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Energy Balance, Body Composition, Sedentariness and Appetite Regulation: Pathways to Obesity

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ABSTRACT

Energy balance is not a simple algebraic sum of energy expenditure and energy intake as often depicted in communications. Energy balance is a dynamic process and there exist reciprocal effects between food intake and energy expenditure. An important distinction is that of metabolic and behavioural components of energy expenditure. These components not only contribute to the energy budget directly, but also by influencing the energy intake side of the equation. It has recently been demonstrated that resting metabolic rate is a potential driver of energy intake, and evidence is accumulating on the influence of physical activity (behavoiural energy expenditure) on mechanisms of satiety and appetite control. These effects are associated with changes in leptin and insulin sensitivity, and in the plasma levels of gastrointestinal peptides such as glucagon-like peptide-1, ghrelin and cholecystokinin. The influence of fat-free mass on energy expenditure and as a driver of energy intake directs attention to molecules emanating from skeletal tissue as potential appetite signals. Sedentariness (physical inactivity) is positively associated with adiposity and is proposed to be a source of overconsumption and appetite dysregulation. The molecular signals underlying these effects are not known but represent a target for research.

Running title:

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ENERGY BALANCE REGULATION: A DYNAMIC RELATIONSHIP BETWEEN BIOLOGY AND BEHAVIOUR

Weight gain is often explained as a function energy balance, with sustained periods of excess energy intake over energy expenditure thought to promote the accumulation of adipose tissue. Unfortunately however, energy balance is typically portrayed as a 'static' regulatory system, in which reductions in energy intake, or increases in energy expenditure, automatically lead to energy deficit, and in turn, weight loss. This approach is simplistic and belies the complexity of energy balance regulation in humans in the current obesogenic environment. Furthermore, it ignores the potential for behavioral or biological adaptation to restore energy homeostasis during periods of energy deficit or surfeit (1). Rather than being static, the regulation of energy balance is a dynamic process in which perturbations to one component of energy balance may elicit biological and/or behavioral 'compensation' in other components of the system. These auto-regulatory or compensatory responses act to minimize perturbations to energy homeostasis, in turn, body weight (1, 2). For example, it has been suggested that some individuals experience a compensatory reduction in resting energy expenditure, termed adaptive thermogenesis (3), following dietary (4, 5) and exercise-induced (6) weight loss. Compensation may also be behavioural in nature, with dietary (7, 8) and exercise-induced (9, 10) weight loss shown to result in increased fasting hunger (although such changes in subjective appetite do not always translate into changes in actual behavior i.e. food intake (2)).

While often viewed (and studied) in isolation, it is therefore important to recognize that there is a reciprocal relationship between energy intake and energy expenditure. This can take the form of compensatory responses, and the nature and extent of compensation to energy deficit or surfeit will play an important role in determining an individual's susceptibility or resistance to weight loss (11, 12). However, marked inter-individual variability exists in these biological and behavioural compensatory responses (11, 13, 14). The heterogeneity in these compensatory responses elicited by energy deficit in part explains why exercise-and-dietary-induced weight loss is highly variable (11, 13, 14), and typically less then theoretically expected (based on objective measures of exercise-induced energy expenditures or dietary-induced energy deficits) (15, 16). Consequently, the efficacy of exercise or dietary interventions for weight loss must be evaluated in the context of this dynamic regulatory system. However, our ability to discern the inter-relationships between components of energy

balance during energy deficit or surfeit has been restricted, as studies often examine the impact of exercise or diet on individual components of energy balance in isolation. Genetic and epigenetic factors will undoubtedly contribute to an individual's susceptibility or resistance to weight loss (and variability in the underlying biological and behavioral responses), but it is worth noting that genome-wide association studies are currently only able to explain a small proportion of the between-subject variance in body weight or body mass index (17).

THE 'WICKED' PROBLEM OF OBESITY

The notion of biological and behavioural compensation highlights the fact that the regulation of energy balance, and the mechanisms that drive energy intake and expenditure, are tremendously complex. The physiological regulation of energy balance involves the complex interaction between central regulatory pathways and multiple peripheral feedback signals arising from adipose and the gastrointestinal tract for example. It is important to note though that these homeostatic regulatory mechanisms also interact with environmental and psychosocial factors in the overall expression of body weight (18). Indeed, the Foresight Obesity Systems Map (19), which places energy balance at the center of this obesity system, highlights multiple complex, and often inter-related, behavioural and societal factors that mediate the biological regulation of energy balance. However, despite recent advances in our understanding of the neural pathways underpinning the central regulation of energy balance, a unifying theory of how these central neural signals are integrated with peripheral signals of nutrient intake, energy storage, and cognitive and environmental factors, remains elusive (20). This has led to obesity being viewed as a 'wicked' (or insolvable) problem (21).

One major theoretical position in this field is that molecular signals act as key regulators of energy balance, and such research has led to a progressive refinement of our understanding of the central mechanisms purported to control energy homeostasis (i.e. the co-ordination of energy intake and energy expenditure). The idea of a key regulatory signal was also apparent in early theories of appetite and body weight regulation, which were based around control mechanisms stemming from signals arising from glucose metabolism (Glucostatic theory (22), amino acids (Aminostatic theory (23) and adipose tissue (Lipostatic theory (24). While such models ultimately proved inadequate in describing the complexities of eating behaviour in today's modern obesogenic environment, Kennedy's (25) lipostatic theory, in which he

proposed that 'lipostasis' was regulated by circulating metabolites that acted on a hypothalamic 'calorimetric satiety' center to inhibit feeding, still plays a persuasive role in our understanding of the role of leptin in body weight regulation. Interestingly though, it is worth noting Kennedy's (1953) orginal 'lipostatic hypothesis' was only concerned with "the prevention of an overall surplus of energy intake over expenditure", rather than a universal 'thermostat' that defended both upper and lower limits of fat mass. The discovery of leptin led to the apparent confirmation of the lipostatic theory of body weight regulation, and positioned leptin centrally in the control of energy intake and energy expenditure. Later, when it became apparent that exogenous leptin administration in 'normal' obese human (i.e. in those free from congenital leptin deficiency) was ineffective in promoting weight loss (26), obesity came to be viewed as a state of leptin insensitivity or leptin resistance. However, adipose tissue still often occupies a fundamental role in appetite control (27).

This draws attention to the operational conditions under which body weight is actually regulated. It has been argued that regulation of energy balance is asymmetrical; while periods of overfeeding or energy surfeits are met with a weak regulatory response to restore energy balance, energy deficit appears to trigger a number of potent signals designed to attenuate any imbalance and resist weight loss. The asymmetry in energy balance regulation is apparent in under-and-over-feeding studies, in which compensatory changes in huger and food intake are greater in response to energy deficit rather than surfeit (28). Muller et al. (29) has also noted that the inter-individual variability in weight changes during overfeeding is higher than that seen during underfeeding, which is again indicative of 'tighter' regulation of body weight during energy deficit rather than surfeit (29). Such data therefore suggest that the strength of putative feedback signals (such as leptin) vary under differing physiological conditions, and this must be accounted for when modeling the relationships between changes in body composition, signaling pathways and the physiological and behavioural responses to energy balance and imbalance.

Taken together, the previous sections point to obesity as a complex and multifaceted condition. Therefore, it is beyond the scope of this review to address all of the potential pathways or mechanisms that promote the accumulation of adipose tissue and obesity. Rather, our intention is to draw attention to a largely ignored body of evidence (and plausible theoretical explanations) though which appetite (dys)regulation could influence obesity development.

APPETITE REGULATION IN HUMANS

Due to it's potential to readily perturb energy balance, the molecular mechanisms that regulate appetite and food intake, the role that appetite dysregulation plays in the etiology of obese, is of current interest. Day-to-day food intake, which consists of a series of discrete feeding episodes, involves the co-ordination of both homeostatic (e.g. energy need) and non-homeostatic feedback (e.g. food hedonics and environmental factors) (28). A detailed discussion of the molecular mechanisms involved in the regulation of appetite can be found elsewhere (30-33). The homeostatic control of appetite is often conceptualised through a series of physiological processes that initiate and terminate feeding (i.e. satiation), and those which suppress inter-meal hunger (i.e. satiety). Collectively, these processes have been termed the Satiety Cascade (34). In turn, the Satiety Cascade can be extended to describe the expression of appetite on three related levels (Figure 1), and involves psychological and behavioural patterns, peripheral physiological and metabolic events, and neural and metabolic interactions in the brain (34).
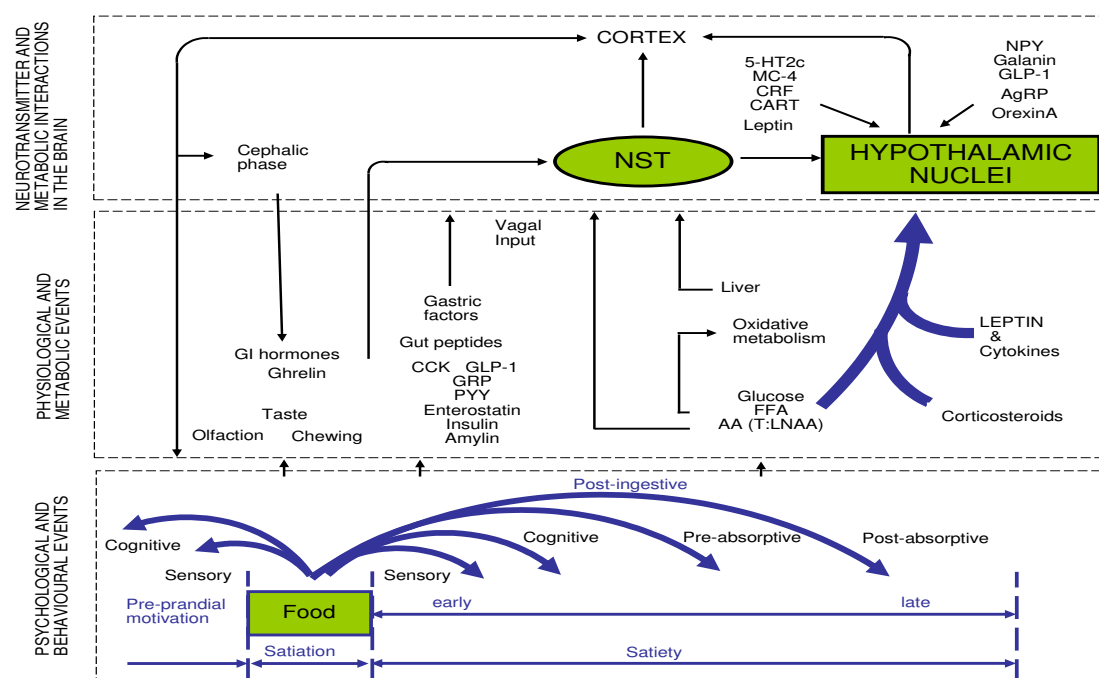
Figure 1: Simple representation of the (mainly) inhibitory mechanisms through which food consumption influences peripheral physiological mechanisms and neural pathways which bring about an adjustment in the appetite response. This scheme shows the integration between the behavioural pattern, profile of peripheral physiological events and action at brain sites. The diagram illustrates the difference between satiation (control of meal size) and satiety (control of inter-meal interval). 5-HT, serotonin; AA, amino acids; AgRP, Agouti related peptide; CART, cocaine and amphetamine regulated transcript; CCK, cholecystokinin; CRF, corticotropin releasing factor; FFA, free fatty acids; GI, gastrointestinal; GLP 1, glucagon like peptide-1; GRP, gastric releasing peptide; MC, melanocortin; NPY,

neuropeptide Y; NST, nucleus tractus solitarius; T:LNAA, tryptophan: large neutral amino acid ratio. Previously published in Boyland, Halford & Blundell (35).

Sensory information derived from the cephalic phase of digestion and afferent vagal signaling elicited by the presence of food in the stomach provide early information to the brain concerning the amount and nutrient content of food consumed (34). Following gastric emptying, the presence of nutrients in the intestine triggers the release of a number of gut peptides such as cholecystokinin, glucagon-like peptide-1, peptide YY and ghrelin, which stimulate local sensory nerves travelling to the hindbrain and provide immediate information about the nutritional content of the ingested food (30). Together, these neural and humoral responses to the ingestion of food help promote the episodic control of feeding via meal termination (satiation) and the subsequent suppression of inter-meal hunger (satiety). During the post-absorptive phase of digestion, metabolic signals arising from the presence of nutrients in the circulation also contribute to the suppression of satiety and meal initiation.

The macronutrient composition of food can influence the expression of the satiety cascade and appetite related processes, with dietary macronutrients exerting a hierarchical effect on satiety (36), food reward (37) and short-term food intake (38-43). When expressed relative to energy content rather than weight of food, protein exerts the strongest effect on satiety whilst fat exerts the weakest effect (44). The differential effects of dietary macronutrients may relate to differences in pre-ingestive cognitive and sensory signals generated at the time of consumption (45) and/or the post-ingestive metabolic effects of these foods (46-48). For example, the macronutrient composition of meals mediates the secretion of post-prandial satiety hormones such as glucagon-like peptide-1 and peptide YY (46-48). However, while the acute effects of different dietary macronutrient intake are becoming clearer, there is on-going debate regarding the effect of long-term diets differing in macronutrient composition on weight loss efficacy (49).

Although satiety (and its dependence on episodic signals) is often perceived as the essence of appetite control, a fundamental factor is the distinction between tonic and episodic signals. In addition to the satiety-based control of feeding, putative long-term (tonic) signals such as leptin and insulin also influence day-to-day food intake, conveying information concerning long-term energy availability to the central nervous system (31). Perturbations to circulating leptin concentrations are thought to alter the hypothalamic expression of orexigenic and anorexigenic neuropeptides (32) A reduction in leptin in response to energy deficit is thought

to promote food intake and reduced energy expenditure via a down-regulation in the expression of proopiomelanocortin and alpha-melanocyte stimulating hormone, and an up-regulation in the expression of neuropeptide Y and agouti gene-related peptide (27, 33). Furthermore, to ensure the expression of long-term energy needs through daily feeding patterns, leptin and insulin are also thought to mediate the strength of short-term episodic satiety signals such as cholecystokinin and glucagon-like peptide-1 via changes in peripheral secretion and central sensitivity (27, 32, 33).

It is important to note that the homeostatic regulation of food intake is moderated by non-homeostatic (e.g. hedonic) signals (50). Indeed, given the large reserves of adipose tissue that characterise obesity, excess food intake in the obese is unlikely to be driven primarily by signals relating to energy need. Indeed, it has been suggested that the homeostatic control of feeding can be easily overridden by hedonic factors in the current obesogenic environment (51). It is important to note though that the neural systems that underlie homeostatic and hedonic feeding are closely linked (50), with leptin and insulin providing a molecular link between the hypothalamic (homeostatic) and mesolimbic (reward related) systems (33). For a detailed review of the neurobiology of hedonic (reward related) control of food intake, see Berthoud et al (50) or Münzberg et al. (52). Recent research has highlighted the importance of distinguishing affective food 'liking' (i.e. perceived pleasurable sensory properties of food) from motivational 'wanting' (i.e. relative attraction towards a specific food over available alternatives) as separable risk factors for over-consumption and weight gain (53, 54). The underlying conceptual basis of the liking and wanting food constructs stem from research exploring the neural basis of palatability and addictive behaviour (53). 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 (55). Both components of food reward are thought to act in parallel to moderate eating behaviour (56), and may have distinct underlying neural pathways in the brain (i.e. dopamine and opioid systems) (57).

BODY COMPOSITION, ENERGY EXPENDITURE AND FOOD INTAKE

For over 50 years the scientific approach to body weight regulation has been dominated by a focus on adipose tissue as a major source of control of appetite, and this has driven the search for, and the identification of, molecular signals that provide an explanation of the mechanistic operations. However, during this period another concept of appetite control was proposed,

but was never taken up in the scientific field and was left dormant for decades. This approch, which orginated from the work of Edholm and collegues (58), sought to examine whether food intake was controlled by the dynamics of adipose tissue (as proposed by the lipostatic theory), or more generally by the body's demand for energy. Recent re-examination of the relationships between the components of body composition, energy expenditure and food intake have shed light on these issues, and they may have important implications for our understanding of appetite regulation and the development of obesity.

Difference in body composition between lean and obese individuals are traditionally thought to be responses to excess food intake and/or low levels of energy expenditure. However, the accumulation of adipose tissue *per se* may also actively promote overconsumption, sedentariness and further weight gain. For example, it is thought that leptin sensitivity, as an appetite signal, is weaker in the obese state due to the development of leptin resistance (59). Therefore, the functional significance of leptin appears to change with progressive increases in adipose tissue; when people are lean, leptin appears to be a potent appetite-inhibiting signal, but with increasing adiposity, the strength of this inhibitory signal weakens and thus, the accumulation of adipose tissue promotes further overconsumption and weight gain (59, 60).

It is also worth noting that addition to excess fat mass, obese individuals also often display increased levels of fat-free mass and resting energy expenditure when compared to lean individuals. However, while protein-energy relationships are thought to be critical for survival time during under nutrition (61-63), few have considered energy expenditure, or its determinants such as body composition, as major sources of feedback in the control of day-to-day food intake (64, 65). 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, and in contrast to the prevailing 'adipocentric' view of appetite regulation, these studies suggest fat-free mass has a stronger influence on day-to-day food intake than fat mass (66-71). For example, Blundell et al. (68) reported that fat-free mass was positively associated with self-selected meal sized and total daily energy intake in 93 overweight and obese individuals. In contrast however, no such associations were found between fat mass and food intake.

It is interesting to note that Lissner et al. (69) reported over 25 years ago that lean body mass (but not fat mass) predicted objectively measured energy intake in 63 non-obese and obese women. These authors argued "the emphasis of research that focuses on the relationship between energy intake and obesity is misplaced because energy requirement appears to be a direct function of lean mass rather than of adiposity". Furthermore, based on his re-analysis of the Minnesota semi-starvation study (72), Dulloo et al. (73) noted that both fat and fat-free mass losses independently predicted the post-starvation hyperphagic response. Importantly, despite the full restoration of body mass and fat mass, hyperphagia persisted until fat-free mass levels were fully restored to pre-starvation levels during recovery from weight loss. Therefore, while putative feedback signals arising from adipose tissue (e.g. leptin) are commonly assumed to provide the molecular link between long-term energy needs and daily food intake, non-adipostatic signals also appear to play an important role. Based on such findings, Blundell et al. (68) has recently proposed that the energy expenditure arising from fat-free mass, as the main determinant of resting metabolic rate (74), 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.

In support of this proposal, a number of studies have demonstrated that resting metabolic rate (but again, not fat mass) is a determinant of within-day eating behavior (70, 75, 76). For example, Caudwell et al. (75) demonstrated in overweight and obese individuals that resting metabolic rate (but not fat mass) was a determinant of daily hunger, self-selected meal size and daily energy intake under conditions of high and low energy density. These findings helps further our understanding of the excitatory drive to eat that embodies modern theories of appetite, and help reconcile the intermittent suppression of eating (i.e. episodic satiety signaling and tonic inhibition) with the intrinsic excitatory drive to eat (which to date, has been poorly defined). Evidence that food intake is linked to the rate of energy expenditure can also be found in animal studies. For example, when the ambient temperature was reduced, laboratory mice were found to increase heat production by non-shivering thermogenesis. Importantly though, body mass was maintained at these lower ambient temperatures due to a concurrent increase in food intake to maintain energy homeostasis (77, 78).
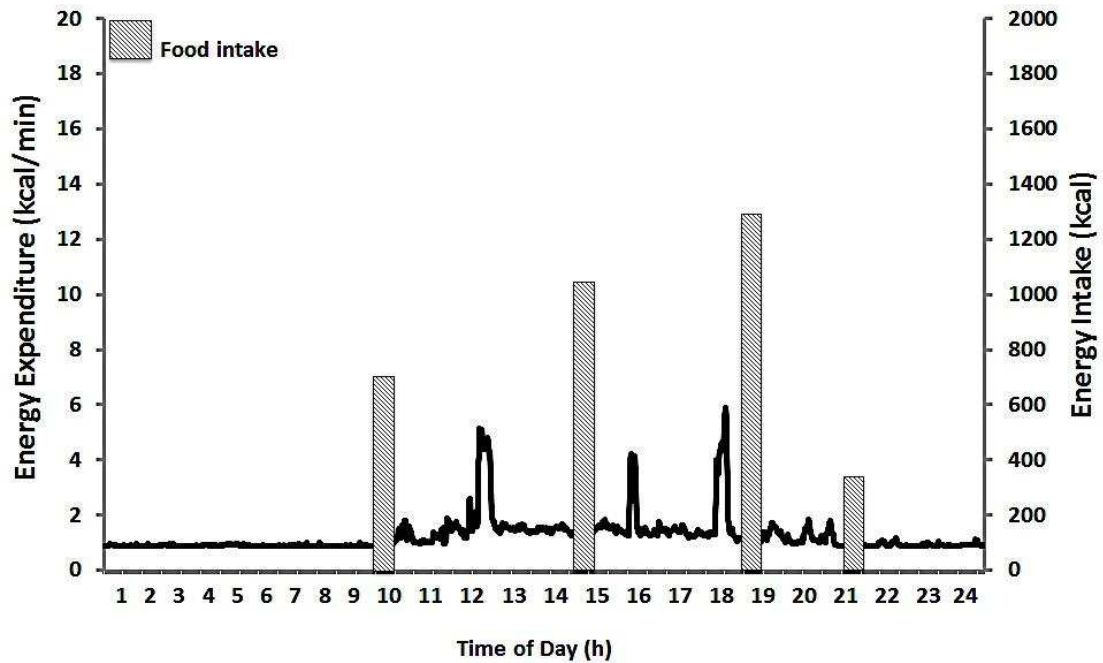
Figure 2: Physical activity energy expenditure (kcal/min) and food intake over a 24-h period. The figure highlights the fact that energy expenditure is a continuous process, while food intake is a discontinuous process consisting of discrete feeding episodes.

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 (79). The need for such a signal becomes apparent when it is considered that while energy expenditure is a continuous process, food intake is a discontinuous process consisting of discrete feeding episodes (Figure 2). At present however, how the demand for energy is translated into motivated behavior (i.e. food intake) is unclear. It has previously been suggested that the energy demand of tissues such as the liver might be translated into tonic hunger signals (80). This notion fits with the proposed 'energostatic' control of food intake (81), in which changes in hepatic energy status (hepatocellular ATP/ADP ratio) resulting from altered fatty acid oxidation is thought to influence energy intake via the stimulation of vagal afferent nerve activity (82). The pharmacological inhibition of fatty acid oxidation (via mercaptoacetate, methyl-palmoxirate or etomoxir for example) has been shown to increase energy intake (82). However, efforts to suppress energy intake by the stimulation of fatty acid oxidation have failed to consistently show an effect on food intake (82, 83). This may be because changes in whole body fat oxidation provide a weak regulatory signal for food intake, with the amount of fat ingested or oxidised on a daily basis very small relative to the total amount of energy stored as adipose tissue (84). Indeed, while it has been suggested that that nutrient metabolism may exert negative feedback on food intake e.g. the glycogenostatic

theory (85), the role of whole body nutrient balances or availability on human eating behaviour remains unclear (86).

This draws attention to the peripheral and central 'sensing' of nutrients such as glucose and free-fatty acids, and their integration with the hypothalamic control mechanisms of food intake and energy balance (87). It is now becoming clear that gastrointestinal lipid sensing and subsequent signaling exert negative feedback via hormonal and/or sympathetic responses that alter hepatic glucose output and food intake (88). Furthermore, nutrient-sensitive neurons within the hypothalamus and other brain regions are thought to detect changes in plasma fatty acid concentration and/or oxidation (89, 90), again mediating hepatic glucose output and food intake in order to maintain whole body glucose and energy homeostasis (91, 92). Interestingly, the action of fat itself could be corrosive and contribute to the pathogenesis of obesity and type II diabetes (93, 94), with rats exposed to chronic high-fat diets exhibiting an impaired ability to sense nutrient (95, 96). However, whether a high fat diet in humans interferes with the molecular mechanisms involved in nutrient sensing, and the specific role that such impairments play in appetite dsyregulation and obesity development in humans, remains unclear.

In addition to fatty acid and glucose nutrient sensing, amino acid sensing mechanisms also exist to help ensure the tight regulation of protein and amino-acid metabolism (97). These amino acid sensors may also play a role in appetite control, potentially providing a mechanism through which the energy demands stemming from fat-free mass is translated into food intake. Millward (64) has proposed the 'protein-stat theory' of appetite regulation, postulating that lean mass, and in particular skeletal muscle, is under tight regulation and food intake is directed to meet the needs of lean tissue growth and maintenance (64). The basis of this theory is the existence of an 'aminostatic' appetite control mechanism (23), in which food intake is adjusted in response to amino acid availability. However, evidence of such regulation, or the existence of a 'protein-stat', is limited. Recent findings indicating that skeletal muscle secretes a large number of myokines are also of interest (98), as these myokines provide molecular links and bi-directional communication between skeletal muscle and organs such as the liver, brain and adipose tissue (99). A number of myokines such as interleukin 6 (100) and irisin (101) have been linked to food intake and energy expenditure in humans, but the specific role that these (and other myokines) play in appetite regulation is unclear.

Cellular energy sensors such as AMP-activated protein kinase (AMPK) may also be involved in translating the demand for energy into behavioral outcomes such as food intake. AMPK is an enzyme involved in 'sensing' the energy status of a cell, and is activated by changes in cellular AMP:ATP and ADP:ATP ratios (102). It is thought to be a key enzyme in the co-ordination of peripheral and central energy homeostasis (103), integrating signals of cellular and whole body energy needs via its effect on anabolic (i.e. ATP consuming) and catabolic (i.e. ATP producing) pathways (104). AMPK has also emerged as a hypothalamic energy sensor that influences both food intake and energy expenditure (102, 103, 105). Increased activation of hypothalamic AMPK has been shown to promote energy intake in animals via alterations in the expression of hypothalamic orexigenic or anorexigenic neuropeptides (103, 105, 106). Inhibition of hypothalamic AMPK is thought to promote whole body energy expenditure via increased sympathetic nervous system activity and subsequent increases in thermogenesis in brown adipose tissue and fat oxidation within skeletal muscle and white adipose tissue (107).

AMPK has been shown to display nutrient-specific activity and to be modulated by a range of hormones implicated in appetite and energy balance regulation e.g. leptin, adiponectin, ghrelin and T4 (108). Furthermore, AMPK activity is altered by the nutritional state of the body i.e. fasting increases hypothalamic AMPK activity and feeding inhibits AMPK activity (106), while exercise also activates skeletal muscle AMPK (109). While further work is needed to specifically examine the role that AMPK plays (if any) in the relationships observed between fat-free mass, resting metabolic rate and food intake, it does represent a plausible mechanism through which whole body energy needs are 'sensed' and translated into day-to-day feeding behaviors.

In this regard, a recent study has examined how energy needs arising from fat-free mass could be detected by the brain (110). Using brain positron emission tomography, Weise et al (110) reported significant associations between fat-free mass, but not fat mass, and several brain regions involved in the homeostatic control of appetite. A link between fat-free mass, hunger and cerebral blood flow in the periacqueductal gray was highlighted. As noted by the authors, this area is a key station on the ascending homeostatic pathways, and neural activity here can plausibly be envisaged as part of a system that transforms fat-free mass-induced energy demand into motivated feeding behavior. While these data and others suggest a fundamental relationship between energy expenditure and the energy acquired through food, the mechanism(s) that translates the energetic demand arising from fat-free mass and resting

metabolic rate into a motivational drive to eat are unknown. However, a number of plausible molecular signals or pathways exist, and the identification of a specific mechanism through energy needs are translated into motivated feeding behavior remains fundamental to future work.

Fat-free Mass, Resting Metabolic Rate and Food Intake: Implications for the Accumulation of Adipose Tissue

Recent recognition that fat-free mass and resting metabolic rate play important roles in day-to-day food intake have important implications for our understanding of appetite regulation and adipose tissue accumulation. The excitatory drive stemming from fat-free mass and resting metabolic rate (and potentially, other components of energy expenditure), would be under tonic inhibition from adipokines such as leptin. However, the progressive accumulation of adipose tissue with obesity development would lead to leptin (and insulin) resistance, attenuating the strength of this tonic inhibition. In contrast however, the tonic drive to eat stemming from fat-free mass and resting metabolic rate, which are elevated in the obese state, would remain unabated. Therefore, the development of obesity *per se* may further promote overconsumption (and appetite dysregulation) in obese individuals, as the accumulation of adipose tissue creates a mis-match between the tonic inhibitory and excitatory drives to eat stemming from fat mass and fat-free mass/resting metabolic rate, respectively. Interestingly, Cugini et al. reported that the relationship between body composition and hunger varied between lean and obese individuals (67, 111), with a negative association reported between fat mass and hunger in lean but not obese individuals (see Figure 3). Furthermore, it has been reported that in young, lean active men and women fat mass is inversely associated with energy intake (59). These data fit with the notion that the influence of fat mass on appetite may vary with its level of accumulation, with a threshold of fat mass (specific to each individual) existing at which fat mass changes from being inhibitory to disinhibitory.
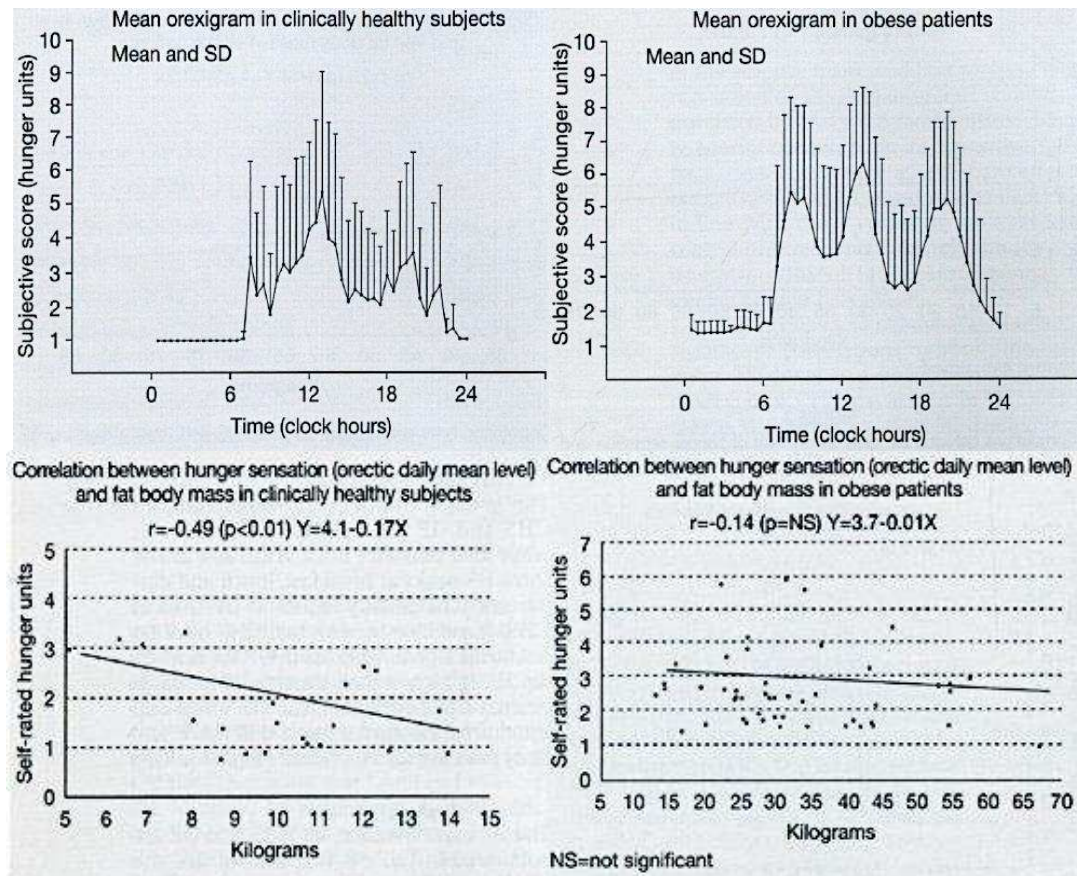
Figure 3: Top panel- 24 hr 'orexigram' of subjective hunger in clinically healthy (n = 22) and obese individuals (n = 48). Mean daily hunger and hunger peaks significantly higher in obese compared to healthy individuals. Bottom panel- correlations between subjective hunger and fat mass in clinically healthy (n = 22) and obese individuals (n = 48). Subjective hunger was negatively associated with fat mass in clinically healthy, but not obese, individuals. These data suggest that fat mass does not inhibit hunger in the obese to the same extent as in lean individuals. Figures originally published in Cugini et al. (112).

Is it Fat-Free Mass or Energy Expenditure *per se* that Drives Food Intake?

Given that fat-free mass is its main determinant of resting metabolic rate, and the two parameters co-vary strongly (113), it is important to establish whether it is fat-free mass (or more specifically, a molecular signal arising from fat-free mass) or energy expenditure *per se* that drives food intake. To address this, Hopkins et al. (70) modeled the associations between body composition, energy expenditure and food intake in the context of total energy balance in 59 men and women. After controlling for age and sex, both fat-free mass and resting metaboic rate (but not fat mass) predicted daily energy intake. However, a mediation model using path analysis indicated that fat-free mass had no 'direct' effect on food intake, but rather 'indirectly' influenced food intake via its effect on resting energy metabolism. These

data therefore suggest that the effect of fat mass was being channeled through energy expenditure (with fat mass typically explaining 6-7% of the between-subject variance in resting metabolic rate (113)). However, this does not rule out the possibility of fat-free mass exerting an independent biological action on food intake and hunger. It is also worth noting that fat mass, and in particular, brown adipose tissue, plays an important role in thermogenesis (114). While increasing the amount or activity of brown fat would help promote a negative energy balance via increased energy expenditure, to date, the activation of brown adipose tissue or thermogenesis via pharmacological targets in humans has been of limited value in the treatment of obesity.

In agreement with these findings, Piaggi et al (71) found that twenty four hour energy expenditure and respiratory quotient independently predicted food intake in 107 men and women. Again, mediation analysis indicated that fat-free mass did not have any direct effect on energy intake, with 24 hour energy expenditure accounting for 80% of the observed effect fat-free mass exerted on energy intake. However, it is worth noted that food intake was 159 ± 40% of weight maintenance needs during the 3-day *ad libitum* measurement period. Therefore, these data provide insight into over-consumption rather than the mechanisms that control day-to-day food intake under conditions of approximate energy balance.

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, as noted above, a molecular signaling pathway arising from lean tissue cannot be dismissed. Indeed, Cameron et al. (115) has recently reported that skeletal muscle mass was a stronger predictor of energy intake (assessed using 3-day food records) than fat-free mass or resting metabolic rate in 304 post-pubertal adolescents. These recent studies on relationships among body composition, resting metabolic rate, total daily energy expenditure and food intake that have been published in the last four years suggest a different biological approach to appetite regulation. This formulation is shown in Figure 4, which indicates separate roles for fat-free mass and fat mass as tonic modulators of appetite and separate systems for short-term episodic controls (as indicated in Figure 1).
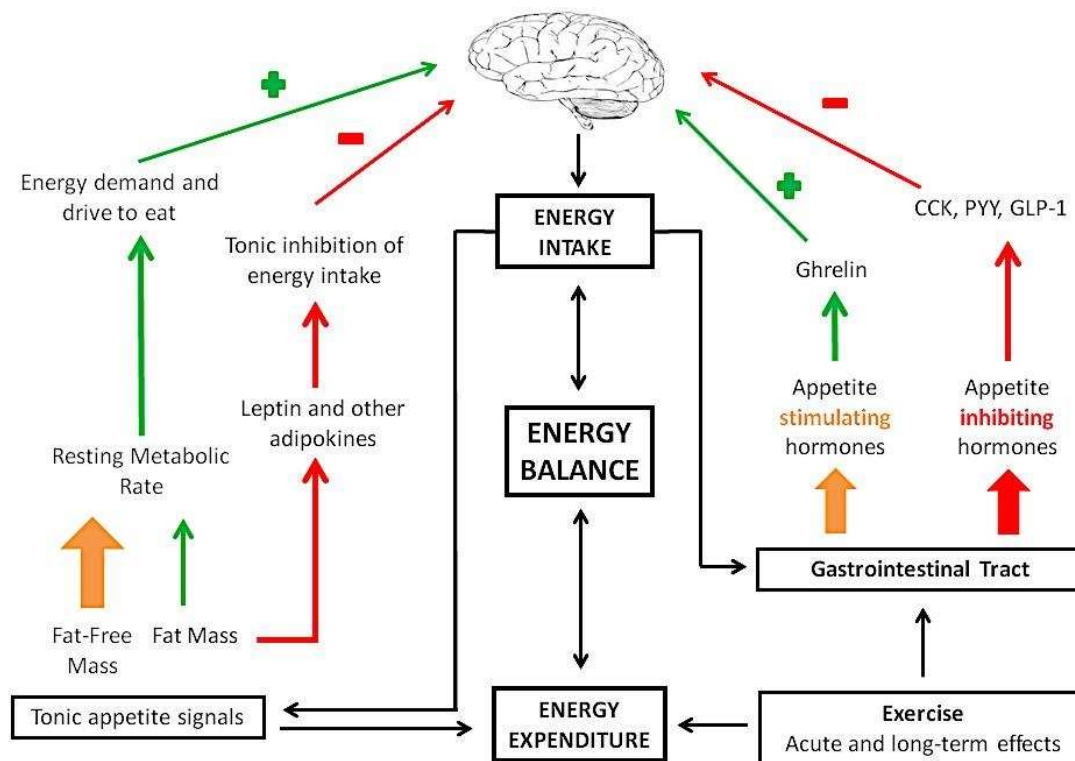
Figure 4: Formulation of the major influences on appetite control using an energy balance framework. Green arrows denote processes that stimulate feeding, while the red arrows demote processes that inhibit feeding. There is a distinction between tonic and episodic processes, with episodic signals arise as a consequence of food consumption while tonic signals arise from body tissues and metabolism. The effect of fat mass on energy intake reflects a lipostatic view of appetite control; leptin is a key mediator of the inhibitory influence of fat on brain mechanisms. The metabolic demand for energy arises from energy requirements generated by the major energy using organs of the body (heart, liver, brain, GI tract, skeletal muscle) and reflected in resting metabolic rate. The overall strength of the drive for food is the balance between the tonic excitatory and inhibitory processes. It is proposed that, as adipose tissue accumulates in the body, the tonic inhibitory effect of fat on energy intake becomes weaker (due in part to leptin and insulin resistance). Therefore as people become fatter it becomes more difficult to control appetite. Figure originally published in Blundell et al. (60).

SEDENTARY BEHAVIOR AS A PATHWAY TO OBESITY

The question of whether food intake is controlled by signals arising from adipose or lean tissue, or driven more generally by the body's demand for energy is not new. Indeed, Edholm and colleagues examined whether energy expenditure created a demand for food in a series of studies employing army cadets over 50 years ago (58, 116, 117). While Edholm et al (58) reported that there was no relationship between total daily energy expenditure and daily food intake within a single day (58), a strong relationship was found when daily energy expenditure and daily energy were averaged across a week (117). Furthermore, Mayer et al. (118) demonstrated a non-linear relationship between occupational energy expenditure and daily

energy intake in Bengali jute mill workers. Daily occupational physical activity and energy intake were closely matched at higher levels of expenditure. However, at low levels of occupational physical activity, this coupling was lost such that daily energy intake exceeded expenditure in those performing 'sedentary' or 'light' work. It is also worth noting that while body mass in the light work, medium work, heavy work and very heavy work classes did not differ, those in the sedentary group were much heavier. Not only do such findings highlight a role for energy expenditure as a putative feedback signal in control of appetite, but these data also suggest that physical activity (or indeed, sedentary behavior) can mediate the sensitivity of appetite regulation. Interestingly, the idea that physical inactivity could compromise appetite regulation was recognized by Henry Taylor in the 1970s, who related the homeostatic control of appetite to the physical activity performed:

> ...'the late Henry Taylor favoured a model that linked energy intake to expenditure in a J-shaped curve (personal communication, late 1970s). The first part of his concept was that energy intake was in exact homeostasis with energy expenditure under conditions of high energy expenditure. The second part was that there is a failure of homeostasis in sedentary lifestyles because of its accompanying low energy expenditure. He postulated that bodily signals go awry in sedentary lifestyles; when a person does no physical work, the body will not recognize that it is being overfed. Sedentary persons may lose the innate ability to compensate for inactivity by reducing their eating'.
>
> (cited by Jacobs, 2006 p 1234) (119).

It has been proposed that the ability to detect over-or-under-consumption is improved at higher levels of habitual physical activity, with a stronger coupling between energy intake and energy expenditure seen in those with higher total daily energy expenditures (120). Indeed, some have suggested that the primary rationale for promoting physical activity may not relate to the increased energy expenditure associated with such activity, but the effect physical activity has on the sensitivity of appetite regulation (121). Cross-sectional studies have shown that habitually active individuals are able to better compensate for high-energy preloads during subsequent feeding episodes than their sedentary counterparts (122, 123). Furthermore, following six weeks of aerobic exercise training, previously sedentary individuals were again able to better distinguish and adjust subsequent energy intake following high and low energy pre-loads (124).

While the mechanisms remain unclear, these differences between active and inactive individuals may relate improvements in post-prandial satiety signaling. King et al. (9) examined the effects of 12 weeks of supervised aerobic exercise on hunger and satiety in 58 overweight and obese individuals. Two separate processes were identified 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). This increase in meal-related satiety may relate to changes in post-prandial satiety signaling, with Martins et al. (10) reporting that exercise-induced improvements in post-prandial satiety coincided with a significant increase in the post-meal suppression of acylated ghrelin and a tendency toward increased post-prandial GLP-1 release following 12 weeks of aerobic exercise. However, the molecular mechanisms through which physical activity mediates the sensitivity of appetite control of appetite control remain unknown at present.

Taken together, these data suggest stronger homeostatic control of appetite in active individuals that promotes more accurate coupling between energy intake and energy expenditure. This notion, which fits with Mayer's (118) study in Bengali jute mill workers, has led Blundell et al. (120) amended the 'inverted U' relationship proposed by Mayer (118) between physical activity and appetite regulation (Figure 5), with 'regulated' and 'non-regulated' zones of appetite 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 (promoting the overconsumption of food at low levels of physical activity). However, at higher levels of physical activity, appetite and food intake are regulated such that energy intake better matches energy expenditure (which promotes the maintenance of energy balance, albeit at higher levels of absolute intake and expenditure) (120). This proposed model between physical activity status and appetite regulation has received support from a recent systematic review, in which Beaulieu et al. (125) plotted standardized energy intakes (z scores) against physical activity level using data from ten cross-sectional studies that compared energy intake between active and inactive individuals. This analysis again revealed a J-shaped relationship between physical activity level and energy intake (Figure 5- Panel B).
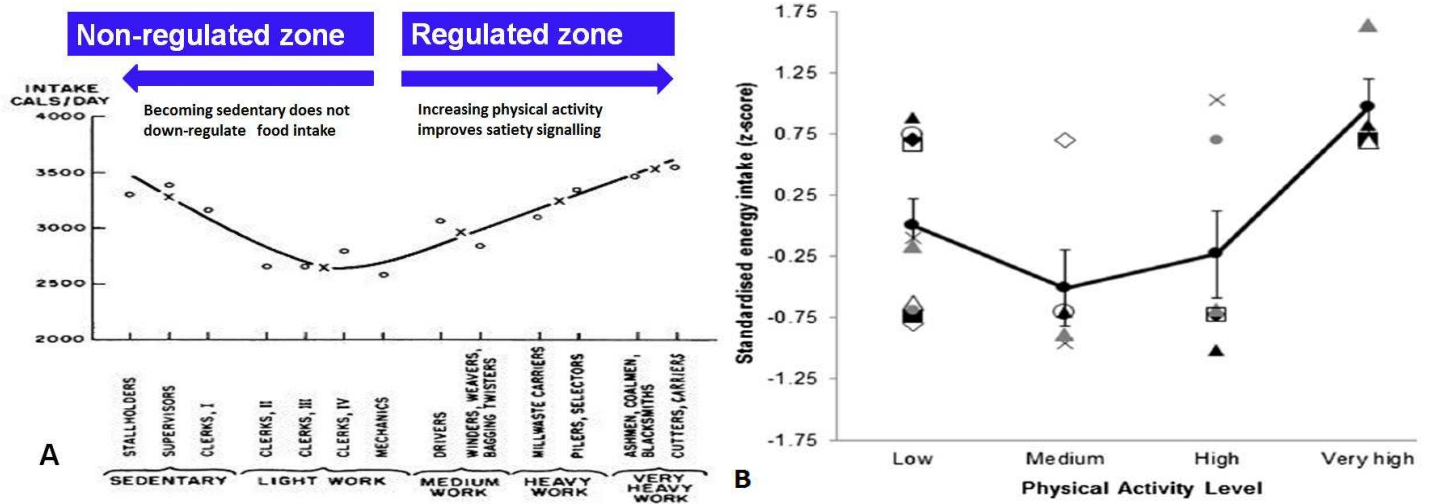
Figure 5: Panel A- Regulated and non-regulated zones of appetite with varying levels physical activity (120). Model based on Jean Mayer's study in Bengali jute mill workers (118). Figure previously published in Blundell (120). Panel B- Standardized energy intake by physical activity level from ten cross-sectional studies comparing energy intake between active and inactive individuals. Trend analysis confirmed significant linear ($P < 0.05$) and quadratic ($P < 0.01$) relationships between physical activity level and energy intake. The thick black line indicates the mean of the z-scores. Figure previously published in Beaulieu et al. (125).

In line with this relationship, Shook et al. (126) recently reported that energy intake (estimated from changes in body composition and energy expenditure) was positively associated with the amount of physical activity performed in the upper four quintiles of activity performed, but no relationship was seen in the lowest quintile of activity. Compared with the highest quintile of physical activity, individuals in this lower quintile of activity (who had the highest body weights at baseline) also reported higher cravings for savory foods ($P = 0.03$) and levels of disinhibition (although this was not significant after correcting for body weight; $P = 0.07$). The lowest activity quintile also gained the greatest fat mass (1.7 ± 0.3 kg) during a one year follow up period (after adjustment for changes in moderate to vigorous physical activity and baseline fat mass). Furthermore, Mayers et al (127) reported that the percentage of time spent sedentary (<1.5 metabolic equivalents of task- assessed using accelerometry during 6-7 days of continuous free-living monitoring) was positively associated with increased adiposity and a 'disinhibited' appetite' in 71 individuals (body mass index = 29.9 ± 5.2 kg/m^2). Taken together, findings of improved appetite regulation at higher levels of physical activity would appear to provide little support for the (incorrect) notion suggested by some that exercise or physical activity play little role in treatment of obesity (128).

However as previously noted, changes in energy expenditure can perturb other components of energy balance. Therefore, while increased levels of physical activity may promote better

appetite control, to fully understand the impact of increased physical activity on body weight regulation, changes in total daily energy expenditure must also be examined. Interestingly, it has recently been suggested that total daily energy expenditure is under homeostatic control, with the upper limits of daily energy expenditure 'constrained' in humans. Using doubly labelled water and accelerometry in a diverse sample of males and females (N = 332), Pontzer et al. (129) reported that total daily energy expenditure increased in positive fashion with low levels of physical activity, but total daily energy expenditure plateaued at higher levels of physical activity (see Figure 6). These data were taken to suggest that high levels of physical activity were associated with some form of metabolic adaptation that attenuated the impact of high physical activity on total daily energy expenditure, and limited total daily energy expenditure within a narrow upper range (129). While cross-sectional in nature, these data are consistent with the compensatory reductions in resting energy expenditure (i.e. adaptive thermogenesis) seen following dietary-induced (3) and exercise-induced (6) weight loss.
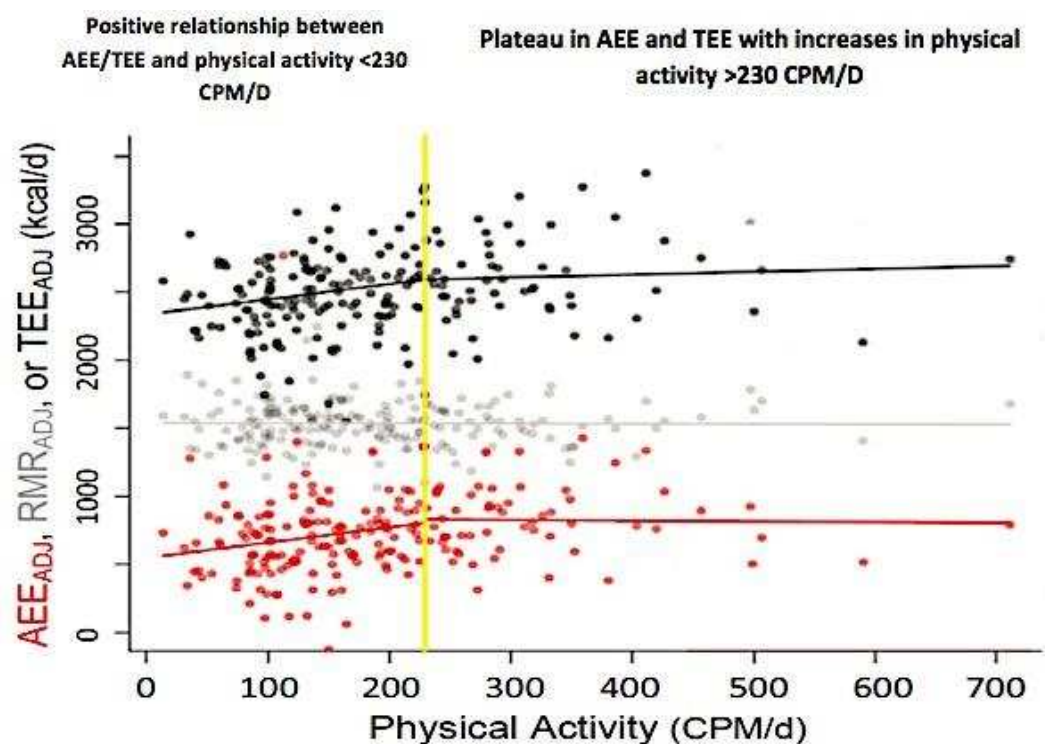
Figure 6: The relationship between total energy expenditure and physical activity in a diverse sample of males and females (n = 332). CPM/d, mean counts per minute per day (as measured using tri-axial accelerometry); AEE, activity energy expenditure; RMR, resting metabolic rate; TEE, total energy expenditure. Figure adapted from Pontzer et al. (129).

The findings of Pontzer et al. (129) may be interpreted to suggest that the promotion of physical activity will be of little benefit for weight loss, as increased physical activity energy expenditure will not translate to increased total daily energy expenditure. However, it is

important to note that at the lower levels of physical activity (<230 CPM/d; Figure 4), where most obese individuals are likely to reside, a strong positive relationship was still observed between physical activity and total daily energy expenditure. Therefore, from a public health standpoint such findings should not be used as a reason against the promotion of physical activity, as increases in physical activity in those at the lower end of the physical activity spectrum, who will likely benefit the most from increases in physical activity, will still result in increased total daily energy expenditure.

SUMMARY

Energy balance involves the complex, but highly coordinated, integration of peripheral signals of nutrient intake with long-term signals of energy status. These homeostatic regulatory signals are, in turn, mediated by multiple behavioural and societal factors in the overall expression of body weight. Consequently, while on one hand the accumulation of adipose tissue can be explained by a 'simple' imbalance between energy intake and energy expenditure, the mechanisms that drive intake and expenditure in the prevailing obesogenic environment are tremendously complex. The dynamic relationships between individual components of energy balance during energy deficit or surfeit can provide important insight into the development of obesity. Indeed, the 'pathways to obesity' are often inter- connected, circular and encourage further weight gain. For example, the accumulation of adipose tissue, which by definition characterises obesity, can exacerbate subsequent weight gain via the promotion of leptin and insulin resistance and resultant appetite dysregulation. Furthermore, changes in the physical activity of the body should not be seen as contributing solely to energy expenditure. In keeping with proposals made more than 60 years ago (but either ignored or overlooked), appetite regulation seems to be tightly linked to energy expenditure. Indeed, as noted by Henry Taylor 'at low levels of PA appetite signals go awry and the body does not recognise that it is being overfed' (119). Evidence indicates that there is a weak coupling between energy intake and energy expenditure in sedentary individuals or those displaying low levels of daily physical activity. Importantly however, a strong coupling between energy intake and energy expenditure is seen at high levels of 'energy turnover'. This emphasises the importance of promoting physical activity for weight management, with increased levels of physical activity associated with higher total daily energy expenditures and more sensitive appetite regulation.

Conflict of Interest:

The authors declare no conflict of interest.

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