THE REGULATION OF FOOD INTAKE IN HUMANS

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ABSTRACT

Knowledge of the regulation of food intake is crucial to an understanding of body weight and obesity. Traditionally, food intake has been researched within the homeostatic approach to physiological systems pioneered by Claude Bernard, Walter Cannon and others; and because feeding is a form of behaviour, it forms part of what Curt Richter referred to as the behavioural regulation of body weight (or behavioural homeostasis). The idea was that eating behaviour is stimulated and inhibited by internal signalling systems (for the drive and suppression of eating respectively) in order to regulate the internal environment (energy stores, tissue needs). It is also important to note however that day-to-day food involves the co-ordination of both homeostatic and non-homeostatic feedback. The term 'obesigenic environment' has entered into scientific discourse and implies that the potency of the external environment is in part responsible for the increases in food intake that is one of the causal agencies underlying the epidemic of obesity. This approach has 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 a major cause of an increase in food intake associated with the rise of obesity resides in the hedonic rather than the homeostatic system.

INTRODUCTION

Knowledge of the regulation of food intake is crucial to an understanding of body weight and obesity. Strictly speaking, we should refer to the control of food intake whose expression is modulated in the interests of the regulation of body weight. Food intake is controlled, body weight is regulated. However, this semantic distinction only serves to emphasize the importance of food intake. 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 feeding is a form of behaviour, it forms part of what Curt Richter referred to as the behavioural regulation of body weight (or behavioural homeostasis) (3). This approach views food intake as the vehicle for energy supply whose expression is modulated by a metabolic drive generated in response to a requirement for energy. The idea was that eating behaviour is stimulated and inhibited by internal signalling

systems (for the drive and suppression of eating respectively) in order to regulate the internal environment (energy stores, tissue needs).

Although there has always been a field of research dedicated to the study of food intake stimulated by the external environment, the rise of obesity in the last 20 years has accelerated thinking about this issue. The term 'obesigenic environment' has entered into scientific discourse and implies that the potency of the external environment is in large part responsible for the increases in food intake that is one of the causal agencies underlying the epidemic of obesity. This approach has 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 a major cause of an increase in food intake associated with the rise of obesity resides in the hedonic rather than the homeostatic system. This does not mean that the so-called 'energy homeostasis system' is no longer important.

Since the middle 1990s there have been impressive advances in the molecular infrastructure of the brain's homeostatic networks which have given some precision to knowledge of how regulatory processes operate. At the same time the use of neural pathway studies in animals, and neurobiological procedures, including fMRI scanning, in humans, have refined understanding of the brain's hedonic networks. Interestingly there is evidence of cross-talk between the neurochemical substrates of the two systems. This is an exciting concept that offers the possibility of some re-unification of the dualism underlying homeostatic and hedonic processing of information. It is against this scientific landscape that the control (regulation) of food intake in humans can now be addressed.

FOOD INTAKE AND APPETITE CONTROL

Appetite fits into an energy balance model of weight regulation but it is not necessary to believe that appetite control is an outcome of the regulation of energy balance. Appetite is separately controlled and is relevant to energy balance since it modulates the energy intake side of the equation. This happens because appetite includes various aspects of eating patterns such as the frequency and size of eating episodes (gorging versus nibbling), choices of high fat or low fat foods, energy density of foods consumed, variety of foods accepted, palatability of the diet and variability in day-to-day intake. All of these features can play a role in encouraging energy intake to exceed energy expenditure thereby creating a positive energy balance. If this persists then it will lead to weight gain. Moreover, there appears to be no unique pattern of eating or forms of energy intake that will exclusively or invariably lead to an excess of energy intake over expenditure. Nevertheless, some characteristics of the expression of appetite do render individuals vulnerable to over-consumption of food- these characteristics can be regarded as risk factors. These risk factors and other modulating features of the expression of appetite will be disclosed by an analysis of how appetite is regulated.

CONCEPTUALISATION OF THE SYSTEM CONTROLLING FOOD INTAKE BEHAVIOUR

It is now accepted that the control of appetite is based on a network of interactions forming part of a psychobiological system. The system can be conceptualised on three levels (Figure 1). These are the levels of psychological events (hunger perception, cravings, and hedonic

sensations) and behavioural 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 (4). Appetite reflects the synchronous operation of events and processes in the three levels. When appetite is disrupted as in certain eating disorders, these three levels become desynchronised. Neural events trigger and guide behaviour, but each act of behaviour involves a response in the peripheral physiological system; in turn, these physiological events are translated into brain neurochemical activity. This brain activity represents the strength of motivation to eat and the willingness to refrain from feeding.
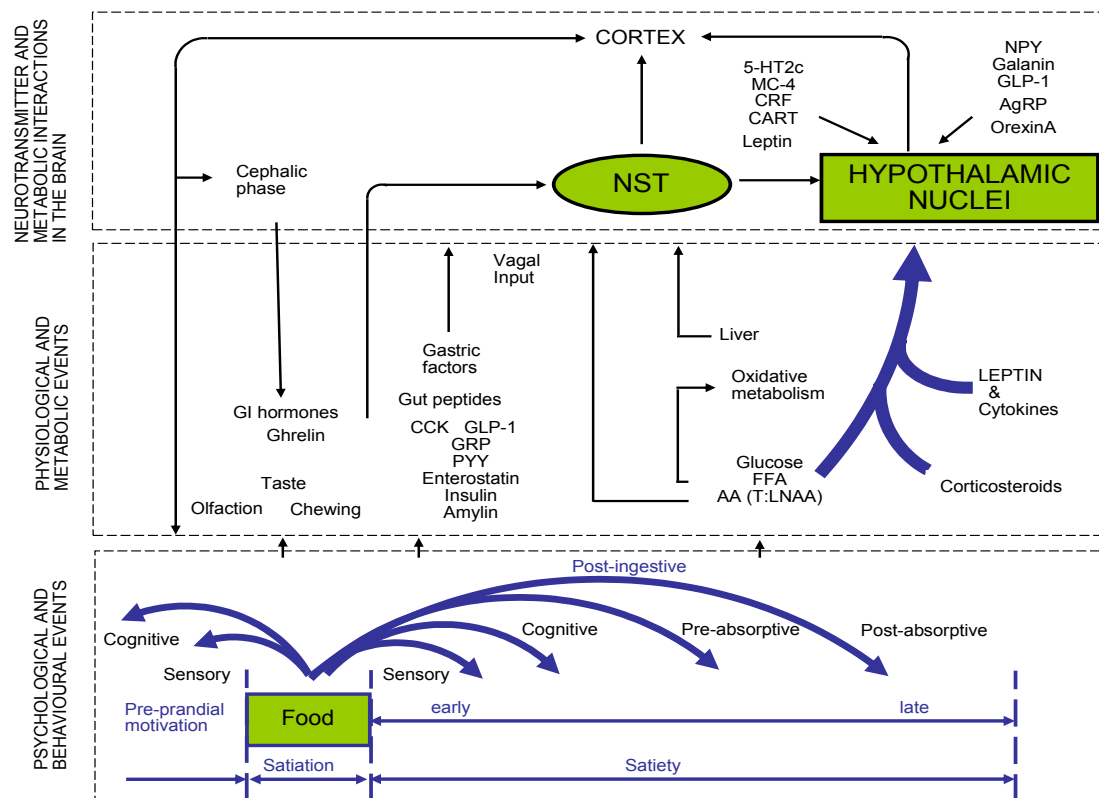

Figure 1. Diagram showing the expression of appetite as the relationship between three levels of operations: the behavioral pattern, peripheral physiology and metabolism, and brain activity. PVN, paraventricular nucleus; NST, nucleus of the tractus solitarius; CCK, cholecystokinin; FFA, free fatty acids; T: LNAA, tryptophan: large neutral amino acids (See (4)for detailed diagram).

The lower part of the PsychoBiological System (Figure 1) illustrates the appetite cascade which prompts us to consider the events which stimulate eating and which motivate organisms to seek food. It also includes those behavioural 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.

Even before food touches the mouth, physiological signals are generated by the sight and smell of food. These events constitute the cephalic-phase of appetite. Cephalic-phase responses are generated in many parts of the gastrointestinal tract; their function is to anticipate the ingestion of food. During and immediately after eating, afferent information provides the major control over appetite. It has been noted that `afferent information from

ingested food acting in the mouth provides primarily positive feedback for eating', while that from the stomach and small intestine is primarily negative feedback (5).

EPISODIC AND TONIC SIGNALS FOR APPETITE CONTROL

It is useful here to distinguish between signals involved in appetite control. Traditionally, a distinction has been drawn between short-term and long-term regulation of appetite, but the connotation of episodic and tonic is more functionally appropriate (6). 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 intimately associated with the signaling of satiety. Tonic signals arise from tissue stores, including adipose tissue, and exert a tonic pressure on the expression of appetite. These two sets of signals, one set responding sharply to changes in behaviour and the other providing a slow modulation, are integrated within complex brain networks that control the overall expression of appetite.

Satiety Signals and the Satiety Cascade

Important 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 so are 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. The cascade demonstrates how satiation, the complex of processes which brings eating to a halt (cause meal termination), and satiety, those events which arise from food consumption which serve to suppress hunger (the urge to eat) and inhibit further eating, coordinate our eating behaviour controlling the size and frequency of eating episodes (4).

Initially the brain is informed about the amount of food ingested and its nutrient content via sensory input. The gastrointestinal tract is equipped with specialised chemo- and mechano-receptors that monitor physiological activity and pass information to the brain mainly via the vagus nerve (7). 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, which accurately reflect the food consumed, may be metabolised 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 (8). Many of these chemicals are peptide neurotransmitters, and many peripherally administered peptides cause changes in food consumption (5). Currently, a good deal of interest is being shown in these peripheral signals of appetite control, and some will be described below.

Cholecystokinin (CCK)

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 (9). 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 (10, 11). This signal is transmitted via afferent fibres 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 (12). As in rats, intestinal infusions of fat produce a reduction in food intake and promote satiety in humans (13). In humans the satiety effect of fat infused directly into the duodenum can be blocked by the CCKA receptor antagonist loxiglumid (14). 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 feeding behaviour 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 agonists 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. The action of CCK certainly acts in concert with other meal related events, such as gastric distention for example.

Glucagon-like-peptide (GLP)-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 (15, 16). 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 (17). 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 lean male volunteers. This marked reduction in food intake and enhancement in satiety is also observed in overweight/obese male patients with type 2-diabetes. In obese men, intravenous GLP-1

potently reduces food intake either during or post-infusion (18) 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 lean and obese. 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. None the less, 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 behaviour.

Peptide YY $_{3-36}$ (PYY)

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, peptide YY (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. (19) 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 free fatty acids), some forms of fibre and bile acid (10, 11). In humans, endogenous PYY is released predominantly after rather than during a meal (19, 20) 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-saturatable mechanism. Moreover, some of the effects of peripheral PYY $_{3-36}$ on food intake are should be either independent of or dependent on vagal afferents running from the periphery to the brain (21, 22).

With regard to the effect of PYY on human appetite, Batterham et al. (19) 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 both lean and obese subjects caused a 30% reduction in lunch intake post infusion and decreased the 24 h energy intake by 23% in lean and by 16% in the obese (20). The natural plasma levels of PYY were lower in the obese than in the lean subjects, and were inversely correlated with the body mass index. The lower levels of PYY in the obese 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 (23-25). Nonetheless, PYY $_{3-36}$ (in the form of a PYY $_{3-36}$ nasal spray from Nastech Pharmaceuticals, AC162352 a synthetic version of human PYY $_{3-36}$ from Amylin Pharmaceuticals, and CJC-1681 from Conjuchem) and an Y2 agonist (TM30338 7TM Pharma) are currently in clinical development.

Amylin

Much recent 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 (26). 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, body weight and body mass of rats (27). Amylin administration blocks the hyperphagic effects of (28). 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 diabetics, has been shown to alter body weight in diabetic insulin treated obese (29-31) and non-diabetic obese (32). In lean health volunteers pramlintide induces reductions in meal intake and duration, and reduces pre meal appetite (33). Similar effects of pramlintide on intake and eating behaviour are reported in obese (with and with out type 2 diabetes) (34, 35).

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 (36). 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. 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.

TONIC SIGNALS FOR APPETITE CONTROL

Ghrelin and the Hunger Drive

Ghrelin is found both in the gut and the brain, the gut being the major source of plasma ghrelin. The highest concentrations of ghrelin are found in the stomach, and then in the small intestine. Endogenous ghrelin levels appear responsive to nutritional status; for instance, human plasma ghrelin immunoreactivity increases during fasting and decreases after food intake. It is also found in hypothalamic nuclei critical to energy regulation (37). Unlike the other peripheral peptides described earlier, ghrelin stimulates rather than inhibits feeding behaviour. Both peripheral and central infusions of ghrelin have been shown to stimulate food intake in rats and mice (38). Decreased endogenous ghrelin levels are observed in genetically obese rats and mice, and in dietary-induced obese rats exposed to a high fat diet (39). The peripheral effects of ghrelin may be vagally mediated but a direct effect of circulating ghrelin on the CNS cannot be ruled out given that receptors are found for it on the Accurate Nucleus outside the blood brain barrier and that it can cross the blood brain barrier also (37).

It has been proposed that ghrelin, linked to the initiation of eating, acts as a compensatory hormone. This means that in obese people and in animals experimentally made fat, 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. This means that when weight is lost, for example following a period of food restriction and weight loss, ghrelin levels would rise and therefore promote the feeling of hunger. This is likely to be one of the signals that makes the loss of body weight so difficult to maintain and so ghrelin blockade may prove a useful anti-obesity treatment.

Role of Leptin

One of the classical theories of appetite control has involved the notion of a so-called long-term regulation involving a signal, which informs the brain about the state of adipose tissue stores. This idea has given rise to the notion of a lipostatic or ponderstatic mechanism (40). Indeed this is a specific example of a more general class of peripheral appetite (satiety) signals believed to circulate in the blood reflecting the state of depletion or repletion of energy reserves which directly modulate brain mechanisms. Such substances may include satietin, adipsin, tumour-necrosing factor (TNF or cachectin- so named because it is believed to be responsible for cancer induced anorexia), adiponectin and resistin together with other substances belonging to the family of neural active agents called cytokines.
In 1994 a landmark scientific event occurred with the discovery and identification of a mouse gene responsible for obesity. A mutation of this gene in the ob/ob mouse produces a phenotype characterized by the behavioural trait of hyperphagia and the morphological trait of obesity. The gene controls the expression of a protein (the ob-protein) by adipose tissue and this protein can be measured in the peripheral circulation. The identification and synthesis of the protein made it possible to evaluate the effects of experimental administration of the protein either peripherally or centrally (41). Because the ob-protein caused a reduction in food intake (as well as a possible increase in metabolic energy expenditure) it has been termed `leptin'. There is some evidence that leptin interacts with NPY, one of the brain's most potent neurochemicals involved in appetite, and with the melanocortin system. Together these and other neuromodulators are involved in a peripheral-central circuit which links an adipose tissue signal with central appetite mechanisms and metabolic activity. In this way the protein called leptin probably acts in a similar manner to insulin which has both central and peripheral actions; for some years it has been proposed that brain insulin represents a body weight signal with the capacity to control appetite.

At the present time, the precise relationship between the ob-protein and weight regulation has not been determined. However, it is known that in animals and humans which are obese the measured amount of ob-protein in the plasma is greater than in lean counterparts. Indeed there is always a very good correlation between the plasma levels of leptin and the degree of bodily fatness (42). Therefore although the ob-protein is perfectly positioned to serve as a signal from adipose tissue to the brain, high levels of the protein obviously do not prevent obesity or weight gain. However, the ob-protein certainly reflects the amount of adipose tissue in the body. Since the specific receptors for the protein (namely ob-receptor)

have been identified in the brain (together with the gene responsible for its expression) a defect in body weight regulation could reside at the level of the receptor itself rather than with the ob-protein. It is now known that a number of other molecules are linked in a chain to transmit the action of leptin in the brain. These molecules are also involved in the control of food intake, and in some cases a mutation in the gene controlling these molecules is known and is 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.

Leptin based obesity treatments for most obese individuals seem inappropriate given they appear leptin insensitive rather than leptin deficient. Nonetheless, studies have shown for individuals with leptin deficiency leptin treatment produces dramatic weight loss, an affect associated with marked decreases in hunger (43-45). 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 (45, 46). Under the right physiological conditions such as diet-induced normalization of endogenous leptin levels, the effects of exogenous leptin on human appetite could be still exploited to treat obesity (47-49). However, this has yet to be robustly demonstrated.

The Role of Fat-free Mass and Resting Metabolic Rate in the Excitatory Drive to Eat

As discussed above, leptin's primary role in appetite control maybe as a putative tonic inhibitory peptide, providing an enduring or continual inhibitory influence on the drive to eat. This is consistent with the notion that episodic and tonic inhibitory signals arising from adipose tissue and gastrointestinal peptides modulate a constant excitatory drive to eat (50). However, the source of this excitatory drive has been poorly defined, with current models of appetite control better able to account for the inhibition, rather than initiation, of feeding (6). Recently, a number of studies have sought to re-examined the specific roles that fat mass, fat-free mass and energy expenditure play in the control of food intake (51). These studies sugest fat-free has a stronger influence on driving day-to-day hunger and food intake than fat mass under conditons of (approximate) energy balance (52-55) (52, 54, 56, 57). For example, Blundell et al. (54) reported that fat-free mass predicted self-selected (*ad libitum*) meal sized and total daily energy intake in 93 overweight and obese individuals. In contrast, no associations were found between fat mass or food intake. These findings have been replicated in a number of studies employing a wide range of participants (52-55). Furthermore, resting metabolic rate, of which fat-free mass is the main determinant (58), has also been shown to be an independent predictor of within-day hunger and food intake (56, 57, 59). For example, Caudwell et al. (57) reported that resting metabolic rate, but again, not fat mass, predicted daily hunger, *ad libitum* meal intake and daily energy intake under conditions of high and low energy density in overweight and obese individuals.

Based on such findings, Blundell et al. (54) has proposed that the energy expenditure arising from fat-free mass, as the main determinant of resting metabolic rate, represents a physiological source of hunger that drives food intake at a level proportional to basal energy requirements. This long-term (tonic) signal of energy demand would help 'tune' energy intake to energy expenditure, and help ensure the maintenance and execution of key biological and behavioural processes. These findings suggest that the classical 'adipocentric' model of appetite control should be revised to reflect the influence of resting

metabolic rate and energy demands. Acting conjointly, the influence of resting metabolic rate (and other components of energy expenditure), and signals stemming from adipose tissue and gastrointestinal peptides, would provide a stronger account of the role of whole-body peripheral signals involved in human appetite control. There is a need however to examine how fat mass and fat-free mass influence food intake under varying conditions of energy balance, as it is possible that fat mass and other regulatory signals (such as leptin) may influence food intake more strongly during negative energy deficit for example.

Given that fat-free mass and resting metabolic rate co-vary strongly, it is also important to establish whether it is fat-free mass or energy expenditure *per se* that drives food intake. In this regard, Hopkins et al. (56) reported using mediation analysis that the effect of fat-free mass on energy intake was mediated by resting metabolic rate i.e. fat-free mass had no 'direct' effect on food intake but rather 'indirectly' influenced food intake via its effect on resting energy metabolism. In agreement with these findings, Piaggi et al (60) has also reported, again using mediation analysis, that fat-free mass did not have any direct effect on energy intake in 107 individuals, with 24 hour energy expenditure accounting for 80% of the observed effect fat-free mass exerted on energy intake. Taken together, these findings suggest that food intake is driven by energy expenditure *per se* rather than a molecular signaling pathway arising from fat-free mass (or specific organ masses such as skeletal tissue). However, whether the relationship between resting metabolic rate and food intake is a function of, or independent, of total daily energy expenditure requires further examination. Indeed, such model cannot distinguish between the effects of fat-free mass-associated energy expenditure and the effects of any molecular signaling arising from lean tissue that may also co-vary with resting metabolic rate.

These findings suggest that energy arising from fat-free mass and resting metabolic rate represent a potential physiological source of hunger that drives day-to-day food intake at a level proportional to basal energy requirements, fat mass (and associated adipokines such as leptin) appears not to strongly influence day-to-day food intake under conditions of energy balance. However, if energy expenditure and energy intake are linked as part of a biologically regulated system, then a mechanism must exist that 'tunes' energy intake to the rate of energy expenditure (61). While the potential mechanisms or signals remain unclear, it has previously been suggested that the energy demand of tissues (such as the liver) might be translated into tonic hunger signals (6). This notion fits with the energostatic control of food intake (62), in which hepatic energy status influence energy intake through the stimulation of vagal afferent nerve activity (63). It is also worth noting that 'aminostatic' (64) and 'protein-stat' (65) theories of appetite regulation have previously been proposed, in which amino acid availability and lean tissue needs are linked to food intake. However, evidence of such regulation is limited. It is also now clear that skeletal muscle secretes a large number of myokines (66), which provide a molecular signal for bi-directional communication with other organs (67). However, while myokines such as interleukin 6 (68) and irisin (69) have been linked to food intake and energy expenditure, the specific role that these (and other myokines) play in appetite regulation and food intake is unclear.

PHYSICAL ACTIVITY AND REGULATION OF FOOD INTAKE

The relationship between hunger, food intake, and perturbations in energy expenditure (EE) induced by adjustments in physical activity are now being better understood. Some

individuals believe that the energy expended will automatically drive up hunger and food intake to compensate for the energy deficit incurred. However, whether EE is increased (imposed exercise) or decreased, individuals continue to eat in their habitual form. Evidence shows that interventions of acute exercise generate little or no immediate effect on levels of hunger or daily energy intake EI (see (70-73) for reviews). Contrary to the widespread belief, there is no immediate compensatory increase in hunger and food intake. One reason that studies do not demonstrate an increase in EI could be that they fail to track EI for a sufficiently long period following the increased physical activity interventions, and that the exercised-induced increment in EE is not large enough to stimulate appetite. However, even with a high dose of exercise (gross exercise-induced increase in EE = 4.6 MJ) in a single day and tracking EI for the following two days, there is no automatic compensatory rise in hunger and EI (74). Most of the evidence indicates that exercise-induced changes in post-absorptive physiology (energy metabolism) appear to have only a weak influence on eating behaviour. However, this picture could change with longer-term physical activity by altering the sensitivity of appetite regulation.

Does Physical Activity affect Appetite Sensitivity?

Appetite sensitivity is related to the capacity to detect over- or under-consumption (positive or negative energy balance) and to exert a compensatory response. This can be achieved through the modulation of satiation signals and by compensating for a particular energy intake 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 regulate their food intake and energy balance because of an increased appetite sensitivity. Long et al. (75) demonstrated that habitual exercisers have an increased accuracy of short-term regulation of energy intake 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 energy intake following the high energy preload compared to the low energy preload. Similarly, Martins et al. (76) 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 energy intake following high and low energy pre-loads following the exercise intervention. Furthermore, King et al. (77) examined the effects of 12 weeks of supervised aerobic exercise on hunger and satiety in 58 overweight and obese individuals. 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 signalling following chronic exercise, and may be an important factor which determines whether individuals successfully lose weight or not.

Interestingly, findings of improved appetite sensitivity with increased physical activity are in line with Jean Mayer's work 60 years ago. Mayer et al. (78) demonstrated a non-linear relationship between energy expenditure and energy intake in Bengali jute mill workers. Daily occupational physical activity and energy intake 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 energy intake exceeded expenditure. Such work has led Blundell et al. (79) to suggest an 'inverted U' relationship between physical activity and appetite regulation (Figure 2), 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 energy intake 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 energy intake better matches energy expenditure. This would promote the better maintenance of energy balance, albeit at higher levels of absolute intake and expenditure (79).
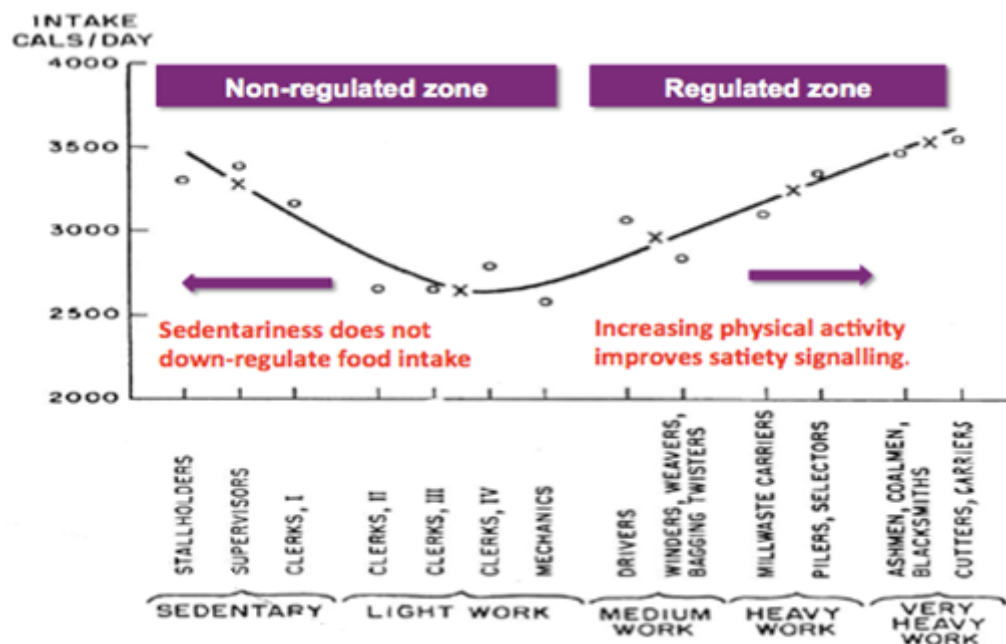

Figure 2: Regulated and non-regulated zones of appetite with varying levels physical activity. Model based on Jean Mayer's study in Bengali jute mill workers (78). Previously published in Blundell (79).

While the mechanisms behind this improvement in appetite regulation 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 (80-82), and insulin sensitivity is known to be involved in satiety induced by particular foods (83) and in the compensatory response to high energy loads (84). A further mechanism by which exercise could affect appetite is through altering gut peptide action. For example, cholecystokinin (CCK) is implicated in the short-term regulation of appetite, and levels of CCK have been shown to rise after exercise (85). Interestingly, Martins et al. (86) measured fasting and post-prandial levels of orexigenic (total and acylated ghrelin) and anorexigenic (PYY, GLP-1) peptides in 15 overweight and obese individuals during 12 weeks of supervised aerobic exercise. A significant increase in fasting hunger was again seen following the intervention (p < 0.01), 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 (p = 0.07). These hormonal responses would have acted to augment satiety during the post-prandial period. However, the specific role that changes in appetite-related peptides play in activity-induced improvements in appetite regulation remains to be determined.

Individual Variability

Most studies examining the effects of exercise on body weight and food intake tend to report the mean data and overlook the inter-individual variability. It is unlikely that a fixed dose of exercise will be effective to the same extent in all individuals. The concept of individual variability is not necessarily new. Indeed, the classic genetic studies conducted by Claude Bouchard were instrumental in identifying the variability in response to over-feeding interventions in twins (87). It is now clear that large inter-individual variability exists in a range of physiological responses such as cardiovascular fitness, insulin sensitivity and blood pressure in following standardized exercise interventions (which cannot be explained by differences in adherence to the intervention) (88). This exercise-induced variability in response reflects random and measurement error (89, 90), and also biological variability (91). In terms of biological variability, this is likely to be determined in part by physiological and/or behavioural compensatory responses to exercise, mediated by underlying genetic/epigenetic factors (91). Unfortunately, such heterogeneity in response to exercise is rarely acknowledged, and has not been incorporated into recent approaches to exercise prescription or weight management in which a 'one size fits all' approach is adopted. Recent evidence also shows that despite performing mandatory and supervised exercise, there is a large inter-individual variability in weight loss following 12 weeks of exercise (92-94). Figure 3 shows clearly the range in weight loss and that some individuals lose more than, while other lose less than the predicted weight loss of 3.7kg. Further analysis of the data revealed that individuals who lost less then the predicted weight were compensating via an increased drive to eat and food intake. Although acute studies show that exercise does not immediately drive up food intake, it has been demonstrated that compensation does begin to occur if daily physical activity persists. Over periods of up to 16 days partial compensation occurs so that increased eating accounts for approximately 30% of the increase in energy expended (95-97). A recent systematic review by Donnelly et al. (73) concluded that long-term exercise training (12 weeks to 18 months) had no significant impact on energy or macronutrient intake. However as noted by the authors, methodological limitations such as self-reported energy intakes, unsupervised exercise sessions, a lack of objective measures exercise-induced energy expenditure, and low total exercise-induced energy expenditure, mean that it is difficult to draw conclusions concerning the long-term effects of exercise training (> 12 weeks) on appetite and energy intake due to the lack of well-controlled studies.
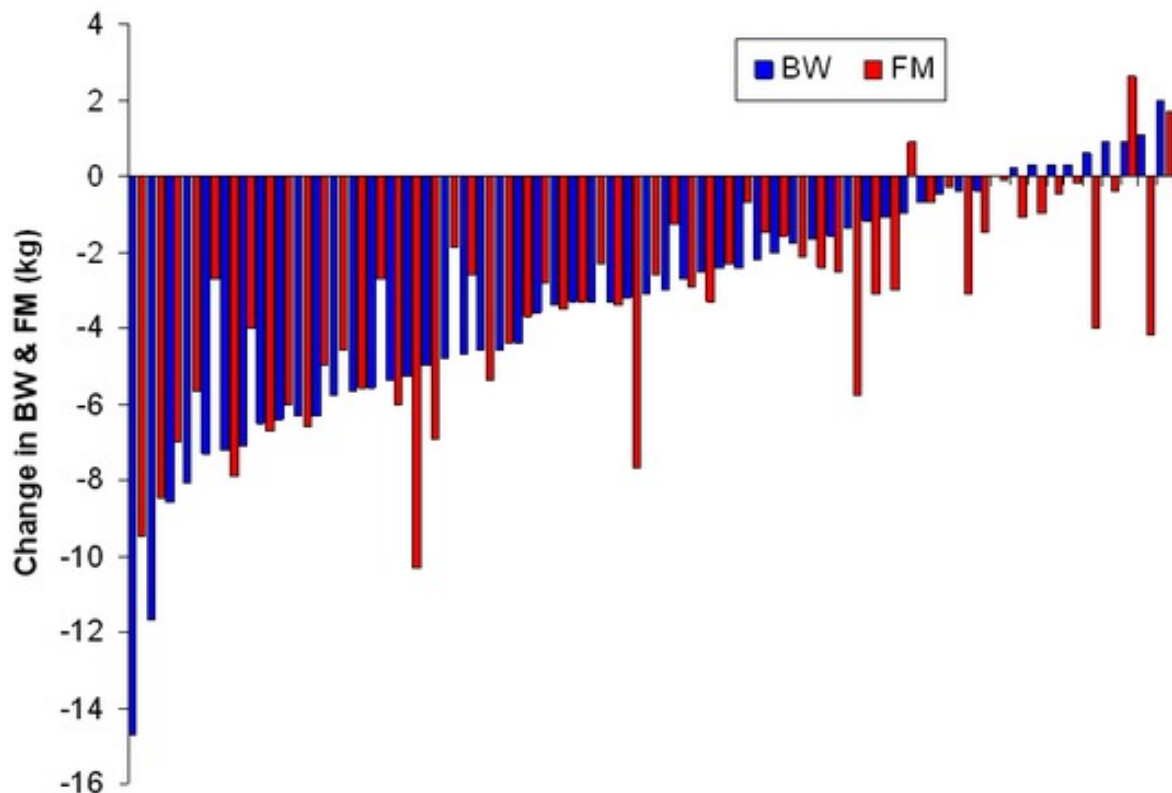
Figure 3. Variability in weight loss response to 12 weeks supervised exercise (92). BW, body weight; FM, fat mass.

Until recently, this heterogeneity in the biological and behavioural responses to exercise has not been acknowledged in the study of appetite control or body weight regulation. By focusing on the group (mean) response, it has been (incorrectly) assumed that all individuals will respond in the same fashion to the same volume of exercise. However, this is not the case. Recognition of such variability in response to exercise also raises the issue of how we characterise this inter-individual variability. Studies have categorised individuals as 'responders' or 'non-responders' based on the change seen in a single variable such as maximal aerobic capacity for example (see Mann et al. (88) for a review). This approach may help identify individuals or 'sub-groups' of individuals that benefit from an exercise intervention despite no apparent improvement at the mean or group level. However, it is important to note that classifying individuals as non-responders based on the change in a single variable can be misleading. Individuals display a range of physiological and psychological benefits following exercise training, and these will not be recognized when individuals are labeled as 'non-responders' based on a single variable. It also needs to be established whether 'poor responsiveness' is evident across a range of phenotypes, reproducible or amenable to change. Such issues are of particular importance in light of studies demonstrating adverse responses to exercise training in a small minority of individuals (91).

It is possible that a compensatory increase in food intake could also be due inappropriate food choices and a feeling that food self-reward is justified, or from misjudgements about the energy cost of physical activity (calories expended) relative to the rate of eating-induced intake (calories consumed). Empirical evidence demonstrates that when physical activity is combined with high-fat, energy dense foods, the beneficial effects of activity on energy

balance can be reversed (98). An increase in physical activity does not automatically protect against inappropriate food choice.

Physical Activity and Energy Balance

Although the loose coupling between exercise-induced EE and EI has positive implications for weight control for increases in EE, unfortunately it has negative implications for decreases in EE. Recent findings have confirmed that there is no down regulation of appetite and EI remains at some stable preferred level when EE is reduced. Inactivity-induced reductions in EE occur in the natural, free-living environment due to a variety of reasons (e.g., injury, increase in energy-saving devices, increase car use). Two independent studies have demonstrated that EI is not down-regulated in response to activity-induced reductions in EE, hence a positive energy balance occurs (99, 100). Therefore, a reduction in EE does not automatically reduce food intake. Considering eating tends to be a sedentary activity, inactivity could even increase food intake.

HOMEOSTATIC AND HEDONIC PROCESSES OF APPETITE CONTROL

A key issue in the study of appetite control is the relationship between hedonic (of or relating to reward) and homeostatic drives arising from biological needs (101). 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 (102). This view is compatible with the link between energy density and palatability (103) and also that the consumption of fats and sugars "energy-dense nutrients" may be under neuro-regulatory control (104). However, the idea of reward as a consequence of the fulfilment of nutritional need is not sufficient to explain non-homeostatic food intake (non-compensated patterns of over or under consumption) and it is perhaps more useful to try and distinguish the neural substrates of homeostatic and hedonic systems and to assign them separate identities (105).

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 (desire) for palatable foods (106). However, the cannabinoid system has been shown to interact with homeostatic processes in a number of ways: Leptin signalling becomes defective when hypothalamic endocannabinoid levels are high (107); activation of CB1 receptors prevent the melanocortin system from altering food intake (108); furthermore, CB1 receptors can be found on adipocytes where they may directly increase lipogenesis (109). 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) (110, 111). 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 (112). Therefore, homeostatic

processes may interact with hedonic signalling to override selective reward deficit. Erlanson-Albertsson (113) summarized how ingestion of palatable food can offset normal (homeostatic) appetite regulation (figure 4). In the brain, research shows that energy deficit is registered in the hypothalamus leading to the release of hunger signals and the activation of their receptors. Consumption of 'standard' food generates information on its energy content and taste in the brain stem. This information is transmitted to the hypothalamus leading to the release or up-regulation of various satiety peptides, causing consumption to cease. However, a different scenario is apparent when the reward system is activated by highly palatable food. With ingestion of palatable food, taste sensing is different than with standard food; information is transmitted to the reward circuit, leading to the release or upregulation of reward mediators like dopamine, endocannabinoids, and opiates. The reward circuit has connections with appetite-controlling neurones in the hypothalamus that can increase the expression of hunger peptides such as NPY and orexins, while blunting the signalling of satiety peptides like insulin, leptin and cholecystokinin. Therefore when food is highly palatable, the drive to eat is maintained, with continued eating now mediated by reward rather than biological need (see figure 4).
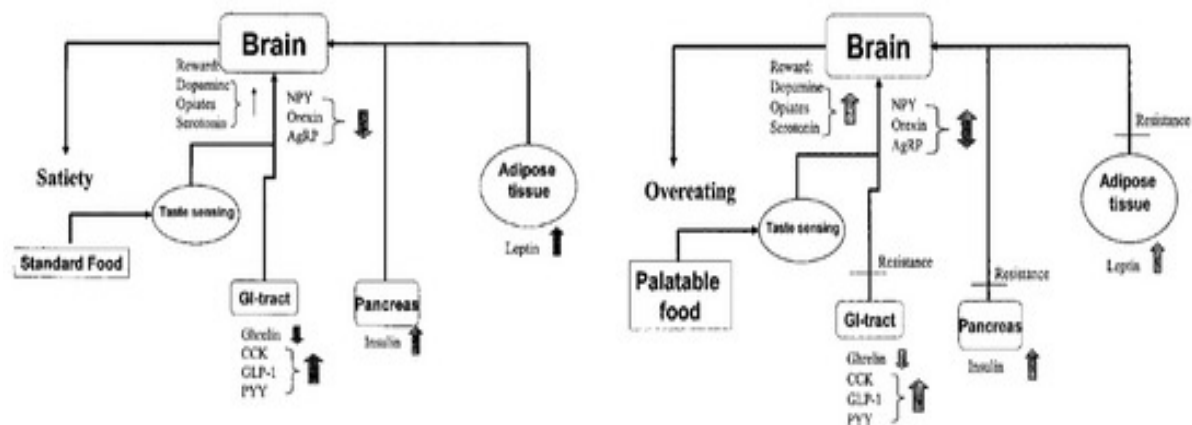
Figure 4. Hunger and satiety signalling during consumption of standard (left) and palatable (right) food (113). Left. Hunger and satiety signalling during intake of a standard meal. Hunger signals, such as ghrelin in the stomach and NPY, orexin, AgRP in the hypothalamus, are depressed after intake of standard food, while satiety signals like CCK, GLP-1, PYY, insulin and leptin are raised. Food intake is terminated as a result. Right. Hunger and satiety signalling after a period on a diet of palatable food. Hunger signals are either depressed, like ghrelin in the stomach and NPY in the hypothalamus, in response to a meal consisting of palatable food or raised, as for orexin and AgRP in the hypothalamus. Satiety signals like insulin and leptin are increased. Palatable food induces resistance to several satiety signals, documented for CCK, insulin and leptin, resulting in overeating. Food intake is driven by an increased activity in the reward system (dopamine, serotonin and opiates), triggered by the attractiveness of the taste.

Hence although homeostatic and hedonic systems can be given separate identities (105), they are also- to an extent- inseparable, with neural cross-talk permitting functional interactions which may influence the organization of feeding behaviour. From this standpoint, the interaction of homeostatic and non-homeostatic pathways in the neuro-regulatory control of feeding may be more important than the two systems studied in isolation. From behavioural and anatomical observations, (114) suggested that projections from the hypothalamus to the nucleus accumbens may modulate the motivation to feed 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 (115).

Liking vs. Wanting Food

Food 'liking' and 'wanting' are emerging constructs in a conceptual approach to food hedonics where separable processes of affect and motivation can be viewed as major influences on food intake. Liking and wanting achieve importance in light of the recognition of the contrast between homeostatic and hedonic processes that control eating (116, 117). The liking and wanting constructs stem from research exploring the neural basis of palatability and addictive behaviour (118). With principle focus on distinct dopamine and opioid pathways in the brain, the research suggests that processes of liking and wanting can be separately manipulated to produce patterns of behaviour that are either exclusively affective (rewarding) or motivational (driving) in conjunction with a food stimulus. The proposal that food reward may comprise separable liking and wanting components has since attracted a great deal of attention and controversy among scientists concerned with human food intake and obesity. Many people would assume that liking and wanting are identical phenomena, both of which signify a positive attraction to food. The logical view is that liking and wanting co-vary in a natural two-way sequence. In behavioural terms we assume that a change in liking will lead to proportional adjustments in wanting and, likewise, differences in wanting will predict changes in liking. Therefore, some researchers suggest that a clear behavioural distinction might not be possible. However, there are strong grounds for recognizing that liking and wanting can be clearly dissociated and have distinct identities. This means that they have much greater resolving potential for understanding the role of hedonics on eating and therefore on overconsumption. Thus, the issue of liking vs. wanting is concerned with the functional significance of these two distinguishable processes, operating within the hedonic domain, for overconsumption and weight regulation in humans.

Liking and wanting are thought to reflect processes that can operate without conscious awareness. This means that they have implicit components. However, their explicit counterparts express themselves subjectively in the form of hedonic feelings from the ingestion of a specific food (i.e. explicit liking) and the intent or desire to consume a specific food (i.e. explicit wanting). Under normal circumstances, explicit liking ('I like this') is closely associated with explicit wanting ('I want this'). However, there is also evidence to suggest that wanting can be 'irrational'; i.e. when implicit wanting for a food is greater than explicit wanting, and not proportional to experienced or expected liking (118, 119).

Liking and wanting appear to have separate and disproportionate roles in promoting overconsumption. In terms of liking, some individuals at risk of weight gain may experience an exaggerated hedonic response to palatable foods, so that foods are enjoyed more and therefore eaten in greater amounts for longer periods of time (120, 121). Conversely, susceptible individuals may have a diminished ability to experience pleasure from food and therefore consumption of palatable food is driven up to satisfy an optimum level of stimulation (122). Processes of wanting may also bring about vulnerability to weight gain through increased reactivity towards cues signalling the availability of food (123). Moreover,

a reduced ability to resist the motivation to eat when satiated may promote non-homeostatic overconsumption (124). A widely held notion is that wanting rather than liking may be the crucial process in maintaining an obese state. For example, research on chronic drug abusers indicate that repeated drug taking behaviour and strong motivation to obtain a 'fix' can occur in the absence of any pleasant sensations during ingestion (125). Moreover, food liking is often a rather stable characteristic within an individual and appears relatively uninfluenced by increasing weight status (126). The implication is that liking may be important in establishing the motivational properties of food, but once these are retained it is the up-regulation of wanting in an obesigenic environment " insensitivity to homoeostatic signals but over-reactivity to external cues" that promotes overconsumption by influencing what and possibly how much is eaten from moment to moment.

ROLE OF SWEETNESS IN APPETITE CONTROL

Sweetness is a potent psychobiological phenomenon. The importance comes about because the sweet taste, in nature, is normally associated with the presence of energy and therefore humans (and other animals) are likely to be strongly attracted to sweetness in foods and drinks. The sweet taste is also associated with a potent pleasure sensation. Sweetness can make foods palatable that otherwise would not be pleasant to eat; it can also raise the palatability of foods that are already pleasant. In this way sweetness offers an important strategy to increase the attractiveness of foods and to encourage consumption. The hedonic properties of sweetness means that it embodies strong reward potential with the capacity to reinforce its own consumption and behaviour associated with consumption. For this reason it can be expected that sweetness will exert positive and distinctive effects on eating behaviour, food selection and other aspects of appetite control. It is likely that sweetness is likely to have a 'facilitative' or 'permissive' effect on eating behaviour.

Although all sensory features of foods exert marked effects on eating, sweetness may have a privileged position among the taste sensations. Sweetness can confer biological meaning and it can be argued that humans have a genetic preference for sweetness. This could have arisen because sweet receptors are innate and there is a universal association, in nature, between sweetness and energy yielding (useful) properties of foods. For this reason it is arguable that sweetness may have qualitatively distinct attributes of pleasure – because of the unique role of sweetness in nature. However, sweetness can be conferred through different types of molecules, which may have distinguishable properties. The sweet taste is likely to exert a potent action on appetite through two G-coupled receptor proteins, TIR2 and TIR3, which form a broadly tuned taste receptor. Interestingly, this taste receptor is found in the mouth and in the intestine where it is linked to the secretion of peptides (GLP-1 and GIP) that have a function in metabolism and satiety (127). This draws attention to the impact of sweetness on satiation and satiety, which influence different components of the eating pattern. Different experimental designs are required to examine the effect of sweetness on these two processes. Most experiments have studied effects on satiety, although an action of sweetness on satiation (meal size) is likely to be more profound.

Uncoupling sweetness and calories

In studying sweetness, one key issue is to identify the action of sweetness *per se* from the effects of sweetness plus energy (usually glucose, sucrose, fructose). Sweet taste signalling

suggests that the actions of sweetness and energy can be dissociated anatomically. Many sweet tasting foods provide a combination of sweetness and energy. The satiety cascade (see Figure 1) indicates how both of thee factors contribute to the control of appetite. Therefore in order to study the specific action of sweetness on appetite it is important to consider the distinction between the 'additive' and 'substitutive' strategies (128). Figure 5 shows an experimental model in which sweetness and caloric content are varied independently. For example, artificial sweeteners can be added to non-sweet materials without altering the energy value. These 2 types of material can be used to compare the effect of sweetness on appetite with energy held constant. This is called the additive procedure. Artificial sweeteners can also be used to replace a carbohydrate sweetener so as to maintain an equivalent level of sweetness whilst reducing energy value. This is called the substitutive procedure. In the design of experiments the additive procedure is required to assess the effects of sweetness (holding energy constant), whilst the substitutive procedure is required to demonstrate adjustments to change in energy (sweetness held constant).
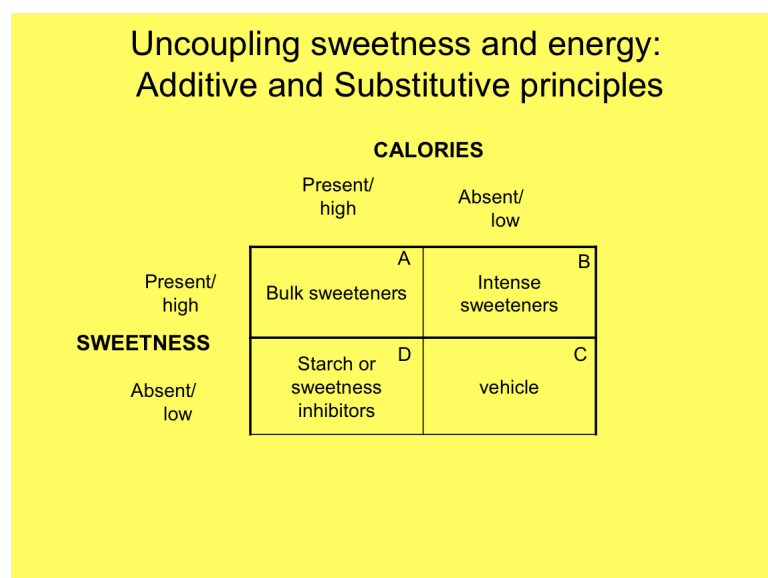

Figure 5: an experimental model in which sweetness and caloric content are varied independently.

Using this experimental model it can be demonstrated that sweetness and energy do exert different and dissociable effects on short-term appetite control including the intensity of hunger and the size of meals (128). Particularly noteworthy is the observation that sweetness alone can exert a mild facilitatory effect on hunger or the desire to eat, which is suppressed by the addition of calories to this sweet stimulus. Such an effect can also be readily demonstrated when the physiological system is mildly depleted – for example by a bout of exercise (129). These types of precisely controlled experiments are necessary to demonstrate theoretically the effects of sweetness when uncoupled from energy. However, such effects may not be observed so clearly when substances are consumed with other foods as part of a natural diet outside of the research unit.

There has also been recent interest in the potential disparate effects of glucose and fructose ingestion on appetite regulation and food reward, in part due to the use of high-fructose corn syrup in soft drinks (see Page and Melrose for a review(130)). It has been suggested that

the ingestion of fructose results in higher subjective ratings of sweet taste than glucose ingestion, but these ratings of sweet taste diminishes more rapidly following fructose ingestion (131). It is also well established that the ingestion of fructose does not directly stimulate the release of insulin from pancreatic β-cells (132), and this may be of importance to feeding behaviour as insulin is considered to be a peripheral satiety hormone (133) and also to be involved in the central regulation of food reward (134). Furthermore, acute fructose ingestion has also been shown to result in an attenuated reduction in ghrelin (135) and smaller increases in leptin and GLP-1 compared to glucose (136). While this metabolic profile may be hypothesised to promote hunger and food intake, it should be noted however that these studies did not measure subjective appetite or food intake. Functional MRI studies also suggest that glucose and fructose ingestion may be associated with differing brain responses (130), with the ingestion of fructose compared with glucose resulted in greater brain reactivity to food cues in the visual cortex and left orbital frontal cortex for example (137). However, not all studies support differences in hypothalamic activity following glucose or fructose administration (138). Consequently, while these data suggest that the metabolic responses to glucose and fructose differ, further research is needed to determine whether these differences moderate actual feeding behaviour in humans. Furthermore, whether the long-term ingestion of diets differing in glucose or fructose composition differentially effects appetite regulation or body weight is unknown.

Comparing sweet and non-sweet tastes

In studying the effects of sweetness on satiety it is relevant to ask whether sweet foods will suppress appetite to a greater or lesser extent than isoenergetic foods with a non-sweet (or savoury) taste. In a series of studies it has been demonstrated that a non-sweet lunch has a stronger suppressive effect on appetite sensations than a sweet tasting lunch (139). These studies also threw light on the relative strength of sensory-specific satiety. Interestingly, a sweet lunch suppressed the appetite for sweet foods to a lesser degree than a savoury lunch suppressed appetite for savoury foods. Consequently there is a lack of equi-potentiality among sensory qualities concerning their sensory specific effects, with sweetness displaying relatively weak sensory specific action. In a related study it a was demonstrated that the daily temporal profile (circadian rhythm) of the appetite for something sweet remained at a fairly high level throughout the day and was not markedly suppressed following meals (139). This was in contrast to the appetite for savoury foods, which fluctuated markedly across the day and was severely affected by meals. The results of these studies show that sweet carbohydrates are less satiating than non-sweet carbohydrates, and that the preference for something sweet appears to be preserved across the day. Under these circumstances sweetness seems to have a facilitatory or permissive effect on appetite.

Sweetness (sugar) and fat

Considering the effects of food materials on appetite, there is considerable debate concerning the capacity of sugar or fat to induce overconsumption and to cause weight gain. Short-term intervention studies demonstrate that fat has a much greater capacity to induce 'passive overconsumption' than sugar, largely because of its higher energy density (140). In addition, the analysis of large survey databases has drawn attention to the concept of the sugar-fat seesaw in which these materials tend to be inversely related to each other in the diet (141). In epidemiological studies the relative contribution of sugar and fat to weight gain

can be seen more clearly when the database is improved by removing those 'under-reporting' subjects whose reported intakes are physiologically implausible. When this is done there is a positive relationship between categories of BMI and fat intakes, but no relationship with sugar (142). Obese people consumed greater amounts of fat than lean subjects but similar amounts of sugar. This finding tends to confirm an earlier report that obese people have a strong attraction to the fatty taste and a preference for high fat foods (143). Moreover, some of the most palatable high fat foods occur in the form of cakes and pastries in which the sugar content can also be high. These food items constitute the sugar-fat combination, and this sweet-fat taste is a potent food stimulus. Interestingly, when the consumption of high fat-high sugar foods is analysed according to body weight, obese female subjects were found to consume a significantly greater weight than subjects in other weight categories (144). These studies have indicated that there are likely to be considerable differences among appetite responses to sweetness alone, and sweetness in combination with other food attributes (particularly fat).

Sweetness, Liking and Wanting, and Binge Eating

The attraction of the sweet-fat combination for certain groups of people draws attention to the hedonic aspect of sweetness. It is the role of sweetness in mediating the role of pleasure that is possibly its most celebrated attribute. Recent advances in food hedonics have defined separate roles for 'liking' and 'wanting' (145) and a specific anatomical locus has been proposed for the molecular hedonic impact of sweetness (146). Importantly, a novel experimental procedure has been developed to evaluate the strength of liking and wanting in human subjects using a range of visual food stimuli varying in sweetness and fattiness (117). The effect of sweetness on these processes has been tested by using a sweet or savoury sensory preload on liking, wanting and the actual food consumption preferences in female subjects varying in the tendency to show binge eating. Those subjects who scored high on the binge eating scale showed an increased general liking for all foods, but specifically selected from the test buffet those foods high in the sugar-fat combination (Figure 6). Interestingly, the effect of sweetness was revealed by an increase in implicit wanting for all foods following the sweet preload. These results have shown, once again, that certain individuals (high binge eaters) show a tendency to prefer, and to consume, the high sugar/high fat combination, indicating an impact of the sweet component on satiation (during consumption). It also appears that sweetness (as a sensory preload) can exert effects after consumption (during satiety) by increasing the unconscious (implicit) wanting for foods (147).
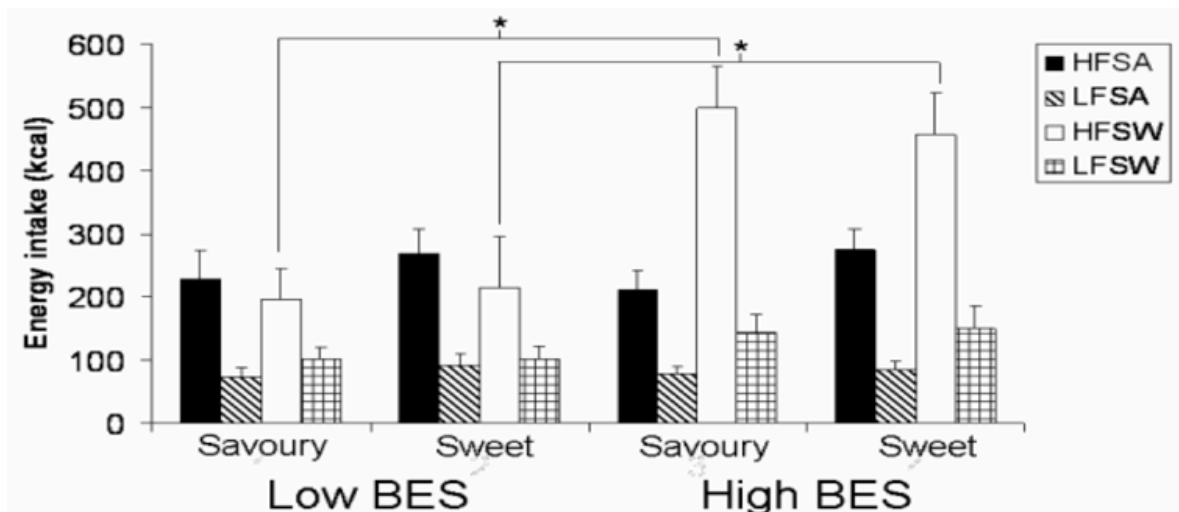
Figure 6: Mean energy intake according to fattiness and taste properties of test mean foods after savoury and sweet preload for high and low BES groups. * P < 0.05

Sweet preferring phenotypes

The above sections have indicated that particular types of people – obese or binge eaters – can display a strong preference for sweetness when combined with fat in foods. There also exist people who show a strong preference for sweetness per se, and who consume large volumes of sweet low-energy beverages (148). In these sweet preferring phenotypes the uncoupling of sweetness and energy exerts a specific effect on the short-term control of appetite indicating that the habitual consumption of sweetness without energy can re-program the appetite system (149). It is therefore not possible to claim that sweetness will have the same impact on all individuals.

CONCLUSION

The regulation of food intake can be understood in terms of appetite control and is expressed through integrated sequences of behavior accompanied by oscillating episodic signals and long-term tonic signals. Within the prevailing obesigenic environment, the precision of appetite control is undermined, and the neural integration of these signals favors overconsumption leading to weight gain. This gain in adipose tissue appears to further destabilize the control of appetite through the actions of both leptin and insulin resistance and through a favouring of hedonic over homeostatic mechanisms. Therefore, the control over appetite becomes progressively less accurate and sensitive as obesity develops. The balance between tonic and episodic signalling (and the transformation of these signals within the brain) and the balance between homeostatic and hedonic processes ultimately determine the willingness or reluctance of people to eat or not eat. The logic concerning weight gain can also be applied to weight loss, and there is now clear evidence that in response to the negative energy balance induced by physical activity, some people compensate by increasing food intake so as to resist weight loss, whereas others do not and consequently lose weight. The message from studies on food intake regulation and appetite control is that there exists considerable variability underlying the strength of satiety, the willingness to eat and the degree of susceptibility to environmental stimulation; managing the

epidemic of obesity is made substantially more difficult (and complicated) by this variability. A global perspective suggests that sweetness is a quality that has a generally positive effect on the expression of appetite, and this can lead to a facilitation of eating. Some people may be particularly susceptible to these effects; others will be resistant. Consequently, the potent psychological and behavioural components of sweetness cannot be captured in a single summary statement.

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