. This system is further challenged by dynamic changes in energy balance and functional losses or gains in metabolically active tissue. It is therefore perhaps of little surprise that the homeostatic control mechanism of appetite appears unable to adequately match energy intake to energy needs in a permissive external environment that promotes overconsumption and sedentariness.

A large body of data has been accumulated on the regulation of adipose tissue and the impact of this on appetite (energy) homeostasis. More recently, roles for FFM and RMR as important excitatory features of homeostatic appetite control have emerged. Together, these features provide further understanding of the tonic excitatory and inhibitory signals of homeostatic appetite control. This feedback is in turn modulated by the action of an array of (predominately inhibitory) episodic GI signals and satiety hormones. A challenging issue is to determine how the post-prandial action of episodic satiety hormones and GI mechanisms can effectively brake the metabolic drive to eat in order to keep energy intake under control and prevent a positive energy balance and adipose tissue accumulation. An increased understanding of the mechanisms of homeostatic appetite control has led to numerous strategies aimed at improving appetite in attempt to counter weight gain and promote weight loss. To date, these attempts have been largely ineffective, but this represents a target for future research.

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EXPERT COMMENTARY

Overconsumption can be understood through an examination of homeostatic appetite control since appetite is a fundamental feature of humans that links biology with behaviour. This process is made complicated by the fact that humans are omnivores and- considered on a global scale – the food repertoire is huge. This situation incorporates two issues: what to eat, and how much to eat. The first represents the challenge of food choice. Because the food supply is so diverse and often unpredictable, there is no strong biological programming of what food should be eaten; feeding behaviour has to be adaptable and directed to whatever is available in the particular environment. Food choice is influenced by learning and, of course, the ultimate purpose is to provide nutrients to maintain life. However, the patterns of eating are extremely diverse and heavily influenced by culture and by those attributes of foods that determine their attractiveness. One major issue for humans living in advanced technological societies is that the preference for foods is liable to be determined by peripheral attributes unrelated to the nature and quality of the nutrient composition. This means that the behaviour of eating cannot be a tightly regulated variable.

A major issue with relevance to obesity is the relationship between appetite control and body fat. It has been suggested body fat is mechanistically regulated and, in turn, food intake is controlled in the interests of regulating the adipose tissue mass [77]. A feature of this situation is the proposition that food intake itself is biologically regulated via energy homeostasis. In other words, food intake is reducible to the control of energy homeostasis. In this approach, the condition of obesity can be understood through the application of a biological reductionist ideology in which molecular mechanisms regulating energy homeostasis in turn regulate FM. This position is not shaken by the comment that the presence of a world-wide epidemic of obesity provides rather good evidence that body fat is not a tightly regulated variable [6]. Moreover, given the earlier comments about food choice, it can be appreciated that the amount of energy that people put into their mouths is heavily dependent on foods selected. Since this selection is not heavily programmed by biology, a regulation of energy intake through biology alone is problematic.

Of course, the presence of adipose tissue is central to the definition and existence of obesity. This adipocentric view appeared to be fully confirmed by the discovery of leptin which is assigned key roles in energy homeostasis and the biological regulation of FM. This approach has dominated the research agenda for over a quarter of a century and has fostered the view that the solution to obesity can be found in the molecular operations of adipose tissue. It is worth considering that the functions of body fat have evolutionary significance and vary between species; even within mammals body fat depots serve different adaptive functions depending on the ecological circumstances [178,179]. It may also be asked what principles of obesity management have emerged

from a primary focus on body fat? The most potent treatment for obesity did not arise from investigations of FM regulation or the molecular basis of adiposity. Bariatric surgery involves removing or by-passing a healthy organ, the stomach, which is not believed to be the cause of obesity but which logically should prevent consumed food from being digested and absorbed. As is well documented, significant weight loss is achieved by a counterintuitive suppression of appetite (and associated changes in endocrine signals).

It is worth debating whether the regulation of body fat should be the central focus of research on obesity with an associated concentration of research on adipose tissue. The argument for a regulation of energy homeostasis linked to the regulation of body fat, can be contrasted with the equally legitimate view of obesity as the output of a complex system. This complex system approach posits dynamic interactions among aspects of the nutritional, psychological, social and biological environments. The approach set out in this review envisages a complex obesity network embracing homeostatic appetite control within an energy balance framework. The key proposition is that the drive for food arises from the demand for energy to maintain the body's vital organs and metabolic processes. This concept does not require a tight regulation of intake (as embodied by the idea of energy homeostasis). This view has evolutionary coherence since it posits that food intake is driven by the need to supply energy to meet metabolic activity of vital organs rather than to regulate the amount of body fat. It can account for several puzzling features of obesity including the question of why certain people continue to express a strong drive for food in the presence of large amounts of stored energy in the body; and why the drive for food actually increases as people gain weight (FFM and FM). Furthermore, if it is established that losses of FFM drive hunger and food intake during periods of weight loss, strategies that attenuate these losses (e.g. protein or amino acid supplementation or exercise) may be of particular interest in the future. The formulation proposed here does not minimise the search for molecular mechanisms, but does alter the direction of the search and brings into play tissues and organs related to fat-free mass in addition to fat stores.

KEY POINTS

1. Homeostatic appetite control embodies both excitatory and inhibitory signals that influence appetite and food intake via tonic (long-term) and episodic (short-term) control mechanisms.
2. Energy expenditure and its determinants such as fat-free mass and resting metabolic rate are key tonic drivers of appetite and food intake.
3. The interactions between energy expenditure and energy intake are a central feature of appetite control.

4. Molecular signalling pathways linking energy expenditure and energy intake are key targets for research.
5. Fat mass influences appetite through positive and negative processes and its effect is modulated by the amount adipose tissue.
6. Gastrointestinal peptide signalling plays a role in the episodic control of appetite but there is no unique satiety peptide.
7. Individual variability in postprandial peptide profiles is a noticeable property of episodic appetite control, and this variability helps to explain differing patterns of eating and treatment outcomes to weight loss interventions.

Figure Legends

Figure 1: Figure shows the satiety cascade above changes in subjective hunger (mm) and total ghrelin (pg/ml) in response to high-fat and high-carbohydrate meals during the early and late phases of satiety. The focus is placed on changes in ghrelin since this is thought to be the most closely related to patterns of hunger. These phases have been mapped onto the phases of the Satiety Cascade to provide a visual representation of how profiles of hunger and peptides are modulated by additional homeostatic and non-homeostatic factors in the overall control of appetite. HF, high-fat; HC, high carbohydrate.

Figure 2: This figure shows the mean responses of insulin, total ghrelin, glucagon-like peptide-1 and peptide tyrosine tyrosine to high-fat and low-fat isoenergetic meals of the same weight (Panel A). To illustrate the individual variability inherent in these appetite-related hormones, the individual profiles for glucagon-like peptide-1 (Panel B) and ghrelin (Panel C) in response to high-fat and low-fat meals are displayed in Data adapted from Gibbons et al. [16]. HF, high-fat; LF, low-fat, GLP-1, Glucagon-like peptide-1; PYY, peptide tyrosine tyrosine.

Figure 3: Schematic representation of the biological factors involved in homeostatic appetite control. This figure has been adapted from MacLean et al. [14], and was originally published as a summary of a National Institute of Health working group on the biological aspects of appetite control (June, 2015). The figure shows the interaction between tonic and episodic biological processes that, in turn, can be modulated by the energy expenditure involved in daily patterns of activity and sedentariness. The figure illustrates an approach to homeostatic appetite control within and energy balance framework. In turn, this framework will be incorporated within the complex system map of obesity [180]. EI, energy intake; EE, energy expenditure; GI; gastrointestinal; CCK, cholecystokinin; GLP-1, glucagon-like peptide-; PYY, peptide tyrosine tyrosine; FFM, fat-free mass; FM, fat mass; RMR, resting metabolic rate; TEF, thermic effect of food; EAT, exercise activity thermogenesis.

Figure 4: Panel A shows the mean hunger suppression after high-fat and low-fat meals, while Panel B shows the individual profiles of hunger for each participant after the same meals. Data adapted from Gibbons et al. [16]. HF, high-fat; LF, low-fat.

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** This systematic reviews examines the effectiveness of exercise for weight loss, and supports the use of exercise as a weight loss intervention (particularly when combined with dietary change).

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