

Obesity Etiology

Metabolic vs. hedonic obesity: a conceptual distinction and its clinical implications

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Summary

Body weight is determined via both metabolic and hedonic mechanisms. Metabolic regulation of body weight centres around the ‘body weight set point’, which is programmed by energy balance circuitry in the hypothalamus and other specific brain regions. The metabolic body weight set point has a genetic basis, but exposure to an obesogenic environment may elicit allostatic responses and upward drift of the set point, leading to a higher maintained body weight. However, an elevated steady-state body weight may also be achieved without an alteration of the metabolic set point, via sustained hedonic over-eating, which is governed by the reward system of the brain and can override homeostatic metabolic signals. While hedonic signals are potent influences in determining food intake, metabolic regulation involves the active control of both food intake and energy expenditure. When overweight is due to elevation of the metabolic set point (‘metabolic obesity’), energy expenditure theoretically falls onto the standard energy–mass regression line. In contrast, when a steady-state weight is above the metabolic set point due to hedonic over-eating (‘hedonic obesity’), a persistent compensatory increase in energy expenditure per unit metabolic mass may be demonstrable. Recognition of the two types of obesity may lead to more effective treatment and prevention of obesity.

Keywords: Body weight regulation, energy expenditure, food reward.

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Introduction

The mechanism by which body weight is regulated by metabolic signals has been studied for several decades. The initial proposal of a lipostatic mechanism for body weight regulation in 1950 (1) triggered an intense search for lipostatic signals, including various parabiotic rodent models (2–4), which may act on the hypothalamic control centre (5–7). The discovery of leptin in 1994 by positional cloning of the *obese* gene (8) marked the beginning of an era in which our knowledge of the neuroendocrine regulation of body weight rapidly expanded. Overwhelming experimental evidence has now accumulated in support of a homeostatic regulatory system for body weight. Under such a homeostatic system, an individual's body weight in adulthood is usually maintained at a relatively constant level, fluctuating only slightly within a narrow range around the body weight 'set point'. This is true not only in people with 'normal' weights but also in people who are overweight or obese. The exception is seen in people who are in a non-steady state, with their body weights gradually increasing over time while they are developing obesity. We will deal with this exception in greater detail later. The controversy related to the concept of a body weight regulatory system is not so much about whether or not homeostatic mechanisms exist, or how they function, but about how this system would account for the current obesity epidemic. If body weight is determined by a genetically programmed set point, why are more and more people obese now than just a few short decades ago, when the population genome pool is considered identical to what we now have? Additionally, strictly with regard to body weight, why does it matter whether or not people eat unhealthy foods or consume energy dense junk foods and beverages since the set point model states that body weight will always return to an individual's set point range no matter how the weight may temporally deviate from it?

There have been alternative models to the set point concept to circumvent this problem that would seem to be irreconcilable with the assumptions of a strict homeostatic metabolic set point model. For example, the settling point model seems to fit the population data better by assuming no active metabolic regulation of body weight (as opposed to the set point model) (see (9)). Explanations for the obesity epidemic are also provided by variants of the thrifty gene hypothesis, which focuses upon the adaptive value of enhanced energy storage in the presence of caloric abundance (see (10–14)). Most of the models assume an asymmetrical defense of set point weight and recognize the fact that evolution has provided us with a set of genes that enable the body to defend itself more rigorously against weight loss than against weight gain (see (12,15)).

More recently, evidence has emerged to support the existence of a hedonic system controlling food intake and body weight. This system is operated by neuroendocrine pathways related to the reward characteristics of ingested foods (16–18) and is non-homeostatic with regard to the body's metabolism and energetic balance. The dual central nervous system (CNS) mechanisms involved in homeostatic as well as hedonic regulation of body weight have been reviewed extensively in several previous reviews (19–21). Taken together, we believe that the obesity epidemic is a manifestation of a metabolic disorder that results in expression of an elevated body weight set point in some people (metabolic obesity), and also a hedonic disorder in other individuals that results in persistent and excessive net caloric intake which sustains body weight significantly above the individual's metabolic set point (hedonic obesity). In this article, we will review the evidence that supports this conclusion, as well as how the two types of obesity may be distinguished and treated differentially based upon their underlying aetiology.

Body weight regulation and underlying mechanisms of the common forms of obesity

Homeostatic mechanisms and body weight set point

Under relatively constant environmental conditions, an individual's body weight is 'auto-regulated', i.e. the body senses and processes various metabolic signals regarding its energetic status and adjusts its metabolic responses without conscious control. The conscious mind can direct an individual's feeding behaviour and physical activities, but it is not a sustaining factor in the determination of body weight. The homeostatic regulation of body weight is similar to that of other physiological parameters, such as body temperature, blood pressure or blood glucose. The principle of all these homeostatic systems is analogous to a feedback thermostatic system, by which room temperature is regulated such that it is maintained within a narrow range around a pre-set temperature. In general, body weight seems to oscillate in a similar manner (22) and is stable over a long period of time in most individuals; people may lose 5–10 lb or more in response to an acute illness (23), but regain it fairly rapidly after recovery from the illness without much conscious effort. Similarly, it is commonplace for many individuals to find that following a weight gain of 5–10 lb during a vacation or holiday season, their weight falls back to its previous level after they resume their 'normal' life.

Underlying such phenomena is a regulatory system consisting of an extremely complex neuroendocrine network termed the homeostatic energy balance circuitry. A full description of the components of this network and the supporting evidence thereof would require an extensive

review of a large body of the literature. Thus, we refer the interested readers to several specific reviews on this topic (6,24–31). For the purpose of this article, it suffices to point out the existence, as supported by overwhelming evidence, of a CNS neuroendocrine energy balance circuitry, which is composed of specific nuclei in various brain regions, most prominently the hypothalamic arcuate nucleus (ARC), the paraventricular nucleus, the lateral hypothalamic area and the nucleus of solitary tract of the hindbrain (32). It is also important to point out that genetic, epigenetic, imprinting and early developmental factors may all influence how the circuitry functions in a given individual (see (21,25)). The most important feature of this CNS circuitry is the programmed body weight set point (see (6,24)), which

demarcates a threshold level, above and below which, opposite sets of metabolic reactions will be activated in order to restore the set point body weight (see Fig. 1). More specifically, energy surplus or deficit leads to a change in body weight above or below the set point body weight, which is sensed by the energy balance circuitry of the brain through an array of feedback signals from the periphery. For example, leptin, an adipocyte-derived hormone that is expressed in proportion to adipocyte size and fat mass (33–39), serves as one such feedback signal. The circulating leptin level (an indicator of the body's fatness) is sensed by specific neurons in the hypothalamus, particularly the POMC/CART and AgRP/NPY neurons, as well as other leptin-responsive neurons in the homeostatic energy

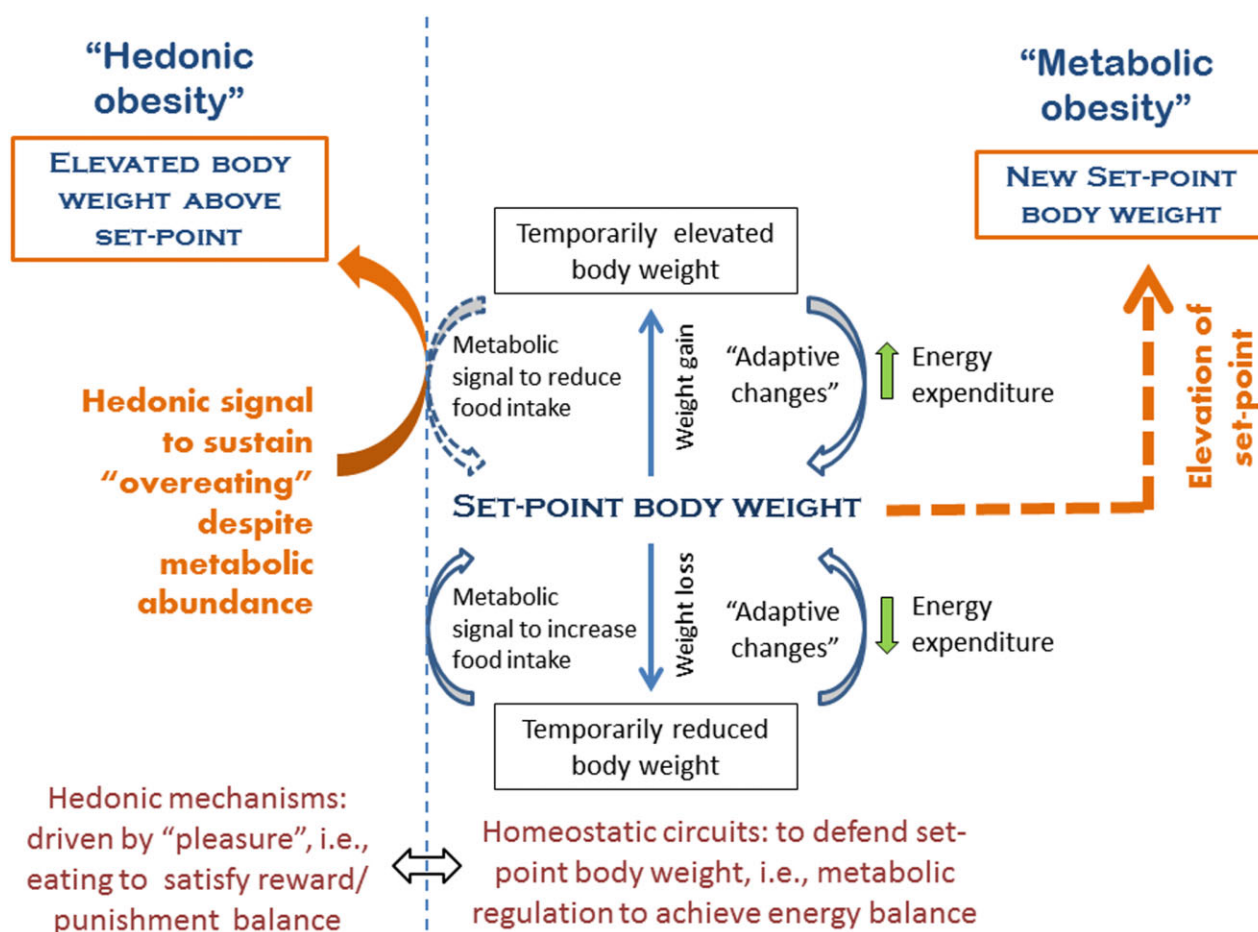


Figure 1 Metabolic and hedonic obesity as related to their respective mechanisms of weight gain. The homeostatic weight regulatory system located primarily in hypothalamus and brainstem accounts for weight regulation around a body weight set point. Deviation of body weight from this set point elicits a compensatory increase or decrease in food intake (cumulative over a long time period) and energy expenditure (both resting and non-resting) in an opposite direction in order to restore the previous body weight set point. Obesity results from an elevation of the metabolic set point (see details in the text) that is characterized by an elevated body weight which is metabolically defended just as normal body weight is defended at its set point; we term an elevated body weight set point 'metabolic obesity'. Hedonic eating is governed by the reward system to satisfy the need of pleasure and is non-homeostatic with regard to energy balance. Dysfunction of the reward system may lead to hedonic over-eating in susceptible individuals in the face of metabolic signals indicating an energy surplus, leading to sustained weight gain above the metabolic set point weight; we term this form of obesity 'hedonic obesity'.

balance circuit (see (26,27,30,40)). Activation of these neurons then acts in concert to prompt anabolic or catabolic functions in response to changes in the circulating leptin level. Increased leptin signalling associated with weight gain elicits catabolic activities by increasing energy expenditure and suppressing food intake, promoting weight loss, whereas decreased leptin signalling associated with weight loss elicits anabolic activities by reducing energy expenditure and increasing food intake, promoting weight gain.

In addition to leptin, the CNS energy balance circuitry receives numerous other feedback signals that in various ways reflect the body's energy status (see (6,26,40–43)). Well-recognized peripheral signals include insulin, which also serves to measure the body's adiposity (see (26,40)) and circulating levels of fatty acids, glucose and amino acids, which may reflect the fuel availability (see (6,41)). Ghrelin, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1) and various other gut hormones also provide feedback signals about current feeding status (see (42,44)). Direct nervous transmission of taste stimulation relayed by the cranial nerves and various visceral signals transmitted by the vagus nerve also participates (see (32,43)). Although many of these sensory systems are primarily involved in regulating short-term energy balance, i.e. meal size and feeding frequency, some of them may also provide afferent signals to the homeostatic energy balance circuitry and work in concert with lipostatic signals, such as leptin and insulin, to regulate long-term energy balance and, hence, body weight (see (26,41,43,45)). The direct participation by some of the meal-related signals, such as ghrelin and peptide YY (PYY), in the regulation of the activities of ARC neurons (see (42,44)) may provide an explanation for the ability of short-term feeding signals to cause changes in the long-term energy balance.

Defining metabolic obesity: expression of an elevated body weight set point

There is little doubt that the body weight set point, like body height and other phenotypic characteristics, is influenced by genetic and environmental elements (see (25)). It is estimated that 40–80% of the variance in body mass index is attributable to genetic elements (46,47). There is also good evidence that the body weight set point is modifiable by environmental factors, and that persistent weight gain in response to environmental challenges can, in some cases, lead to an upward shift of body weight set point that will be metabolically defended (48,49). This is well illustrated in rodent models. For example, outbred Sprague-Dawley rats have a characteristic growth trajectory when they are fed *ad libitum* with a regular chow diet; any deviation from this trajectory due to caloric restriction or gavage overfeeding is temporary (50,51).

The rats will quickly return to its 'set point' weight trajectory as soon as they are back to *ad libitum* chow diet. However, when the rats are fed a palatable high-energy (HE) diet, about half of the rats become obese and they now follow a new growth trajectory, which is significantly above the original one (52,53). Importantly, upon a prolonged period of HE diet feeding and weight gain, this new and elevated 'growth trajectory' is defended against overfeeding or caloric restriction just as in the lean rats when they are subjected to the same caloric manipulations (50). Obviously, the tendency for the expression of an elevated body weight set point in response to environmental changes is also encoded in individual rat's genetic constitution. In fact, about half of the outbred Sprague-Dawley rats on HF diet do not become obese during 12–15 weeks of high-fat (HF) feeding (50,52,53). Both obesity-prone and obesity-resistant traits can be selectively bred to produce two separate substrains that are then either 100% prone or 100% resistant to the weight-altering effects of HE diets, respectively (53). The genetic elements in determining the outcomes of environmental influences demonstrated in rodents seem to be present in humans in a similar fashion as not everyone changes his/her set point weight when interacting with an 'obesogenic' environment. We term obesity caused by the expression of an elevated set point of body weight (and now defended metabolically) 'metabolic obesity' (Fig. 1).

The mechanisms by which dietary manipulations (e.g. the HE diet cited earlier) and weight gain lead to a higher defended set point weight are not fully understood. A large body of evidence suggests that diet-induced obesity may lead to the development of secondary leptin resistance (i.e. acquired leptin resistance due to changes in environmental factors such as diet and/or weight gain) (12,27,54–56). Development of leptin resistance may be expected to 'reset' the body weight set point at a higher level by attenuating the catabolic effects of leptin. In addition to leptin resistance, functional impairment or structural modifications of any major component of the homeostatic energy balance circuitry may also be expected to alter the tonicity of this regulatory system, resulting in resetting the set point. For example, loss of synapses on hypothalamic POMC/CART neurons due to environment-triggered reactive gliosis (48,57) and diet-induced inflammation and/or ageing of hypothalamic neurons (58–60) have been observed in obese mice fed a high-fat diet (HFD), compared with their lean controls on normal chow diet. Indeed, permanent inflammation and neuronal damage were observed in the hypothalamus of long-term HFD-fed rats and mice, and similar damage was detected via magnetic resonance imaging (MRI) in the hypothalamus of adult obese humans (60). Mechanisms such as these, triggered by sustained intake of HF/sugar diets, likely participate in the eventual resetting of the body weight set point.

Hedonic control of food intake and evidence of altered hedonic pathways in obesity

The aforementioned set point weight regulation system is a homeostatic regulatory system located primarily in the hypothalamus and brainstem that processes internal metabolic signals, and it has been termed the 'metabolic brain' (21). Distinct from this 'metabolic brain' is the 'cognitive and emotional brain', which, in principle, guides food intake based upon the reward value of the food; the latter is governed by a different set of neuroendocrine signals and is non-homeostatic with regard to energy balance. The brain regions responsible for this reward system are dispersed in the corticolimbic structures (see (61)). Multiple neuronal pathways are involved in reward evaluation, which is also modulated by various other factors such as emotion, stress, arousal and metabolic status. This system integrates basic midbrain and hindbrain functions with more complex cortical functions involving arousal at the sight of palatable food items and the procurement of food. However, narrowly defined, the basic components of the reward system at the midbrain level mediate 'liking' (the level of pleasure or reward) and 'wanting' (the motivation or drive to consume food), which are subconscious processes (62). Implicit 'liking' is believed to be mediated by mu-opioid receptor signalling as well as the CB1 cannabinoid receptor signalling networks (see (20)) centred in the nucleus accumbens (NAc) of the ventral striatum and ventral pallidum, whereas implicit 'wanting' is chiefly encoded in the mesolimbic dopaminergic neurons that project from ventral tegmental area (VTA) to NAc. Importantly, structures involved in reward calculation (NAc, ventral pallidum and VTA) have connections to other brain areas, including the hippocampus, amygdala, gustatory and orbitofrontal cortex (via thalamus and substantia nigra), hypothalamus and brainstem (see (20)). These connections are believed to play an important role in coordinating conscious and unconscious components related to hedonic eating.

Alterations in the food reward system leading to excessive caloric ingestion and obesity may be explained in part on the basis of two prevailing hypotheses related to the 'liking' and 'wanting' aspects of the reward system. The 'gluttony hypothesis' posits a positive correlation between the amount of dopaminergic signalling in an individual and the pleasure derived from the sensory experience of ingestion, whereas the 'reward deficiency' hypothesis suggests that a deficiency in dopaminergic signalling is the cause of overindulgence of the food in an attempt to achieve pleasure (see (21)). Evidence obtained in animal and human studies supports both hypotheses (63,64). For example, sustained exposure to sucrose or a palatable mixed diet in rats can lead to elevated dopamine release and transporter expression, as well as down-regulation of dopamine D1

and D2 receptor expression in the NAc and dorsal striatum (63–66). The changes seen in the dopamine reward pathway, particularly the down-regulation of dopamine receptors, are similar to those seen in addictive states, and the concept of 'food addiction' has been proposed as an explanation for over-eating and obesity (67). Advocates of the food addiction concept, in fact, compare the increasing consumption of rewarding food items potentially resulting from reward deficiency to the well-known addictive process of drug tolerance (68).

Numerous animal studies demonstrate the relationship between defects in the mesolimbic reward system and the onset and/or maintenance of obesity. Geiger *et al.* demonstrated that laboratory rats fed a cafeteria diet for 15 weeks developed obesity, which was associated with reduced extracellular levels of dopamine in the NAc (69). While the dopaminergic response was not elicited in these obese rats by the regular chow diet, it was by the cafeteria diet, suggesting that a diet-induced alteration in the food reward system stimulated the drive to indulge in the cafeteria diet and resulted in sustained overfeeding. Decreased excitability of the mu-opioid receptor signalling system (encoding 'liking') has also been tested in animal models. Schwindinger *et al.* used a genetic mouse model deficient in G protein γ_3 -subunit, which is believed to be essential in mediating mu-opioid receptor signalling, and showed that these mice were resistant to diet-induced obesity because of a lesser preference to the HF diet than their wild-type littermates, which became obese on the same diet (70).

In human studies, functional MRI (fMRI) has shown correlations between obesity and overactivation of brain regions corresponding to many components of the reward system, including the gustatory cortex, somatosensory regions, and the limbic and paralimbic regions, in response to palatable food stimuli (71–75). A negative correlation was also seen between obesity and activation of frontal brain inhibitory regions, implicating a dysfunction related to increased impulsivity or decreased executive function (75,76). Marked overactivation of many brain regions of the reward system is also consistently seen in obese patients with the rare congenital leptin deficiency (77,78). Interestingly, an extraordinarily active rather than underactive frontopolar cortex, an area of the brain assumed to mediate response inhibition, was seen in an adolescent girl with congenital leptin deficiency (78). This neuronal phenomenon was correlated with strong cognitive control and a very strict behavioural pattern, which the subject appears to have acquired in compensation for the feeding stimulatory effects of leptin deficiency and resulting hyperphagia (78). Nevertheless, in general, obesity may be characterized by an overactivation of reward-encoding brain regions and/or a deficiency in cortical inhibitory networks.

Not only is altered reward responding to food stimuli seen in the already obese, but Stice *et al.* demonstrated that many of these corticolimbic responses are predictive of future weight gain in adolescents (79–81). Thus, these data support the notion that hedonic eating can indeed lead to obesity.

Hedonic obesity: elevated body weight sustained by hedonic over-eating that overrides homeostatic metabolic signals

A primary characteristic of the hedonic system, with regard to the onset and maintenance of obesity, is its ability to override energy homeostatic signals in response to rewarding food items. In individuals susceptible to developing disorders of the hedonic system, the drive to eat can be strong enough to override inhibitory signals arising from the metabolic effects of food and potentially stimulate weight gain. We term obesity resulting from sustained hedonic over-eating in the face of metabolic signals for energy surplus ‘hedonic obesity’ (Fig. 1). Evidence for hedonic signals overriding metabolic signals is strong in rodent models (82). For example, in the outbred diet-induced obese rats mentioned earlier, despite the establishment of an elevated set point weight trajectory when fed an HE diet, these animals over-eat when provided an even more palatable food (chocolate flavoured Ensure) and become even more obese, reaching weights significantly above their usual set point weight curve (83). As long as the chocolate Ensure is available, they maintain excess caloric intake and an elevated growth trajectory. Once the Ensure is removed, homeostatic regulation is re-asserted and the body weight returns to its usual set point curve (83). In humans, it has been shown that obese children and adults display hyper-responsiveness to food stimuli in the limbic and paralimbic regions in comparison to normal weight controls. Importantly, more obese individuals than normal weight controls display a failure to attenuate food-elicited response after a meal (73,74), suggesting that the satiety signal (metabolic) is being overridden by the reward signal (hedonic). Other supportive evidence for hedonic-driven weight gain comes from population surveys. According to one recent study, the prevalence of ‘food addiction’, using the Yale Food Addiction Scale (84), was 5.4% in a general population, and these ‘food addicts’ were about 25 lb heavier than the non-food addicts (85). Using the same scale, the percentage of ‘food addicts’ in an obese cohort was 7.7% (85). This number may appear to be low, but the true prevalence of obesity caused by hedonic over-eating is likely greater than that represented by the percentage of obese individuals who qualify as food addicted. The phenomena of binge eating, stress-induced eating, night eating and ‘grazing’ (snacking continuously throughout the day) may

all contribute to obesity, and the prevalence of these conditions is certainly greater than that of food addiction. For example, only 57% of obese binge eaters meet the diagnostic criteria for food addiction by the Yale Food Addiction Scale according to one study (86). In summary, while we believe that the prevalence of hedonic obesity is greater than that of ‘food addiction’, its prevalence is unknown at this time.

Distinguishing hedonic obesity from metabolic obesity

Presence of the adaptive changes in energy expenditure in non-set point body weights

Although not without controversy (87,88), we believe that adaptive or compensatory changes in energy expenditure are present in individuals who have deviated from their respective set point weights (89,90). The ‘adaptive changes’ have repeatedly been demonstrated, with particularly convincing data arising from well-controlled human studies in metabolic wards (89) and other controlled environments (91).

In their well-controlled human study at Rockefeller University (89), Leibel *et al.* recruited weight-stable normal weight or obese study subjects. These participants were admitted to the clinical research centre, and the study was conducted essentially in-house for the entire study period. The subjects were underfed or overfed, using a liquid formula diet, to lose or gain 10% of their usual body weights. After weights were stabilized at respective target levels (at least 14 d, and confirmed by respiratory quotient measurement), resting energy expenditure (REE) was determined by indirect calorimetry, and total energy expenditure was determined by differential excretion rates of 2 isotopes of water and by indirect calorimetry in a respiration chamber, in which physical activity was monitored. They found that a weight loss of 10% resulted in a significant reduction in resting and non-REE (each was reduced by 3–4 kcal kg⁻¹ fat-free mass [FFM] d⁻¹). Conversely, a 10% weight gain resulted in an increase in total energy expenditure of 8–9 kcal kg⁻¹ FFM d⁻¹, of which the change in non-REE was the larger component. In their study, the magnitude of the adaptive changes in energy expenditure was not affected by sex or initial body weight. There is evidence that such adaptive changes in energy expenditure persist in otherwise weight-stable individuals for as long as body weights remain deviated from the metabolic set point. This statement is supported by the demonstration of reduced energy expenditure in long-term weight-reduced individuals in several different studies (92–94).

Capture of the adaptive changes in energy expenditure exhibited in people with a non-set point body weight

While an individual's energy expenditure in the waking hours may vary widely on a daily basis (in response to physical and mental activities and the thermal effects of digestion), REE is relatively constant under normal physiological conditions. Only a 2% variation (including measurement error) was seen in REE in the same individuals on different days (95). REE is proportional to the body's metabolic mass, another relatively constant parameter, which historically has been represented by various surrogate measurements, such as total body weight, FFM, total body surface area, individual organ mass or cellular mass (96).

REE correlates well with FFM (97), and scaling REE to FFM is widely used in various studies (89,98,99). Inter-subject variance is largely accounted for by the differences in the individuals' FFM, so that while REE varies widely in different individuals, REE expressed per FFM is much closer among individuals. FFM can explain a major part of the inter-subject variance (63%) (95). Fat mass (FM), age, and possibly race and sex may also explain a smaller but significant portion of the variance (FM 6.7%, age 1.7%) (95). Interestingly, in various regression modelling, there remains a large portion of the variance unexplained by FFM, FM, age, race, sex or other factors such as thyroid hormone levels (93,95,100–102). This unexplained 'residual variance' was estimated to be 26.6% of the total between-individual variance (95).

What is this unexplained residual variance? We assume that in the general population, there exist people who exhibit a significant component in their REE that is mass-independent. Such a component may be produced by some unusual and yet unrecognized physiological activity that, on the one hand, is present at rest but, on the other hand, is analogous to the non-REE in that it is largely mass-independent. Non-REE produced by mental/physical work, stress, anxiety or any other physiological variations during the waking hours cannot be accounted for by metabolic mass as previously stated. Therefore, if a mass-independent physiological activity is present in some individuals at rest, their REE would appear to be an outlier in the usual REE–mass relationship. The mass-independent physiological variation we are interested in here is the 'adaptive change' in energy expenditure in individuals whose body weights are significantly deviated from their set point levels. We suggest that such adaptive changes are present in some of the weight-gained and weight-reduced people in the general population and may therefore constitute an inter-individual variance that is at least part of the thus-far-unexplained 'residual variance'. In other words, because of the presence of the mass-independent energy expenditure at

rest, it is likely that the 'adaptive' changes exhibited in people with a non-set point weight may be captured simply by looking for the REE outliers on the usual REE–FFM regression line (89,103–109). Total energy–FFM regression may also be used to capture the adaptive changes after weight loss or weight gain (89), but more sophisticated methodology in a controlled environment would have to be used.

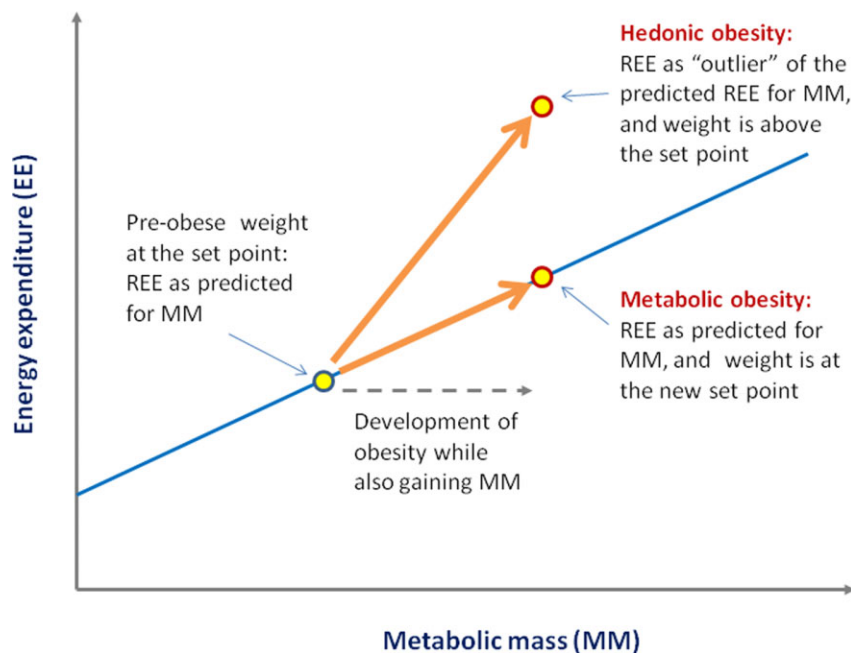
Distinguishing 'hedonic obesity' from 'metabolic obesity'

As stated previously, the measured energy expenditure of an obese individual can be compared with the predicted values based upon the REE–'mass' relationship of an appropriate reference group. While a 'normal' REE or total EE in an energy–'mass' relationship signifies a stable metabolic set point weight, a value that is significantly greater than what is predicted by the EE–'mass' regression line would signify an above-the-set point body weight, i.e. by definition 'hedonic obesity'. Contrarily, the REE–'mass' relationship in people with 'metabolic obesity' is indistinguishable from that of normal weight individuals because the body weights are at their respective set points in both, except that the former is 'obese' by weight. Figure 2 illustrates the difference in REE/mass in a hypothetical person who develops metabolic obesity vs. hedonic obesity. We should emphasize that the above remains a testable hypothesis at this point, and validation would require future studies that directly address this issue.

Although conceptually of critical importance, REE should not be the only clinical criterion used to predict whether an individual is at his/her set point weight. In making the distinction between 'hedonic obesity' and 'metabolic obesity', additional diagnostic tools should be used to corroborate the diagnostic evidence as a whole. These may include comparisons of daily caloric intake to calculated caloric needs per unit body mass (this method is perhaps more attainable in general clinical practice but likely less accurate) and potential use of the Yale Food Addiction Scale or addiction criteria in cases where compulsive over-eating is suspected. Individuals with obesity and eating disorders or food addiction should practically be considered to have hedonic obesity until proven otherwise.

It is quite possible that in the real world, one may find few pure cases of 'hedonic obesity' or 'metabolic obesity' as the division is an artificial one. Both metabolic and hedonic forces are operating in any given individual. For example, it is quite conceivable that an individual who initially suffers from 'hedonic obesity' may eventually develop secondary leptin resistance if he/she remains obese long enough, leading to an elevation of the body weight set point, the hallmark of 'metabolic obesity'. However, it is not inconceivable that, depending upon their individual genetic

Figure 2 Distinct features in energy expenditure in 'hedonic obesity' vs. 'metabolic obesity'. In this hypothetical illustration, we use resting energy expenditure (REE) regressed to 'metabolic mass' (MM). REE/MM falls onto the regression line in the case of normal weight and metabolic obesity, as both are at the respective set points, whereas REE/MM is significantly above the regression line ('outlier') in the case of hedonic obesity as the body weight is above the set point.



makeup, some may never develop 'metabolic obesity' in their lifetime, despite a persistent state of hedonic obesity. Of clinical importance is the identification of the predominant factor that underlies an individual's obesity phenotype at the time of clinical intervention.

Clinical considerations in treating obesity

To the extent possible, successful obesity treatment must address the underlying aetiology of the condition. One obvious example in addressing the underlying cause is the use of recombinant leptin to treat the rare obesity due to leptin deficiency (110,111). In treating the more common forms of obesity, we propose that practitioners make a distinction between hedonic causes and metabolic causes, as we have carried out in this article. This distinction recognizes the alterations in molecular mechanisms and CNS pathways that lead to the development of these two types of obesity in most individuals. We believe that conceptualizing metabolic obesity vs. hedonic obesity is the first step towards more rational and more tailored treatment. Behavioural and lifestyle modification, including traditional behaviour therapy and possibly pharmacotherapy, would be the primary treatment modality for hedonic obesity, whereas metabolic modification, pharmacological and/or other forms of intervention would be needed to treat metabolic obesity. Bariatric surgery, depending upon patient characteristics and the specific procedures used, appears to modify hedonic pathways and possibly alter the metabolic body weight set point and therefore may be suitable for treating both hedonic and metabolic obesity.

Current state of obesity treatment

Intensive behavioural therapy and lifestyle coaching delivered by trained healthcare professionals does appear to be effective for modest levels of weight loss. The efficacy of this treatment modality was demonstrated at the 'population' level in large-scale randomized clinical trials, such as the Diabetes Prevention Program (DPP) (112) and the 'Look AHEAD' clinical trials (113). In these trials, behavioural and lifestyle modification consists of dietary guidance, exercise prescription and behavioural treatment aimed at enhancing adherence to dietary and exercise prescriptions (114). In the DPP trial, 38% of participants had achieved 7% or more weight loss at the average 2.8-year follow-up. The average weight loss in the lifestyle group was 5.6 kg, as compared to 0.1 and 2.1 kg, respectively, in the placebo and the metformin groups (112). In the even larger 'Look AHEAD' lifestyle intervention trial of over 5,000 people, an 8.6% weight loss was achieved at 1-year follow-up and 6% weight loss at the median 9.8-year follow-up (113,115).

Despite this impressive achievement, more than a half of the participants in these trials were 'non-responders' to lifestyle treatment, as defined by less than 7% weight loss. Moreover, in many weight management centres where treatment is actually more concentrated, results are even more disappointing. The percentage of the non-responders to behavioural modification protocols appears to be much greater, perhaps in part because the patients seen in these centres represent the most difficult-to-treat. We submit that many of these individuals may have a formally diagnosed binge eating disorder, or meet food addiction criteria, and

thus are not likely to respond to a generic lifestyle intervention protocol. Additionally, in people with intractable weight problems or repeated weight cycling, co-existence of psychological disorders, such as depression, anxiety, impulse-control disorder or other emotional problems, is frequently seen (116). The co-existence of these psychological problems certainly makes treatment more difficult. Finally, we believe that there is a significant fraction of obese individuals who would not respond well to behavioural treatment alone as their obesity is metabolic in nature. Unless the body weight set point is lowered, any volitional weight loss would only be temporary.

Currently available medications approved for treatment of obesity are few. The mechanisms of action of most anti-obesity medications are 'unknown' but may utilize aspects of the molecular and cellular pathways of both the hedonic and the metabolic systems. The recently Food and Drug Administration (FDA)-approved anti-obesity medication Qsymia (a combination of phentermine and topiramate) provides an excellent example. Phentermine is a sympathomimetic amine, which helps release noradrenaline (norepinephrine) and dopamine, and exerts anorexic effects through both the hedonic and the metabolic pathways (117,118). Topiramate, the other active component of Qsymia, also produces anorexia, but exerts metabolic effects as well, possibly via increased substrate oxidation, mitochondrial metabolism and thermogenesis (119,120). The appetite suppressive effects of lorcaserin, a selective serotonin receptor (5HT_{2CR}) agonist recently approved by FDA for the treatment of obesity, may involve metabolic pathway modification as demonstrated by the finding that activation of 5HT_{2CR} increases the POMC-MC4R activity associated with hypophagia (121). However, lorcaserin's anorectic effects appear to be intertwined with a range of psychological effects of serotonin, which is known for its capability to modify anxiety, depression and aggression (122,123). Contrave, which just attained FDA approval for treating obesity, also has dual effects on the hedonic and metabolic weight regulatory systems. In a recent study using fMRI to map activities in specific brain areas in response to food cues, this medication was shown to attenuate activities in hypothalamus but enhance activities in brain regions believed to be involved in hedonic control of food intake, i.e. the anterior cingulate, superior frontal, insular, superior parietal and hippocampal regions (124). Naltrexone, an active component of Contrave, is a mu-opioid receptor antagonist and may be expected to attenuate (125) hedonic-driven consumption of energy dense fats and sweets (126–128). Additionally, naltrexone is believed to block the beta-endorphin-mediated negative feedback inhibition of POMC-neuron activation, thus potentially modulating the functionality of the metabolic energy balance circuitry encoded in the ARC of hypothalamus. Bupropion, the

other active component of Contrave, by virtue of being a noradrenaline/dopamine reuptake inhibitor is believed to attenuate hedonic eating as well, but it also affects metabolic weight regulation by stimulating POMC/CART neurons (129). Quantitatively, the role of the metabolic and hedonic mechanisms in mediating the weight loss effects of each of the anti-obesity medications remains to be determined.

Bariatric surgery, now also termed metabolic surgery (130), was initially developed to treat obesity by restrictive and/or malabsorptive means, but has turned out to be an effective treatment modality that produces profound changes in the regulation of body weight involving both the metabolic and the food reward systems (131–135). It has been shown that after Roux-en-Y gastric bypass (RYGB) surgery, for example, patients have enhanced taste sensitivity for sweet (136), consume less food and beverages high in sugar (137) and fat (137–139), and have decreased hunger ratings (139). Many of these changes may be due to altered hedonic responsivity in the patients (140). Modifications of the brain's reward system after surgery have been detected by fMRI (141) and positron emission tomography scanning using a selective radioligand for the dopamine receptors (142,143). Increases in the postprandial levels of the gut hormones GLP-1 and PYY seen in post-RYGB patients (144,145) and rat models (146) likely contribute to the observed weight loss outcomes. GLP-1 is known to act on the caudal brainstem to regulate appetite, food intake and gastric emptying (147). The GLP-1 receptor agonists exenatide (148) and liraglutide (149) both suppress appetite and cause weight loss. PYY acts on NPY/AgRP and POMC/CART neurons in the ARC of the hypothalamus (150–152) and inhibits appetite and food intake (150,152,153). Similar changes in GLP-1 and PYY after RYGB were also seen after the sleeve gastrectomy (134,154,155). In concert with the post-surgical changes of the hindgut hormones GLP-1 and PYY, changes in foregut hormones, ghrelin and CCK, after sleeve gastrectomy and RYGB are believed to play an important role as well (154). However, weight loss and metabolic changes after these bariatric procedures may not be fully explained by the favourable changes in the gut hormones alone (156,157). Post-operative changes in the autonomic innervations and circulating bile acid levels are among those proposed to play a significant role as well (130,134,158,159). Another area of intense research is the microbiota (160,161), which may play a significant role in mediating some of the post-surgical changes that alter the physiological responses to the food and their interactions with the brain. Increased energy expenditure was demonstrated after RYGB in some rodent models (162,163) and in one human study (164), implying that the body weight set point may have been adjusted downwards after the surgery. However, most human studies show no increase in energy expenditure after RYGB (165–168).

A strategy to consider in future clinical studies

We have observed that the non-respondent rate for any single obesity treatment modality is usually high. This is particularly true for behavioural treatment and pharmacotherapy. We believe this is so because so far we have only measured the efficacy of each treatment in a mixed population of study subjects. We hypothesize that one or the other form of obesity, hedonic obesity or metabolic obesity, may favourably respond to a particular therapy depending upon which system the treatment targets. Note that the respondent rate is usually high with bariatric surgery. We suspect that this is because bariatric surgery has profound effects on both the hedonic and the metabolic systems, as just discussed. If this scenario holds true, we believe that in future clinical studies where a treatment modality is assessed for its efficacy, selecting respective study subjects with predominantly hedonic obesity or metabolic obesity for treatments targeting the food reward system or the metabolic system, respectively, should show better and more congruent treatment outcomes.

Conclusion

Body weight is regulated by two mechanistically discernible systems: the homeostatic metabolic system regulating both food intake and energy expenditure to keep the body weight at a relatively stable set point level and the non-homeostatic food reward system regulating the hedonic control of food intake irrespective of the body's energetics. In recent decades, hedonic over-eating has become an important factor in the obesity epidemic, in large part fuelled by the cheap and readily available processed foods. Sustained over-eating of these 'palatable' energy dense foods can lead to hedonic obesity. These high-calorie processed foods may also modify the homeostatic metabolic system in susceptible individuals, leading to upward shift of the body weight set point and causing metabolic obesity. Hedonic obesity is characterized by greater than normal energy expenditure per unit metabolic mass, whereas metabolic obesity with its body weight at the set point is characterized by the energy expenditure per unit metabolic mass within the expected normal range. Both hedonic and metabolic mechanisms are at work in any given individual, but derangement in either or both may lead to obesity. To the extent possible, consideration should be given in the management of obesity to the use of treatment modalities that target behavioural changes in the case of hedonic obesity and those that may modify the body weight set point in the case of metabolic obesity. Finally, while we are unable to change the genetics underlying either metabolic or hedonic obesity, we can change our obesogenic environment permissive for the development of these conditions. Therefore, in parallel to individual treatment of obesity,

preventive measures should be taken at the population level, and that will require reforms in healthcare legislation and insurance policy (169,170).

Conflict of interest statement

Dr. Yu reports no conflicts of interest; Dr. Vasselli reports grants and other support from Novo Nordisk, Inc., and grants from Pharma Science Nutrients, Inc., outside the submitted work; Dr. Zhang reports that she is an inventor in a patent on the leptin gene, licensed; Dr. Mechanick reports receiving honoraria for lectures and program development from Abbott Nutrition International, outside the submitted work; Dr. Korner reports grants from Covidien, outside the submitted work, and receiving honoraria for lectures from Takeda; Dr. Peterli reports grants from Ethicon Endosurgery Switzerland, outside the submitted work.

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