THE CONTROL OF FOOD INTAKE IN HUMANS

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Updated November 20, 2022

ABSTRACT

Knowledge of the factors influencing food intake is crucial to form an understanding of energy balance and obesity. Classical physiological feedback models propose that eating behavior is stimulated and inhibited by internal signaling systems (for the drive and suppression of eating, respectively) to maintain stability of the internal environment (usually energy or nutrient stores). However day-to-day food intake involves complex interactions of both internal and external inputs coordinated through homeostatic, hedonic, and cognitive processes in the brain. Twenty-five years ago, the term 'obesogenic environment' entered into scientific discourse and implies that prompts, cues, and triggers from the external environment are largely responsible for the increases in food intake that underlie the epidemic of obesity. This approach revitalized interest in the sensory and external stimulation of food intake and has drawn attention to the hedonic dimension of appetite. There is now a very strong current of thought that energy balance regulation is asymmetric and excess food intake is due to poor homoeostatic defense against positive energy balances in an environment rich in available, accessible, and readily assimilated food energy. This does not mean that regulatory signals concerned with energy balance regulation are unimportant. Indeed, they appear to be of incremental importance in prolonged negative energy balances and help explain control and loss of control of food intake as a dynamic continuum.

INTRODUCTION

Traditionally food intake has been researched within the homeostatic approach to physiological systems pioneered by Claude Bernard (1), Walter Cannon (2) and others, and because eating is a form of behavior, it forms part of what Curt Richter referred to as the behavioral regulation of body weight (or behavioral homeostasis) (3). This approach views food intake as the vehicle for energy supply whose expression is modulated by the metabolic requirement to replenish energy stores. The idea was that eating behavior is stimulated and inhibited by internal signaling systems (for the drive and suppression of eating, respectively) in order to maintain stability in the internal environment (energy stores, tissue needs). Since this time, it has become clear that energy intake is not as tightly

regulated under modern environmental conditions as symmetrical negative feedback models initially suggested. Compensatory changes in physiology and behavior are more pronounced in response to negative than positive energy balances. Furthermore, energy intake is determined by eating behavior, which itself, may be determined by a number of complex physiological, environmental, social, and cultural factors. One should not perhaps expect to see strict regulation of food or energy intake on a day-to-day basis in modern environments.

IS EATING BEHAVIOUR REGULATED?

The control of appetite is often viewed to operate within an energy balance model of body weight regulation, but this should not lead to the view that appetite is controlled simply as an outcome of energy balance. Eating (food, energy, and nutrient intake) is a form of behavior, and like many aspects of volitional behavior, the factors leading to changes in that behavior are complex and are the outcome of factors which can be described by behavior change models. Using a COM-B model of behavior (Capability, Opportunity, Motivation, Behavior) (4), these factors include capability (psychological or physical ability to enact the behavior), motivation (reflective and automatic mechanisms activate or inhibit behavior), opportunity (physical and social environments that enables the behavior). Given the interacting and complex nature of these influences it is to be expected that unless homeostatic or other physiological feedback signals are particularly powerful, their effects on eating behavior would be difficult to detect. It is often implied (but not explicitly stated) that eating behavior is part of a feedback loop that is subsumed to the regulation of energy balance, but under the conditions of modern environments, there is little rationale for why eating behavior *per se* should be a regulated phenomenon as described by classic homeostatic models. Eating behavior may show

repeated patterns which are stable over time, but these patterns may be quite different from the concept of regulation described in typical homeostatic models of blood glucose regulation or thermoregulation for example.

While eating behavior is influenced by a number of factors, it is reasonable to argue that some of those factors may become particularly salient under specific physiological or environmental circumstances. This is important as energy balance regulation appears asymmetric, with compensatory changes in physiology and behavior more pronounced in response to negative than positive energy balances. The exact mechanisms that oppose energy deficits are complex, inter-related, and individually subtle (5, 6). While energy expenditure and its components change in response to energy deficits in a quantitatively important manner, it is likely that changes in energy intake (EI) have a greater capacity to produce relatively large alterations in energy balance and body composition (7). The physiological and psychological impacts of weight loss likely occur on a continuum, with the point on this continuum influenced by (i) the degree of energy deficit, (ii) its duration, (iii) body composition at the onset of the energy deficit, and (iv) the psychosocial environment in which it occurs (8). In contrast, as weight is progressively gained there is very little evidence of physiological or behavioral systems exerting negative feedback to actively limit further weight gain. However, there is considerable heterogeneity in the rate of weight gain during overfeeding (9), which may in part, reflect inter-individual variations in physical activity and/or partitioning the excess energy between fat mass (FM) and fat-free mass (FFM) (10, 11).

The implication of asymmetric energy balance regulation would be that appetite is under stronger physiological control in relation to negative energy balances, whereas in a state of energy balance or

positive energy balances weak linkages (negative feedback) exist between physiological functioning, food intake, and the motivation to eat. If energy balance regulation is asymmetric and modern environments are spatially and temporally rich in energy dense foods, it is logical to assume that many of the factors that shape eating behavior and energy intake are due to environmental influences such as sensory and environmental cues for food intake (which are presumably mediated through hedonic and other affective mechanisms). There is now a strong current of thought that a major cause of an increase in food intake associated with the rise of obesity resides in the hedonic rather than the homeostatic system. Some authors argue that in the resource limiting environments in which we evolved, hedonic and homeostatic systems functioned in a synchronized manner to facilitate over consumption during relatively brief periods of food abundance. In an environment where food resources are unpredictable and finite, overconsumption would have been an adaptive behavior limited (capability, opportunity) by environmental uncertainty. Natural selection would favor such behaviors. There would have been little need to evolve systems that protect against weight gain as it would be an improbable outcome in resource limited environments. This does not mean that the so-called 'energy homeostasis system' is no longer important in modern environments. Modern day environments have changed very rapidly and radically relative to the environment shaping energy balance regulation. Therefore, to understand how homeostasis and hedonics may influence food intake in modern environments requires an appreciation of the asymmetry of energy balance regulation, the time course over which such regulation may operate, and the very rapid time-course over which the modern food environment has changed.

FOOD INTAKE AND APPETITE CONTROL

The Motivation to Eat

Within the COM-B model of behavior, motivation is an important factor influencing behavior if capability and opportunity do not constrain behavior (as is the case in today's so called 'obesogenic' environment). In the field of ingestive behavior, motivation to eat usually refers to reflective processes that are subjectively experienced or expressed. They are often believed to relate to underlying physiological or external environmental influences, but have the status of a self-reported, subjectively expressed psychological construct. Appetite has been defined as the subjective expression of willingness or motivation associated with qualitative selection and quantitative consumption of specific foods during an ingestive event (12). Appetite is not necessarily solely related to situations of nutritional depletion and can be influenced by a number of physiological and non-physiological factors. Appetites are specific to certain foods, often learned and frequently sensory specific (13). Unfortunately, the term appetite control is often used without specifying what is being controlled. Does eating behavior change to maintain some constancy and motivation to eat? Does appetite change in order to control food intake around some central tendency? Does appetite change with the aim of changing food intake to regulate energy balance? Often it is the latter view that is implied but not clearly articulated.

Table 1. Key Psychobiological Components of Appetite (14, 15)	
COMPONENT OF APPETITE	**DEFINITION**
Hunger	The subjective sensation described as the primary motivation to eat. An increase in subjective hunger usually predicts meal initiation under *ad libitum* feeding situation. It does not necessarily predict type or amount of food eaten.
Satiation	The process during a meal that generates the negative feedback leading to its termination (within-meal inhibition).
Satiety	The degree of satisfaction and/or fullness following food consumption. This bears some reciprocal relationship to hunger and inhibits further motivation to eating.
Liking	The sensory pleasure elicited by contact with food contributing to the hedonic motivation to consume (wanting).
Wanting	The motivation to consume a specific food, manifesting explicitly (desire to eat) or implicitly.

Because a great deal of human behavior is both reactive and learned, it is possible that the environment can produce prompts, cues, and stimuli that influence learned patterns of motivation to eat. Because eating behavior is a significant determinant of energy balance it is often argued that manipulation or control of motivation to eat (commonly termed appetite control) can be used as a means to prevent excess energy intake and obesity, usually via putative mechanisms of satiety. This is a logical proposition particularly if appetite is not actually very tightly controlled with reference to overconsumption and the development of obesity. Some characteristics of the expression of appetite do appear to render individuals vulnerable to over-consumption of food - these characteristics can be regarded as risk factors that vary between individuals (16). Other significant and salient environmental, acquired, and inherited influences on eating behavior aside, there has been considerable work dedicated to trying to conceptualize

and understand putative mechanisms that may link motivation to eat to food and energy intake.

A CONCEPTUAL THEORETICAL MODEL LINKING PHYSIOLOGY, MOTIVATION, AND BEHAVIOR TO FOOD INTAKE

One of the most commonly accepted theoretical models for the control of appetite is the satiety cascade, a putative network of interactions between physiological, psychological, and behavioral factors which form a psychobiological system. The term psychobiological assumes that physiological functions provide internal cues that may impact motivation to eat, and can be conceptualized on three levels (Figure 1). These are the levels of psychological events (hunger perception, cravings, and hedonic sensations) and behavioral operations (meals, snacks, energy, and macronutrient intakes); the level of peripheral physiology and metabolic events; and the level of

neurotransmitter and metabolic interactions in the brain (17) (see for Andermann & Lowell (18) for a review of the central control of food intake). Appetite reflects the synchronous operation of events and processes in the three levels. Implicit in this theoretical model is the notion that the physiological signaling systems influence motivation to eat and that motivation to eat shapes eating behavior. The model suggests that neural events trigger and guide behavior, but each act of behavior involves a response in the peripheral physiological system. In turn, these physiological events are translated into brain neurochemical activity that is related to the strength of motivation to eat and the willingness to refrain from eating. In this model it is assumed that motivations to eat change with the aim of changing food intake to regulate energy balance. The lower part of the psychobiological system (Figure 1) illustrates the satiety cascade links motivation and behavior to peripheral and central signals related to eating. It also includes those behavioral actions which actually form the structure of eating, and those processes which follow the termination of eating and which are referred to as post-ingestive or post-prandial events.
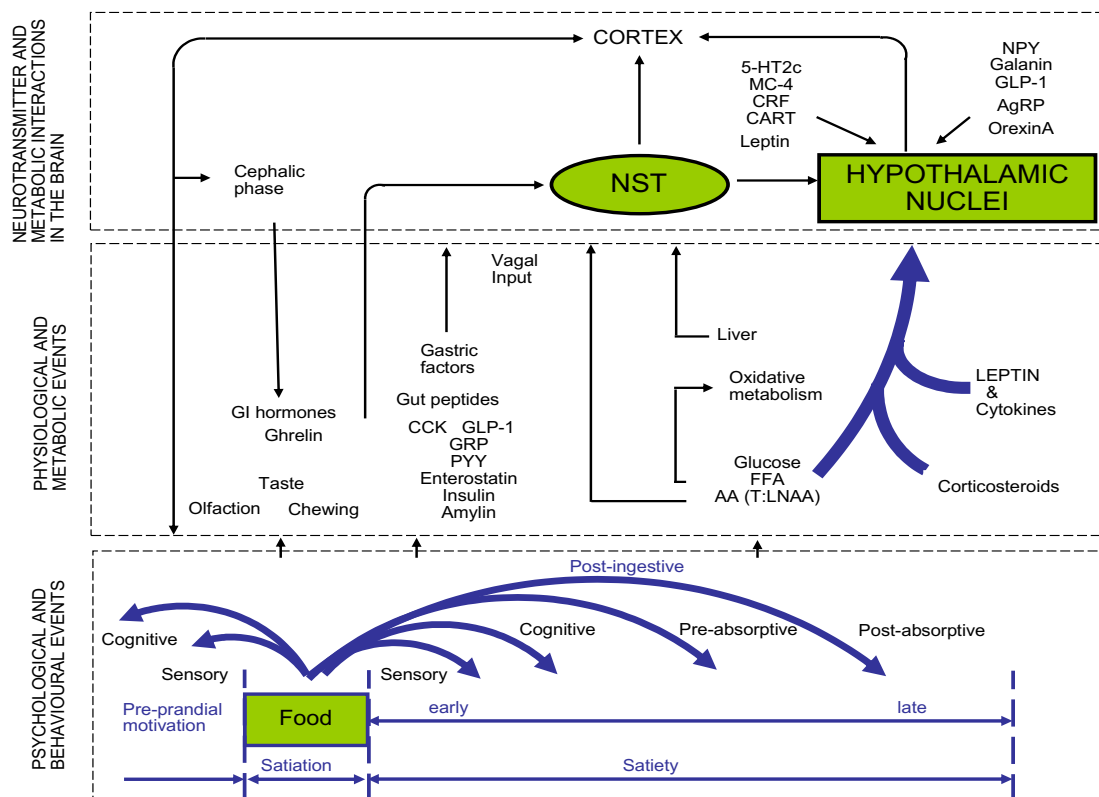

Figure 1. The satiety cascade, as originally presented (17), showing the expression of appetite as the relationship between three levels of operations: the behavioral pattern, peripheral physiology and metabolism, and brain activity. See for Andermann & Lowell (18) for a more recent review of the central control of food intake. PVN, paraventricular nucleus; NST, nucleus of the tractus solitarius; CCK, cholecystokinin; FFA, free fatty acids; T: LNAA, tryptophan: large neutral amino acids.

EPISODIC AND TONIC SIGNALS OF APPETITE CONTROL

Traditionally a distinction has been drawn between episodic and tonic signals in the control of appetite (19). Episodic signals are mainly inhibitory (but can be excitatory) and are usually generated by episodes of eating. These signals oscillate in accordance with the pattern of eating, and most are closely associated with the signaling of satiety. Tonic signals arise from tissue energy stores such as adipose tissue and metabolically active tissues to exert some degree of feedback on the expression of appetite to match day-to-day food intake with longer-term energy needs. These two sets of signals, one set responding sharply to nutrient flux and the other providing a slow modulation of appetite and food intake, are integrated within complex brain networks that control the overall expression of appetite. Examination of these putative mechanisms tend to be more common in acute or short-term studies of ingestive behavior in which the primary change is motivation to eat or eating behavior rather than longer term studies. Short-term experiments are valuable for mechanistic understanding, but such studies often make the assumption that changes in the motivation to eat or eating behavior will translate in the long term into aspect of energy balance regulation. However, concentrating only on short-term effects without considering the longer-term time scale may fail to reveal the way that food intake is affected or energy balance is regulated as the experimental time window is much narrower than is relevant for such regulation to occur (e.g., weeks and months rather than minutes, hours or days). Put simply, many investigators may be looking for evidence of regulation over a period where no such regulation is likely to occur. It is therefore important to distinguish between longer term (tonic) mechanisms of putative energy balance regulation and shorter term (acute, episodic) mechanisms that may affect motivation to eat or EI.

Episodic Appetite Signals

Episodic signals are those physiological events that are triggered as responses to the ingestion of food. These form the inhibitory processes which first of all stop eating and then prevent its re-occurrence and are therefore termed satiety signals. The types of signals involved in terminating a meal (satiation) and preventing further consumption (post meal satiety) can be represented by the satiety cascade. Initially the brain is informed about the amount of food ingested and its nutrient content via sensory input. The gastrointestinal tract is equipped with specialized chemo- and mechano-receptors that monitor physiological activity and pass information to the brain mainly via the vagus nerve (20). This afferent information constitutes one class of 'satiety signals and forms part of the pre-absorptive control of appetite. It is usual to identify a postabsorptive phase that arises when nutrients have undergone digestion and have crossed the intestinal wall to enter the circulation. These products, constitute the flux of energy and nutrients into the circulation, may be metabolized in the peripheral tissues or organs, or may enter the brain directly via the circulation. In either case, these products constitute a further class of metabolic satiety signals. Additionally, products of digestion and agents responsible for their metabolism may reach the brain and bind to specific chemoreceptors, influence neurotransmitter synthesis or alter some aspect of neuronal metabolism. In each case the brain is informed about some aspects of the metabolic state resulting from food consumption. It seems likely that chemicals released by gastric stimuli or by food processing in the gastro-intestinal tract are involved in the control of appetite (21). Many of these chemicals are peptide neurotransmitters, and many peripherally administered peptides cause changes in food consumption (22). (Please refer to ENDOTEXT

chapter 'Endocrinology of The Gut and the Regulation of Body Weight and Metabolism' by Andrea Pucci and Rachel L. Batterham for additional information on gut hormones physiology).

Cholecystokinin

Cholecystokinin (CCK) is a hormone released in the proximal small intestine mediating meal termination (satiation) and possibly early phase satiety. CCK reduces meal size and also suppresses hunger before the meal; these effects do not depend on the nausea that sometimes accompanies an IV infusion (23). Food consumption (mainly protein and fat) stimulates the release of CCK (from duodenal mucosal cells), which in turn activates CCK-A type receptors in the pyloric region of the stomach. Fat in the form of free fatty acids (FFA) of carbon chain lengths C12 and above produce pronounced CCK releases (24, 25). This signal is transmitted via afferent fibers of the vagus nerve to the nucleus tractus solitarius (NTS) in the brain stem. From here the signal is relayed to the hypothalamic region where integration with other signals occurs.

Animal data suggest that endogenous CCK release mediates the pre-absorptive satiating effect of intestinal fat infusions, and may in turn be critical in regulating the intake of fat (26). As in rats, intestinal infusions of fat produce a reduction in food intake and promote satiety in humans (27). In humans the satiety effect of fat infused directly into the duodenum can be blocked by the CCKA receptor antagonist loxiglumide (28). High-fat breakfasts have been shown to produce both greater feelings of satiety (signified by reduced levels of hunger, desire to eat and prospective consumption) and elevated endogenous plasma CCK levels. Collectively, these studies support the theory that CCK plasma levels are a potent fat (or fatty acid) -stimulated endogenous satiety factor, whose effects on food intake and eating behavior are mediated by CCKA receptors.

It has also been shown that synthetic CCK-A type agonists suppress food intake in humans. A drug, known by the number ARL1718, caused a significant reduction in meal size and had a longer duration of action than observed after infusions of CCK itself. A number of other CCK analogues / CCK 1 receptor agonist treatments have been developed including most recently GW181771 (GlaxoSmithKline) and SR146131 (Sanofi-Aventis). Studies with such drugs, together with those on the peptide hormone itself, do suggest that CCK has the properties of a true satiation signal which contributes, under normal circumstances, to the termination of a meal. However, CCK is not uniquely involved in the expression of satiety and is also involved in a spectrum of physiological responses generated following nutrient consumption. The action of CCK certainly acts in concert with other meal-related events, such as gastric distention for example.

Glucagon-Like-Peptide-1

Glucagon-like peptide (GLP)-1 is an incretin hormone, released from the gut into the blood stream in response to intestinal nutrients. Endogenous GLP-1 levels increase following food intake, particular of carbohydrate (29, 30). These studies suggest a role for GLP-1 in mediating the effects of carbohydrate (specifically glucose) on appetite. In healthy men of normal weight, infusions of synthetic human GLP-1 (7-36) during the consumption of a fixed breakfast test meal, enhanced ratings of fullness and satiety when compared to the placebo infusion (31). During a later ad libitum lunch, food intake is also significantly reduced by the earlier GLP-1 infusion. Intravenous GLP-1 also dose-dependently reduces spontaneous food intake and adjusts appetite in healthy weight male volunteers. This marked reduction in food intake and enhancement in satiety is also observed in male

patients living with overweight or obesity and type 2 diabetes. In men living with obesity, intravenous GLP-1 potently reduces food intake either during or post-infusion (32) and, at lower sub-anorectic doses, slows gastric emptying. Reductions in intake and slowed gastric emptying are accompanied by decreased feelings of hunger, desire to eat and prospective consumption, and a prolonged period of post-meal satiety. These data demonstrate that exogenous GLP-1 reduces food intake and enhances in satiety in humans, both those healthy weight and living with obesity. However, it should be kept in mind that the doses of GLP-1 often administered are usually higher than the normal values seen in blood after a meal. Consequently, although GLP-1 receptors could be a possible target for anti-obesity drugs, the physiological role of GLP-1 itself in the normal mediation of satiety is still not confirmed. Nonetheless, GLP-1 through its action as an incretin which prompts the release of insulin, will certainly have some indirect role on the pattern of eating behavior. Interestingly, two of the most promising drug options for people living with obesity are liraglutide and semaglutide; both GLP-1 agonists. These drugs have been shown to decrease hunger (33) and/or increase satiety (34). The action of the pharmacological agents may mean that people living with obesity gain some control over their eating behaviors, however longer-term studies are required to investigate their true potential. In addition, it should be noted that the GLP-1 receptors responsible for the anti-obesity action of semaglutide and liraglutide are located in the brain rather than the periphery.

Peptide YY $_{3-36}$

Peptide YY $_{3-36}$ (PYY $_{3-36}$) is one of the two main endogenous forms of PYY. It is produced from the cleavage of PYY $_{1-36}$ (the other major form of PYY) by dipeptidyl peptidase IV (DPP IV). PYY is a 36 amino acid 'hind gut' peptide released from endocrine cells in the distal small intestine and large intestine. This hormone is similar in structure to the orexigenic neuropeptide NPY (70% amino acid sequence identity), and in the past, PYY has been regarded, like NPY, as a potent stimulator of food intake. However, in a series of studies in rats, mice and in one human study (all included in one paper), Batterham et al. (35) have demonstrated that peripheral PYY $_{3-36}$ administration reduces food intake and inhibits weight gain in rodents. These effects on intake and body weight are not observed in transgenic animals lacking NPY Y2 receptors (the NPY Y2 receptor knock-out), thereby implicating these receptors in mediating the anorectic effects of PYY. PYY release in the distal intestine is triggered by a variety of nutrients, including fats (particularly FFA), some forms of fiber and bile acid (24, 25). In humans, endogenous PYY is released predominantly after, rather than during a meal (35, 36) and causes a decrease in gastric emptying (the so-called 'ileal brake'). Thus, it is more associated with post-meal satiety. PYY (including PYY $_{3-36}$) can cross the blood brain barrier via a non-saturable mechanism. Moreover, some of the effects of peripheral PYY $_{3-36}$ on food intake are either independent of or dependent on vagal afferents running from the periphery to the brain (37, 38).

With regard to the effect of PYY on human appetite, Batterham et al. (35) demonstrated that in healthy humans a 90-minute PYY $_{3-36}$ infusion reduced hunger and subsequent food intake two hours later. In a further report, PYY infusions in people who were either a healthy weight or living with obesity caused a 30% reduction in lunch intake post infusion and decreased the 24 h energy intake by 23% in those with a healthy weight and by 16% in those living with obesity (36). The natural plasma levels of PYY were lower in those with living with obesity than in the healthy weight participants, and were inversely correlated with the body mass index. The lower levels of PYY in those with living with obesity could mean a weaker satiety signaling through this hormone and therefore a greater possibility of over-consumption. However, as the

authors noted these effects required doses greater than the normal physiological range of endogenous PYY and marked nausea was observed in one experiment (39-41).

Amylin

Research has also focused on amylin, a pancreatic rather than a gastrointestinal hormone, which also has a potent effect on both food intake and body weight (42). Peripheral administration of amylin reduces food intake in mice and rats, and meal size in rats. Chronic or peripheral administration of amylin over a period of 5 to 10 days produces significant reductions in cumulative food intake and body mass of rats (43). Thus, amylin appears to be a component part of the appetite regulation system. The effects of amylin on human food intake, food choice or appetite expression has yet to be fully assessed. However, pramlintide (a human amylin analogue), given to replace deficits in endogenous amylin in people with diabetes, has been shown to alter body weight in people living with obesity and diabetes treated with insulin (44-46) and people with obesity without diabetes (47). In healthy weight participants pramlintide induces reductions in meal intake and duration, and reduces pre meal appetite (48). Similar effects of pramlintide on intake and eating behavior are reported in people living with obesity (with and without type 2 diabetes) (49, 50).

Ghrelin

In contrast to the peptides mentioned above, ghrelin is the only known excitatory peptide released in the gastrointestinal system. Ghrelin is a 28-amino acid peptide that stimulates the release of growth hormone from the pituitary (51). Secreted primarily from the stomach, it is also found in a number of other tissues (52, 53). Ghrelin was the first excitatory peptide discovered and acts upon the hypothalamic arcuate nucleus (51, 54, 55). The composition and action of ghrelin is uniquely modified by the addition of an octanoyl group to the serine residue at position three. 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 (56). Ghrelin's effects on food intake are mediated by neuropeptide Y (NPY) and agouti-related protein in the central nervous system (57).

The majority (80-90%) of circulating ghrelin is in the deacylated form (51). Two theories have been proposed, firstly that deacylated ghrelin could result from incomplete acylation of the peptide, with both forms utilising differently regulated pathways, or secondly, that DG could result from the deacylation of ghrelin (58). More recently, deacylated ghrelin has been termed the inactive form. Ghrelin is thought to be involved in meal initiation as it is high during periods of fasting and decreases in response to food intake, thus suggesting a physiological role for ghrelin in meal initiation (59). Intravenous infusion or subcutaneous injection of ghrelin in humans increases both feelings of hunger and food intake (56, 60) and to promote increased food intake, weight gain and adiposity in rodents (60).

Satiety Cascade Peptides

In the overall control of the eating pattern, the sequential release and then de-activation of the peptides described above, can account for the evolving biological profile of influence over the sense of hunger and the feeling of fullness (61). The actions of these hormones therefore contribute to the termination of an eating episode (thereby controlling meal size) and subsequently influence the strength and duration of the suppression of eating after a meal. Evidence of this is shown by Gibbons et al. (62) whereby the post meal period was separated into early and late phases of satiety. It should be noted that whilst the profiles of peptide response shown in

papers often show the expected increase and decrease (in the case of satiety peptides) and decrease and increase (in the case of ghrelin), there is a wide degree of individual variability in peptide responses. This is not often commented on, or shown. Furthermore, the majority of papers do not measure a range of peptides but rather focus on one or two. Individual variability in the release and maintenance of the levels of hormones (or the sensitivity of receptors) may determine whether some individuals are prone to snacking between meals or to other forms of opportunistic eating. The overall strength or weakness of the action of these peptides will help to determine whether individuals are resistant or susceptible to weight gain. Individual variability in the response of gut peptides to different food types has been shown more recently (63) and can be seen in Figure 2. At present, it does not appear that a poor response in one peptide means a poor response in all peptides, and it is likely that the cumulative response of the peptides (of which there are many) is key for the modulation of appetite and EI. Since different foods may produce the same effect on hunger and fullness but display quite distinctive profiles of post-prandial peptides, this suggests that the satiety signaling system is complex and there is no single unique pattern of peptides that defines satiety. This questions to what extent short term satiety can be accounted for by individual changes in putative satiety peptides, and what other factors may contribute to subjective satiety or cessation of eating behavior in humans.
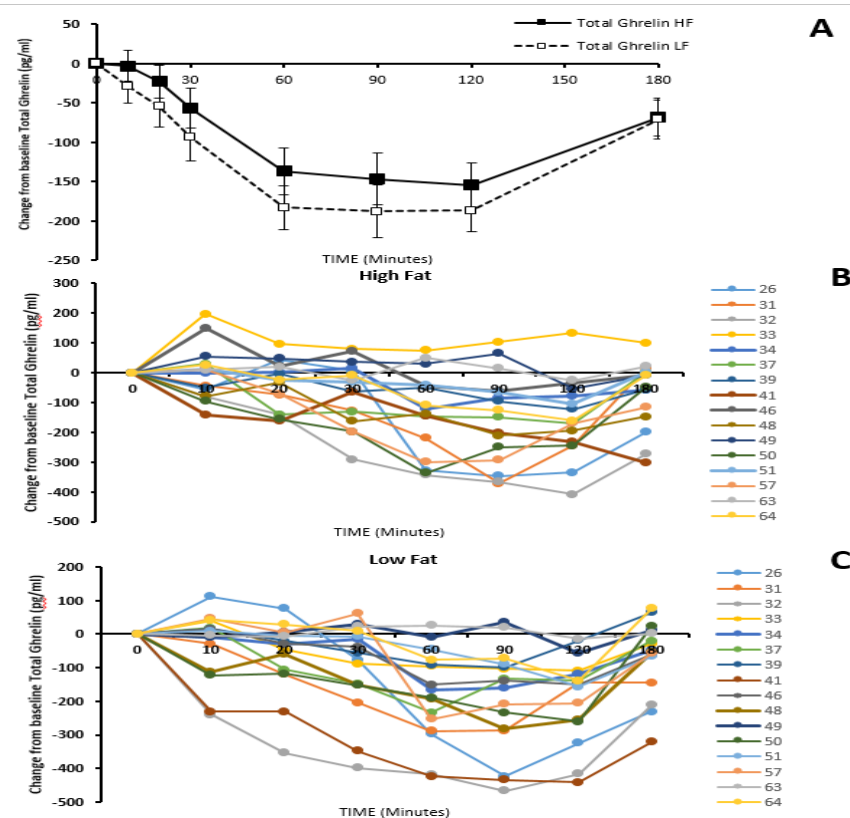

Figure 2. Panel A shows the average ghrelin suppression after high fat and low-fat meals and Panel B and C shows the individual profiles of ghrelin for each participant after both high and low-fat meals. Adapted from (63).

TONIC SIGNALS OF APPETITE CONTROL

Ghrelin and the Hunger Drive

As noted above, ghrelin is an episodic peptide increasing during periods of fasting and decreasing in response to food intake. However, ghrelin is also unique since it has been proposed that in addition to being linked to the initiation of eating, ghrelin also acts as a compensatory hormone. Circulating ghrelin decreases in response to overfeeding and increases in response to chronic negative energy balance such as occurs with exercise or anorexia nervosa (64). This means that in people living with obesity and in animals experimentally made fat, circulating ghrelin levels would be reduced in an apparent attempt to restore a normal body weight status. Therefore, ghrelin illustrates the characteristics of both an episodic and tonic signal in appetite control. From meal to meal the oscillations in the ghrelin profile act to initiate and to suppress hunger; over longer periods of time, some factor associated with fat mass applies a general modulation over the profile of ghrelin and therefore, in principle, over the experienced intensity of hunger. At some point, it seems likely that people living with obesity are insensitive to lower ghrelin levels and/or other factors outweigh the relative importance of circulating ghrelin. When weight is lost, for example following a period of food restriction and weight loss, ghrelin levels would rise (or normalize), and therefore promote the feeling of hunger. This is likely to be one of the signals that makes the loss of body weight difficult to maintain. Ghrelin blockade therefore may prove a useful anti-obesity treatment. Whilst people living with obesity have lower fasting ghrelin levels, they have been shown to show a similar response to infused ghrelin as normal-weight participants, that is, increased food intake (65). Ghrelin levels in people living with obesity do fall after food, but not to the same degree as healthy weight participants in whom

different calorie loads were shown to decrease ghrelin levels in a dose-response manner, but in people living with obesity this clarity was not shown as clearly (66). This points towards a potential mechanism for weight gain to be a consequence of a down regulation of gut peptide signaling and that the sensitivity to ghrelin is being overridden by other factors, for example, hedonic control of appetite.

The Role of Leptin

One of the classical theories of appetite control has involved the notion of a long-term signal, leptin, which informs the brain about the state of energy stored in adipose tissue (67). In 1994 a mouse gene that controls the expression of a protein by adipose tissue which could be measured in the peripheral circulation (leptin) was discovery. It is now well accepted that there is a good correlation between the plasma levels of leptin and adipose tissue (68), and leptin interacts with NPY, one of the brain's most potent neurochemicals involved in appetite, and with the melanocortin system, in the central control of appetite. Alongside other neuromodulators involved in a peripheral-central circuit, leptin links adipose tissue with central appetite mechanisms and metabolic activity. A number of mutations in the genes controlling molecules in the leptin-insulin pathways are associated with the loss of appetite control and obesity. For example, the MC4-R mutation (melanocortin concentrating hormone receptor 4) leads to an excessive appetite and massive obesity in children, similar to leptin deficiency. Studies have shown for individuals with a genetic form of leptin deficiency that leptin treatment produces dramatic weight loss, an effect associated with marked decreases in hunger (69-71). Further, the administration of exogenous leptin to humans, with either an insufficiency in or a specific deficit of endogenous leptin appears to strengthen within meal

satiation and post meal satiety (71, 72). However, leptin-based obesity treatments for most individuals with obesity seem inappropriate given they appear leptin insensitive rather than leptin deficient. Indeed, despite extensive literature on leptin and other putative feedback signals arising from adipose tissue (73, 74), there appears to be limited evidence in humans of the extent to which changes in adipose tissue exert strong negative feedback on motivation to eat or EI in individuals in approximate daily energy balance or modest positive imbalances (as characterize the majority of individuals in the modern environment). As a number of questions still exist regarding the applicability of a 'lipostatic' control system to the regulation of appetite in humans free from congenital leptin deficiency (75). Consequently, recent models of human appetite have attempted to integrate the role of both FM and FFM into the control of appetite and energy balance to better account for the peripheral signals of appetite.

Fat-Free Mass and Resting Metabolic Rate and Associations with Appetite

A conceptual model of human appetite that incorporates the energetic demands of metabolically active tissues has been proposed, with a tonic drive to eat arising from components of energy expenditure (e.g., resting metabolic rate; RMR) and its main determinants (e.g., FFM). This model is based on a series of studies demonstrating that FFM, but not FM, is associated with hunger and EI under conditons of energy balance (76-81) (see Figure 3). For example, Blundell et al. (78) reported that FFM was associated with self-selected (*ad libitum*) meal size and total daily EI in 93 individuals living with overweight or obesity. In contrast, no associations were found between FM and EI. Resting metabolic rate, of which FFM is the main determinant (82), has also been found to be associated within-day hunger sensations and EI (80, 81, 83). These findings have been replicated in studies employing a wide range of participants and under a variety of experimental conditions, with the associations between FFM and EI observed under laboratory (79-81, 84) and free-living settings (85, 86), in new born babies (87), adolescents (88, 89), normal weight women (90), people living with moderate (91) or extreme obesity (92), and people of varying ethnic origin (93, 94). These studies provide evidence that the relationship between FFM and EI exists across the entire age spectrum from birth (87), through childhood and adolescence (88) and into adulthood (78, 81, 84, 93, 95) and older age (96). There is also limited evidence that losses of both FFM and FM may be associated with changes in appetite (97) and weight regain (98) following weight loss, suggesting that integrated models of weight loss that account for FFM and FM losses may better explain changes in appetite during prolonged energy deficit (see below sections). However, there are few prospective longitudinal studies relating changes in functional body composition to appetite or EI, and where there is evidence, it often from studies with extreme weight loss induced via semi-starvation or military training.
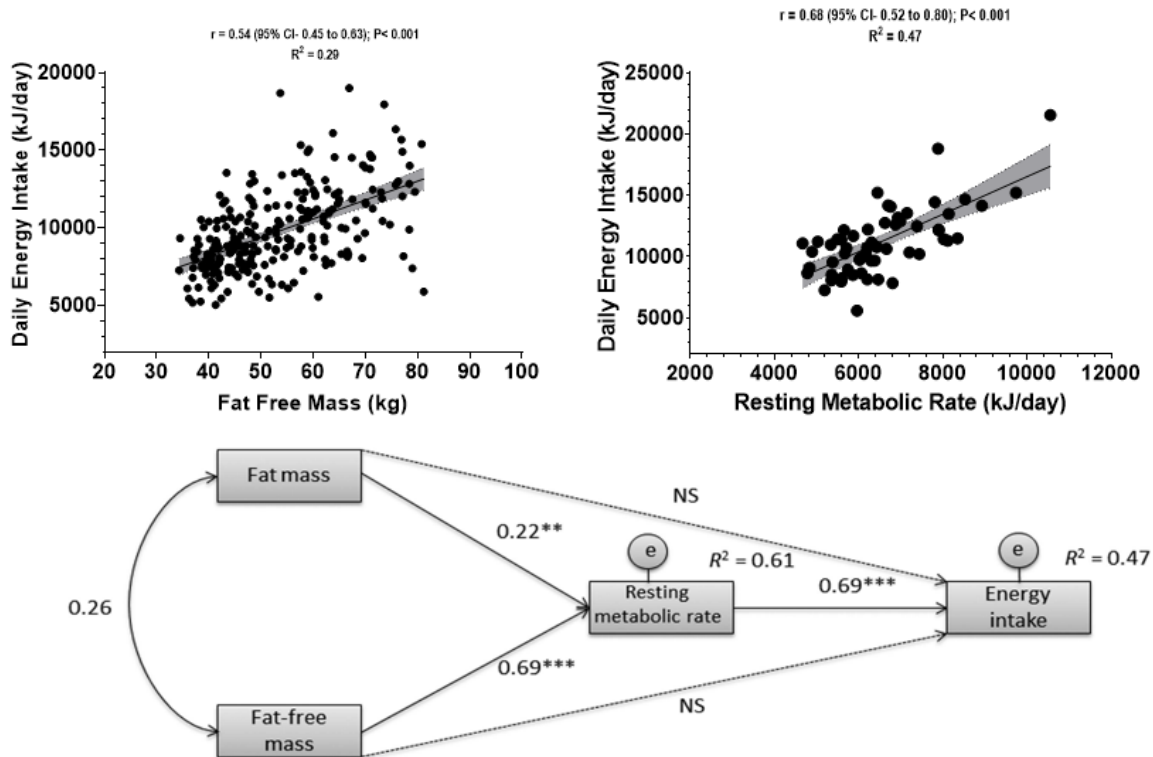
Figure 3. Association between fat-free mass, resting metabolic rate and daily energy intake (top panels), and a path diagram illustrating a mediation model for the direct effects of FM and FFM on RMR and RMR on EI, the indirect effect of FM and FFM on EI mediated by RMR, and the squared multiple correlations (R^2) for RMR and EI. Data originally reported in Hopkins *et al.* (80, 85).

While often not explicitly discussed in relation to models of human appetite, the concept that energy needs exert influence on food intake is not new. In 1962, Kenneth Blaxter (99) noted that the basal metabolism of mature animals of different species increases to a fractional power of weight, with small animals have a higher basal metabolism per kilogram of weight than the large ones. This implies that to maintain body weight, small animals must obtain each day from food a larger number of calories per unit of the weight the large ones. If the total habitual energy expenditures of different species are all about the same multiples of their basal energy expenditure, then both the calorie intake and the basal metabolism are likely to be proportional to the same fractional power of bodyweight. Furthermore, the energetic demands of individual tissue-organs such as the liver (100) or the growth and maintenance of lean tissues (101, 102) have previously been suggested as sources of appetitive feedback. For example, Millward's protein-stat theory suggests that lean mass, and in particular skeletal muscle mass, is tightly regulated such that food intake (specifically, dietary protein) is directed to meet the needs of lean tissue growth and maintenance (101). This theory is based on the existence of an 'aminostatic' feedback mechanism in which food intake is adjusted in response to amino acid availability to meet the protein demands of lean tissue growth and maintenance.

Studies Examining the Associations between Fat-free Mass, Resting Metabolic Rate and Energy Intake

Using statistical mediation models, a number of cross-sectional studies conducted under conditions of energy balance have demonstrated that the effect of FFM on EI is mediated by RMR (80, 103) and total daily energy expenditure (TDEE) (104), suggesting that energy expenditure *per se* may exert influence over EI. For example, Hopkins et al. (80) reported that the effect of FFM on EI was fully mediated by RMR i.e. FFM had no 'direct' effect on EI but rather 'indirectly' influenced EI via its effect on RMR. In agreement with these findings, Piaggi et al. (104) reported that TDEE accounting for 80% of the observed effect that FFM exerted on EI in 107 healthy individuals. Such findings suggest that the associations between FFM and RMR with EI may reflect a 'mass-dependent' effect arising from the energetic demands of FFM and its constituent tissue-organs rather than a specific endocrine signal secreted by these tissue-organs. However, it should be acknowledged that such findings represent statistical rather than biological pathways. Furthermore, skeletal muscle, a major component of FFM by weight, secretes a large number of myokines (105) which provide a molecular signal for bi-directional communication with other organs (106). While myokines such as interleukin 6 (107) and irisin (108) have been linked to food intake and energy expenditure, the specific role that these (and other myokines) play in the control of appetite is unclear.

An important consideration in the proposed relationship between FFM and EI is that FFM is a heterogeneous tissue compartment that is comprised of numerous individual tissue-organs with wide ranging metabolic functions and mass-specific metabolic rates (109-111). Tissue-organ structure and function are tightly coupled and determine their tissue-specific metabolic rate (112). In turn, the tissue-specific metabolic rates of individual organs summate to determine whole-body metabolic rate (e.g., RMR). The maintenance of tissue-organ structural integrity and function is therefore a metabolic priority (112), but to date there has been little attempt to integrate individual tissue-organs and their mass-specific energy expenditures into homeostatic models of human appetite. Recently however, Casanova et al., (113) used whole-body magnetic resonance imaging to examine whether the masses of high-metabolic rate organs (brain, liver, heart and kidneys) were associated with fasting hunger in 21 healthy males (age= 25 ± 3 years; BMI = 23.4 ± 2.1 kg/m^2) (114). As expected, fasting hunger was associated with FFM (r = 0.39; p = 0.09) but not FM (r = -0.01; p = 0.99). Interestingley, the association between the combined masses of the high-metabolic rate organs and fasting hunger (r = 0.58; p = 0.01) was stronger than with FFM as a single uniform body compartment. In particular, liver (r = 0.51; p = 0.02) and skeletal muscle mass (r$_s$ = 0.57; p = 0.04) were strongly associated with fasting hunger. As the masses of the liver and skeletal muscle explained ~17% and ~21% of the variance in RMR, respectively, these findings again suggest that energy expenditure *per se* may exert influence over food intake.

Another important consideration is how behavioral components of total daily energy expenditure (e.g., physical activity or activity energy expenditure) influence energy intake. The effects of physical activity and/or exercise on appetite is discussed below. As noted, physical activity may influence the control of appetite via a number of physiological and psychological pathways (e.g., alterations in gastric emptying (115), appetite-related hormones (116), food reward (117), and eating behavior traits (118)). In addition, physical activity or exercise may also exert influence, albeit modestly, on appetite and EI via its contribution to TDEE. Hopkins et al. reported in 242 individuals in which physical activity and EI were

measured under free-living conditions that activity energy expenditure was independently associated with daily EI alongside FFM and RMR (86). As activity energy expenditure only explained 3% of the variance in total daily EI, its effect on daily EI was much more modest than that seen for FFM or RMR. This is perhaps not surprising given the smaller and more variable contribution of physical activity energy expenditure to TDEE as compared to FFM and RMR (119). It could be argued that while FFM and RMR are well placed to exert stable influence over day-to-day food intake, the contribution of physical activity energy expenditure to daily EI is likely to be weaker and more variable (and therefore, also harder to quantify).

Factors Affecting the Strength of Association Between Fat-Free Mass and Energy Expenditure with Energy Intake

It has been suggested that excess FM may disrupt the coupling between FFM and EI, with associations between FFM and EI weaker in those living with obesity than in healthy weight individuals (90, 95, 104, 120). Early work by Cugini et al. reported that a positive association existed between FFM and hunger, while FM and hunger were negatively associated, in healthy weight individuals (121). However, no such associations were seen between FFM or FM and hunger in those living with obesity (120). Based on these data, the authors suggested that FM accumulation may disrupt the feedback mechanisms linking these tissues to hunger. More recently, Grannell et al. reported a positive association between FFM and EI during an *ad libitum* test meal in 43 individuals living with severe obesity, but the strength of this association was weaker in individuals with a higher BMI (92). To further explore the moderating effect of FM, Casanova et al., (90) examined the linear and non-linear associations between body composition (FFM and FM), energy expenditure (RMR and TDEE) and EI (*ad libitum* test meal intake and

free-living 24-hour EI) in 45 healthy weight and 48 individuals living with obesity. Percentage body fat moderated the associations between RMR (β=-1.88; p=0.02) and TDEE (β=-1.91; p=0.03) with free-living 24-hour EI. Furthermore, FM was negatively associated with test meal EI only in the leaner group (r=-0.43; p=0.004), with a weak non-linear association observed between FM and EI in the whole sample (r^2=0.092; p=0.04).

Such findings point to a non-linear relationships between FM and EI, and this may help account for why negative associations between FM and EI have been observed in healthy weight individuals (121, 122), but studies in those living with overweight or obesity often report no association between FM and EI (79, 88, 91, 123). A weaker negative association between FM and EI at higher body fatness is in line with the notion of leptin and insulin resistance (124, 125), which may alter central and peripheral sensitivity to appetite-related feedback signals (126-128). Furthermore, while the contribution of FM to RMR is smaller than FFM (129), its contribution to RMR becomes proportionally larger as FM increases with excessive weight gain. Therefore, differences in the strength and direction of association between FM and EI at higher body fatness may reflect the increased contribution of FM to body weight and RMR alongside a blunting of its inhibitory influence on EI. It should also be acknowledged that the associations between FM and EI likely reflects both biological and psychological factors. Indeed, Hopkins et al., (85) have demonstrated that psychological factors such as cognitive restraint are robust predictors of EI when considered alongside physiological determinants of EI (e.g. FFM and RMR), and have the potential to play a mediating role in the overall expression of EI (85). A recent paper also suggests that the associations between FFM and TDEE with EI may become weaker with age (96). Based on a secondary analysis of the Interactive Diet and Activity Tracking in AARP Study,

a biomarker validation study of self-reported diet and PA measures in older adults, Hopkins et al., reported that FFM and TDEE (derived from doubly labelled water) predicted self-reported EI in 590 older adults (mean age 63.1 ± 5.9 years). Interestingly, while the associations between FFM or TDEE and EI existed across age quintiles, age moderated the associations between FFM and TDEE with EI such that these associations weakened with increasing age (96). Please refer to ENDOTEXT chapter 'Control of Energy Expenditure in Humans' by Klaas R Westerterp for additional information).

Associations Between Body Composition and Energy Intake During Prolonged Negative or Positive Energy Balances

Another important point to note is that the aforementioned associations between body composition, energy expenditure, and EI are from cross-sectional analysis performed in weight stable individuals at or close to energy balance. However, the effect of FFM on appetite appears to be dependent on energy balance status, with evidence suggesting that losses of FFM may also act as an orexigenic signal during energy deficit. During the Minnesota semi-starvation study (130), 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 (n = 12), hyperphagia remained until baseline levels of FFM were restored. This led to FM accumulation that surpassed baseline levels (i.e., "fat-overshoot"), a phenomenon that has been reported elsewhere following underfeeding or military training (131, 132). As hyperphagia persisted until FFM had been restored to pre-weight loss levels, it was suggested that independent appetitive feedback signals from both adipose tissue and FFM (e.g., a 'proteinostatic' mechanism) contributed to the changes in hunger and

food intake seen and restoration of body weight (133, 134).

While the demands imposed by semi-starvation or military training on energy balance clearly exceed those experienced during common diet and/or weight loss interventions, evidence also exists to suggest that FFM loss during clinically relevant weight loss may also act as an orexigenic signal. Following weight loss, it is commonly suggested that subjective hunger and orexigenic hormone concentrations increase (135, 136), but studies have also reported no change or reduced hunger following weight loss (137-139). The composition of the weight lost, which is a function of initial body fat, the rate and extent of weight loss, diet composition and exercise (140, 141), may also influence any accompanying changes in appetite. It has been suggested that greater FFM loss during weight loss is associated with increased hunger (97) and weight regain (98) following weight loss. To assess whether changes in body composition occurring during weight loss were associated with subsequent energy balance behaviors under conditions of therapeutic weight loss, Turicchi et al. conducted a systematic review and meta-regression examining weight loss studies in weight clinical weight loss was achieved (mean = 10.9%) and weight regain occurred in the follow-up period (mean = 5.4%) (98). They found that while both greater rate and amount of WL predicted weight regain, the composition of weight loss i.e. the (amount of FM and FFM) explained greater variance in weight loss alone (40% vs 29%) (98). Furthermore, Turicchi et al., reported that greater FFM loss following a 12% reduction in body weight via a low-calorie diet was associated with greater increases in hunger in men (r = 0.69, p = 0.002) but not women (r = 0.25, p = 0.24) (97). In line with these findings, after 5 weeks of very-low calorie diet (500kcal/d) or 12 weeks of low-calorie diet (1250kcal/d) Vink (142) reported that greater FFM loss during energy restriction was associated with greater

weight regain during a subsequent 9-month follow-up period. Data examining FFM loss during extensive periods of energy deficit are therefore suggestive that FFM loss may be part of an integrated response driving post-weight loss increases in EI and weight regain, potentially as a means to restore the structural integrity of FFM compartments (although the influence of FFM loss appears more modest than FM loss). These data also emphasize the importance of developing integrative models of energy balance that consider the dynamic relationships between body structure, physiological function, and the way these mechanistic interactions influence key psychological and behavioral determinants of energy balance such as appetite. However, there are few prospective longitudinal studies relating changes in functional body composition to appetite or EI, and further research using advanced imaging methods for tissue-organ composition and multi-compartmental body composition models across a range of initial body compositions and weight losses would provide additional mechanistic insight (97).

Taken together, cross-sectional research in weight stable individuals indicates that greater FFM is associated with increased EI, but research also indicate that FFM loss is associated with increased appetite and EI. If greater FFM is associated with increased appetite, how is it that FFM loss during weight loss is also associated with increased appetite? One explanation is that FFM exerts 'passive' and 'active' effects on appetite under situations of differing energy balance (6, 143). At or near to energy balance, Dulloo et al. (143) has suggested that the energy demand of FFM and its constituent components create a 'passive' background pull on EI that ensures the energetic demands of metabolically active tissues are met through day-to-day food intake. In contrast, during weight loss, FFM loss may act as an 'active' orexigenic signal that stimulates increased hunger and EI in an attempt to ensure the preservation of FFM and the

functional integrity of its constituent tissue-organs (143). However, it should be noted that long-term studies with longitudinal tracking of appetite, body composition and energy expenditure are rare, particularly under-conditions in which body composition is systematically manipulated.

Body weight gain leads to an expansion of FFM which increases RMR, but how such changes causally influence appetite or food intake has not been examined. As weight is gained, both FM and FFM expand but at different rates. While such changes may not drive weight gain *per se*, a higher FFM and associated RMR may increase the background tonic drive to eat, favoring maintenance of a higher body weight. Expansion of FM over the long term induces insulin and leptin resistance, expansion of FFM and, in extremis, some slight elevation of RMR, could account for the apparent diminishing negative feedback from FM as adipose tissue expands (90, 95, 104, 120). Therefore, it may be argued that any putative effect of FFM or RMR on the drive to eat may decrease with increasing BMI, since FFM and RMR increase at a decelerating rate with increase in weight, while the energy content of the body expands disproportionately as FM expands. While factors associated with energostatic models of appetite may be unlikely to drive body weight up in the first place, it is not inconsistent with maintenance of a higher body weight once this is achieved by other means. Thus, it may be that RMR is associated with EI at or close to energy balance, but that RMR (and its primary determinant FFM) become dissociated from the process of overconsumption during significant weight gain as the signal(s) becomes 'overwhelmed' by other stimuli important in driving weight gain e.g., food availability, sensory variety, dietary energy density and food reward.

HOMEOSTATIC AND HEDONIC PROCESSES OF APPETITE CONTROL

Food intake is clearly influenced by homeostatic processes of hunger and satiety, modulated according to short term and long-term signals of nutritional and energy status and moderated by lifestyle factors such as physical activity. However, human eating behavior is a complex phenomenon and people eat for many other reasons too: for friendship and celebration, in response to sadness or stress. All these cognitive and emotional motives converge on the fact that eating is a potent source of reward. It provides the eater with an instant but temporary hit of gratification. The greater the reward, the harder it is to resist the behaviors that produce it even when the consequences are risky or harmful and especially when the risk is removed in time. Therefore, a key issue in the study of appetite control is the relationship between hedonic and homeostatic drives (144). Historically, hedonic processes have been viewed as a function of nutritional need-state. In a state of depletion, the hedonic response (experienced palatability or pleasure) to energy providing foods is enhanced and when replete, the hedonic effect of these foods is reduced (145). This view is compatible with the association between energy density and palatability (146) and also that the consumption of fats and sugars "energy-dense nutrients" may be under neuro-regulatory control (147). However, the idea of reward as merely serving the fulfilment of nutritional need is not sufficient to explain non-homeostatic food intake and it is perhaps more useful to try and distinguish the substrates of homeostatic and hedonic systems and to assign them separate identities (148).

Homeostasis and Hedonics: Cross-Talk and Interaction

Advances in our understanding of the molecular and neural mechanisms behind food intake regulation and appetite control are revealing how the reward system can interact with homeostatic mechanisms. For example, cannabinoid receptors and their endogenous ligands (e.g., anandamide) are implicated in the reward system. Peripheral and central administration of anandamide increased appetite in rodents, and this seemed to be related to alterations in incentive value (wanting) for palatable foods (149). However, the cannabinoid system has been shown to interact with homeostatic processes in a number of ways: Leptin signaling becomes defective when hypothalamic endocannabinoid levels are high (150); activation of CB1 receptors prevent the melanocortin system from altering food intake (151); furthermore, CB1 receptors can be found on adipocytes where they may directly increase lipogenesis (152). Opioid neurotransmission also forms part of the biological substrate mediating reward processes of consumption. For example, endogenous opioids are associated with the reinforcing effect of food (especially when palatable) (153, 154). However, there is evidence to show that in a fasted state, the reinforcing effect of food can be reinstated in enkephalin and β-endorphin knock-out mice (155). Therefore, homeostatic processes may interact with hedonic signaling to override selective reward deficit.

Hence although homeostatic and hedonic systems can be given separate identities (148), they are also - to an extent - inseparable, with neural cross-talk permitting functional interactions which may influence the organization of eating behavior. From this standpoint, the interaction of homeostatic and non-homeostatic pathways in the neuro-regulatory control of eating may be more important than the two systems studied in isolation. From behavioral and anatomical observations (156), it has been suggested that projections from the hypothalamus to the nucleus accumbens may modulate the motivation to eat via metabolic signals. Furthermore, direct and indirect projections from the accumbens to the hypothalamus may explain the ability for mesolimbic processes

"activated by relevant environmental cues and incentives" to essentially hijack the homeostatic regulatory circuits and drive-up energy intake. Further research is necessary to identify the pathways that mediate such interactions; however progress has been made (157).

Liking vs. Wanting Food

The hedonic perspective on appetite control accounts for eating behavior motivated by the expectation or experience of pleasure from consuming specific foods and involves dissociable processes of "wanting" and "liking". The "liking" component refers to the subjective experience of pleasure elicited by the sensory perception of food and is associated with the release of endogenous opioids acting on localized clusters of neurons termed "hedonic hotspots" (158) The "wanting" component of reward refers to the process by which food is assigned motivational significance or "incentive salience attribution" and is associated with the release of the neurotransmitter dopamine in the mesocorticolimbic pathway. This latter component can be activated by thoughts or cues signaling food and often precedes the actual receipt of food (159).

In human neuroimaging studies, regional differences in the neural activation to food stimuli during either anticipatory or consummatory phases of reward processing are broadly supportive of the distinction between liking versus wanting. Response to passive viewing of high- versus low-calorie foods or cues signaling the imminent receipt of a tasty food are more reliably observed in the amygdala and ventral striatum, whereas the response to the actual taste and consumption of a palatable food is associated with activation in the primary taste cortex in the insular and opercular cortices (160). Some researchers have proposed that differences between individuals who are healthy weight and those with obesity in neural activation to palatable food can be understood as a

dissociation in both the direction and region of responding during the anticipatory and consummatory phases of food intake- with greater striatal activation in individuals living with obesity compared to healthy weight controls when a food is wanted but lower activation in liking-related regions when a food is actually tasted (161). However, several inconsistencies in the brain imaging literature have been noted (162), and further research is needed to substantiate this hypothesis.

Liking and wanting for food are often viewed in relation to subjective states or explicit feelings that refer to the everyday understanding of these terms in the context of food choice and food intake (163). Wanting might describe subjective states of desire, craving or perceived deprivation of pleasure, whereas liking is characteristically understood as the perceived hedonic effect of a food, the appreciation of its sensory properties or some evaluative judgment of its potential to give pleasure. As the subjective sensations of liking and wanting often overlap and are subject to interference or misinterpretation, their relationship with behavior is often difficult to discern (163). However, liking and wanting responses to food are not necessarily consciously monitored or even always accessible to the individual. Although people tend to be very good at estimating and reporting their liking for food, they are often unable to accurately gauge their implicit wanting for food (i.e., why they are unconsciously drawn to one food over another).

The hedonic aspect of eating is important in a well-functioning homeostatic system for the directing and motivating an adequate supply of nutrients and energy. Increasingly, evidence for the interplay between liking and wanting with hunger and satiety is helping to clarify the role of hedonics in the control and loss of control over food intake (164). This extension to the conventional homeostatic model recognizes that hedonic processes are affected by acute nutritional

need states and might modulate food intake through their interaction with other physiological processes involved in satiation and satiety. Likewise, cognitive and sensory inputs implicated in food liking and wanting can modulate the metabolic processes associated with homeostatic control over food intake (165). In addition to the effect of liking and wanting on episodic appetite responses, more recent evidence is emerging to suggest that tonic signals of nutritional status might affect liking and wanting for food to influence food preference and the composition of the diet (164).

MODULATION OF APPETITE THROUGH PHYSICAL ACTIVITY

Physical Activity and Control of Food Intake

Some individuals believe that the energy expended during exercise will automatically drive-up hunger and food intake to compensate for the energy deficit incurred. However, evidence shows that interventions of acute exercise generate little or no immediate effect on levels of hunger or daily EI (see (166-170) for reviews). One reason that studies do not demonstrate an increase in EI following acute exercise could be that they fail to track EI for sufficiently long periods after the bout of exercise, or that the exercised-induced energy expenditure is not large enough to stimulate appetite. However, even with a high dose of exercise (gross exercise-induced increase in energy expenditure = 4.6 MJ) in a single day and following tracking of EI for the following two days, there is no automatic compensatory rise in hunger and EI (171).

Exercise training interventions have shown similar findings with regards to EI (169, 172). In a recent systematic review and meta-analysis of exercise training interventions in people living with overweight or obesity, Beaulieu et al. (172) found that among 25 exercise groups, exercise training (ranging 2-72 weeks) did not lead to any significant post-intervention differences in EI compared to non-exercise control groups. Meta-regression showed this was not affected by intervention duration. However, due to the high number of poor-quality studies (i.e., using self-reported measured of dietary intakes), further analyses were conducted in only fair/good quality studies (reduced to 5 exercise groups), and found a 102-kcal post-exercise difference between exercisers and controls. It is important to note that this is an effect observed on the average and does not illustrate inter-individual variability (discussed below). Therefore, over time, on average there may be small compensatory increases in EI in response to the increased energy demands from greater physical activity levels. Indeed, the review also found a small increase in fasting hunger after exercise training in 19 exercise groups (172). Nevertheless, depending on the daily energy expenditure accrued with exercise training, this should still lead to some degree of weight loss and favorable changes in body composition, as reviewed by Bellicha et al.(173). Small positive changes were also observed in relation to eating behavior traits, with a reduction in disinhibition (13 exercise groups) and an increase in restraint (12 exercise groups) assessed by the Three-Factor Eating Questionnaire (172). A small number of studies in the review also suggested that exercise training may reduce reward or preference for high-fat foods (172). Overall, most of the evidence indicates that exercise training in people living with overweight or obesity appears to have a relatively small but positive influence on eating behavior. This effect may be heightened with longer-term physical activity by altering the sensitivity of appetite regulation. It should be kept in mind that most exercise training studies are of modest duration (e.g. up to 72 weeks the meta-analysis of Beaulieu et al. (172)), and the long-term changes in appetite and eating behavior, and the time-course over which these occur, are yet to be fully understood. Fewer studies have examined the relationship between changes in energy expenditure and eating behavior in non-obese participants who do

not have a preconceived goal associated with weight reduction.

Does Habitual Physical Activity Level Affect Appetite Sensitivity?

Appetite sensitivity refers to the capacity to detect over- or under-consumption with the potential to subsequently adjust intake accordingly. This can be achieved by compensating for a particular EI by adjusting the size of the next meal. There is some evidence to suggest that regular exercisers, or habitually physically active individuals, have a better capacity to control food intake and energy balance due to increased appetite sensitivity. Long et al. (174) demonstrated that habitual exercisers have an increased accuracy of short-term regulation of EI in comparison to non-exercisers. In this study, participants were given either a low or high energy preload for lunch, and were then asked to eat ad libitum from a test meal buffet. Energy intake did not significantly differ following the two preloads in the non-exercise group, indicating a weak compensation. However, the habitual exercisers demonstrated nearly full compensation (~90%) by reducing their EI following the high energy preload compared to the low energy preload. This study has been replicated in groups varying in objectively-assessed habitual physical activity levels (175). Similarly, Martins et al. (176) reported that the sensitivity of short-term appetite control increased in previously sedentary individuals following 6 weeks of aerobic exercise training, with participants again better able to adjust subsequent EI following high and low energy pre-loads following the exercise intervention. Furthermore, King et al. (177) examined the effects of 12 weeks of supervised aerobic exercise on hunger and satiety in 58 individuals living with overweight or obesity. Two separate processes were revealed that acted concurrently to influence the impact of exercise on appetite regulation. Post-intervention, a significant increase in fasting hunger was seen, but this increased orexigenic drive was offset by a parallel increase in post-prandial satiety (as measured in response to a fixed energy meal). Therefore, this 'dual process' may reflect the balance between the strength of tonic and episodic signaling following chronic exercise, and may be an important factor which determines whether individuals successfully lose weight or not. Interestingly, these improvements in appetite control appear to be related to satiety and perhaps not to satiation (178), but more research on the interplay between diet composition, satiation/satiety and physical activity level is required, as well as underlying mechanism.

Findings of improved appetite sensitivity with increased physical activity are in line with Jean Mayer's work over 60 years ago. Mayer et al. (179) demonstrated a non-linear relationship between energy expenditure and EI in Bengali jute mill workers. Daily occupational physical activity and EI were closely matched in those performing physically demanding jobs. However, in those performing light or sedentary occupational roles, this coupling was lost such that daily EI exceeded expenditure. Such work has led Blundell et al. (180) to suggest a J relationship between physical activity and appetite regulation, with 'regulated' and 'non-regulated' zones of appetite regulation seen across the physical activity spectrum. Sedentary or low levels of physical activity coincide with an 'unregulated zone' of appetite in which EI and energy expenditure are disassociated (thereby promoting overconsumption of food at low levels of physical activity). At higher levels of physical activity however, stronger regulation of appetite and food intake exists such that EI better matches energy expenditure. This would promote the better maintenance of energy balance, albeit at higher levels of absolute intake and expenditure, i.e. higher 'energy turnover/flux' (180). This non-linear relationship has since been replicated in a systematic review (181) and in a study of over 400 participants (182). The model

proposed by Blundell was recently updated by Beaulieu et al. (183), as shown in Figure 4. Furthermore, emerging evidence from a highly-controlled metabolic chamber study suggests that appetite control is indeed improved at higher levels of energy turnover (184). Longer-term studies are required to understand the impact of high energy turnover on appetite control, but it is believed that high levels of EI relative to expenditure may improve weight management via a favorable impact on physiological adaptations (185).
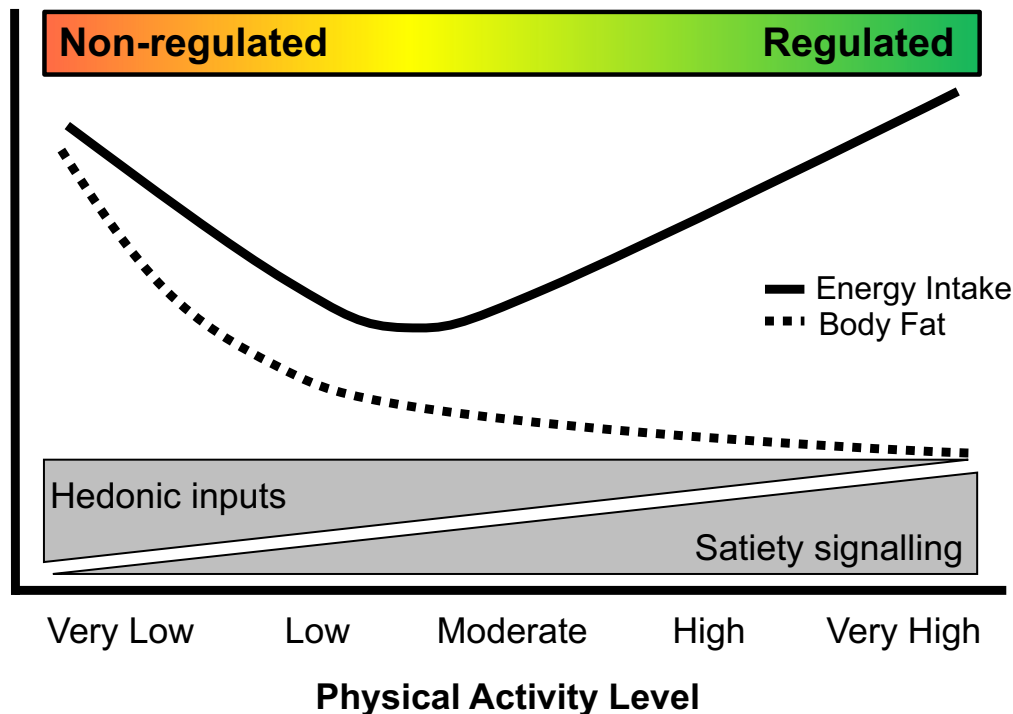

Figure 4. Regulated and non-regulated zones of appetite with varying levels physical activity from Beaulieu et al. (183). Model based on Jean Mayer's study in Bengali jute mill workers (179) and previously published in Blundell (180).

While the mechanisms behind an improvement in appetite control with regular physical activity remains unclear, insulin sensitivity has been proposed as one mechanism by which activity-induced improvements in appetite regulation may occur. Exercise is known to increase insulin sensitivity (186-188), and insulin sensitivity is known to be involved in satiety induced by particular foods (189) and in the compensatory response to high energy loads (190). A further mechanism by which exercise could affect appetite is through altering gut peptide action. For example, CCK is implicated in the short-term regulation of appetite, and levels of CCK have been shown to rise after exercise (191). Interestingly, Martins et al. (192) measured fasting and post-prandial levels of orexigenic (total and acylated ghrelin) and anorexigenic (PYY, GLP-1) peptides in 15 individuals living with overweight or obesity during 12 weeks of supervised aerobic exercise. A significant increase in fasting hunger was again seen following the

intervention, but this was offset by greater satiety in response to a fixed energy meal following the intervention. Interestingly, there was also a significant increase in the suppression of acylated ghrelin following the fixed energy meal, and a tendency toward an increase in the post-prandial release of GLP-1 following the exercise intervention. These hormonal responses would have acted to augment satiety during the post-prandial period. Further work by Gibbons et al. (193) revealed that exercise training had no overall impact on pre and postprandial appetite peptide release; however, differences emerged when participants were classified as 'responders' and 'non-responders'. Compared to non-responders, responders had overall greater suppression of acylated ghrelin and greater increase in GLP-1 and total PYY. This effect was independent of the exercise intervention as differences were observed from baseline. Therefore, the specific role that appetite-related peptides play in activity-induced improvements in appetite regulation remains to be fully understood.

In addition to gastrointestinal mechanisms, it is important to understand how physical activity timing and patterns impact energy balance and appetite control. Physical activity can be prescribed by the FITT principle: frequency, intensity, time (duration) and type, and more recently, timing as another parameter has been proposed, as emerging evidence suggests that when exercise is performed relative to a meal or the time-of-day may influence obesity and cardiometabolic health in both adults and children (194). Indeed, physical activity is also another cue that influences circadian rhythms (195). In a systematic review and meta-analysis of exercise training interventions in individuals living with overweight or obesity (117), only 3 studies (1 RCT) on diurnal exercise timing were identified (196-198). These studies, in addition to observational studies (reviewed in (199)), suggest that early relative to late day exercise timing may lead to greater weight/fat loss. However, a recent RCT suggests no effect of exercise timing on weight loss, but this may have been due to the relatively low dose of aerobic exercise (200). The underlying mechanisms the greater weight loss in response to early exercise timing likely involve an impact on both behavioral and physiological processes regulating energy balance and appetite control (201). Performing morning exercise may lead to greater weight loss by enhancing the satiety response to food throughout the day, reducing the desire for and intake of high-energy-dense foods, and shifting food intake timing to earlier in the day, thus reducing daily energy intake (199). Evidence for this hypothesis is scarce, with an acute study showing that morning exercise led to greater post-exercise satiety; however, this was not examined in response to actual food intake (196). More rigorous research in this area is needed to clarify these proposed effects.

CONCLUSION

The control of food intake in humans is a biopsychological phenomenon. Motivation to eat is an important factor influencing food intake if the environment does not constrain behavior. Food intake is not necessarily solely related to situations of nutritional depletion and can be influenced by a number of homeostatic and non-homeostatic factors. Appetites are often learned and frequently sensory specific. The implication of asymmetric energy balance regulation is that food intake is under stronger physiological control in relation to negative energy balances, whereas in a state of energy balance or positive energy balances the linkages between physiological signaling and subjective motivation to eat are weaker. In obesogenic environments where palatable, energy dense food is ubiquitous, intake can easily exceed energy requirements due to motivation underpinned by food reward. Another consideration is how physical activity or exercise influence energy intake. Physical activity may influence the control of appetite via a number of pathways (e.g., alterations in

gastric emptying, appetite-related hormones, food reward, circadian synchrony).

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