Adaptive thermogenesis in human body weight regulation: more of a concept than a measurable entity?

A. G. Dulloo, J. Jacquet, J-P. Montani and Y. Schutz

Department of Medicine/Physiology, University of Fribourg, Fribourg, Switzerland

Address for correspondence: Dr AG Dulloo, Department of Medicine/Physiology, University of Fribourg, Chemin du musée 5, CH-1700 Fribourg, Switzerland.
E-mail: abdul.dulloo@unifr.ch

Summary

According to Lavoisier, ‘Life is combustion’. But to what extent humans adapt to changes in food intake through adaptive thermogenesis – by turning down the rate of heat production during energy deficit (so as to conserve energy) or turning it up during overnutrition (so as to dissipate excess calories) – has been one of the most controversial issues in nutritional sciences over the past 100 years. The debate nowadays is not whether adaptive thermogenesis exists or not, but rather about its quantitative importance in weight homoeostasis and its clinical relevance to the pathogenesis and management of obesity. Such uncertainties are likely to persist in the foreseeable future primarily because of limitations to unobtrusively measure changes in energy expenditure and body composition with high enough accuracy and precision, particularly when even small inter-individual variations in thermogenesis can, in dynamic systems and over the long term, be important in the determining weight maintenance in some and obesity and weight regain in others. This paper reviews the considerable body of evidence, albeit fragmentary, suggesting the existence of quantitatively important adaptive thermogenesis in several compartments of energy expenditure in response to altered food intake. It then discusses the various limitations that lead to over- or underestimations in its assessment, including definitional and semantic, technical and methodological, analytical and statistical. While the role of adaptive thermogenesis in human weight regulation is likely to remain more a concept than a strictly ‘quantifiable’ entity in the foreseeable future, the evolution of this concept continues to fuel exciting hypothesis-driven mechanistic research which contributes to advance knowledge in human metabolism and which is bound to result in improved strategies for the management of a healthy body weight.

Keywords: Dieting, obesity, starvation, weight regain.

Abbreviations: BMR, basal metabolic rate; CV, coefficient of variability; DIT, diet-induced thermogenesis; EE, energy expenditure; FFM, fat-free mass; LBM, lean body mass; NEAT, non-exercise activity thermogenesis; PAL, physical activity level; SPA, spontaneous physical activity; TEF, thermic effect of food.
In dealing with human beings, value judgements cannot be avoided, but to avoid sterile discussion they must be separated from objective descriptions of adaptive responses

John Waterlow (1)

Introduction

In addressing the topic of adaptive thermogenesis pertaining to the regulation of body weight, it is pertinent to first raise the question of whether body weight is indeed a regulated variable. Given the surge in the global prevalence of obesity during the past decades, it could be argued that body weight is a poorly regulated variable. By contrast, the fact that within a given obesogenic environment there are many adult individuals in whom body weight remains relatively stable over years and decades, apparently without conscious control, might instead suggest that body weight is accurately regulated in these individuals. But constancy per se is not evidence for regulation. A critical feature of any regulated system is that disturbance of the regulated variable results in compensatory responses that tend to attenuate the disturbance and to restore the system to its 'set' or 'preferred' value. The direct application of this approach to test whether body weight is regulated in human beings is difficult because of ethical and practical reasons, but observations on adults recovering from food shortages during post-war famine or from experimental starvation indicate that a return to normal body weight is eventually achieved (2). Conversely, excess weight gained during experimental overeating or during pregnancy is subsequently lost, and most individuals return to their initial body weight. It would seem therefore that the regulation of body weight occurs in many human beings, albeit with varying degrees of accuracy and varying timescale over which this regulation operates. In this context, it is important to emphasize several cardinal features of human weight regulation.

(i) Timescale in achieving energy balance: Human beings do not balance energy intake and energy expenditure (EE) on a day-to-day basis nor is positive energy balance one day spontaneously compensated by negative energy balance the next day (2). Near equality of intake and expenditure most often appears over several weeks. Longer measurements are difficult to conduct and impractical because of cumulative errors.

(ii) Subtle perturbations in energy balance can lead to obesity: The long-term constancy of body weight, i.e. its maintenance within a few kilograms over decades, can only be achieved if the matching between energy intake and EE is extremely precise since a theoretical error of only 1% between input and output of energy, if persistent, will lead to a gain or loss of about 10 kg per decade. Yet, a difference of 5% between energy intake and EE is hardly measurable with techniques that are available today. Many investigators have calculated the magnitude of 'energy gap' necessary to progressively render a population overweight/obese over a number of years or decades (3). These calculations show that small daily imbalance in the range of 50–100 kcal, corresponding to one or half a bar of chocolate (20 g), is more than sufficient to reach an obese state a few years or a decade later. However, this has primarily an academic interest since the energy gap is never constant in real life as both energy intake and EE are fluctuating from day to day in a random or in a non-stochastic (non-random, non-deterministic) manner, but not necessarily in coincidence (in terms of energy intake being in concert with EE) and in the same direction on the same day. Furthermore, the energy gap, when extrapolated over a prolonged period of time, neglects any corrective metabolic or behavioural responses from the body (except the effect of the change in tissue mass which directly influences resting EE).

(iii) Body weight constancy amidst fluctuations: Even in individuals that maintain a relatively stable lean body weight over decades, there is no absolute constancy of body weight over weeks and years. Instead, body weight tends to fluctuate or oscillate around a mean constant value, with deviations from the 'set' value being triggered by events that are cultural (weekend parties, holiday seasons), psychological (stress, anxiety or emotions) and pathophysiological (ranging from minor health perturbations to more serious disease states). According to Garrow (2,4), very short-term day-to-day changes in body weight have a standard deviation of about 0.5% of body weight, while longitudinal observations over periods of between 10 and 30 years indicate that individuals experienced slow trends and reversal of body weight amounting to between 7 and 20% of mean weight. The relative constancy of body weight amidst considerable weight fluctuations can be appreciated from rare data (5) of day-to-day body weight measured over 4 years under free-living conditions in a young healthy man of normal body mass index (BMI) (Fig. 1). This figure encapsulates the complexity and difficulties in studying human weight regulation: poor short-term regulation when examined over days, weeks, and months, but precise regulation when examined over years.

Understanding how these short-term deviations in body weight, and hence poor short-term regulation, are corrected through changes in energy intake, EE, or in both to achieve an accurate long-term regulation of body weight, still remains a challenging issue for human research today. Nonetheless, in such a dynamic state within which weight homeostasis occurs, it is likely that long-term relative constancy of body weight is achieved through a highly complex network of autoregulatory control systems and subsystems through which changes in food intake, body...
composition and EE are interlinked. What then could constitute the autoregulatory control systems that operate through adjustments in EE to correct deviations in body weight?

**Autoregulatory adjustments in energy expenditure**

It has long been proposed that in the overall homoeostatic system for body weight, there is a built-in stabilizing mechanism that operates with a relatively simple physiological negative feedback system (6). As Payne and Dugdale (7) have illustrated, using a computer simulation model for weight regulation, any imbalance between energy intake and energy requirements would result in a change in body weight which, in turn, would alter the maintenance energy requirements in a direction that would counter the original imbalance and would hence be self-stabilizing. The system thus exhibits *dynamic equilibrium*. For example, an increase in body weight would be predicted to result in an increase in EE on the basis of the extra energy cost for synthesis and maintenance of extra lean and fat tissues, as well as for the increased energy cost of carrying a heavier weight; this would then produce a negative energy balance and result in a subsequent decline in body weight to its original ‘set’ or ‘preferred’ value. Similarly, a reduction in body weight would also be automatically corrected since the resulting diminished EE due to the loss in weight will produce a positive balance and hence a subsequent return towards the ‘set’ or ‘preferred’ weight.

**Beyond mass action**

In reality, however, the homoeostatic system is much more complex than this simple effect of *mass action* since the efficiency of metabolism (or metabolic efficiency) may also alter in response to the alterations in body weight. As demonstrated in the ‘weight-clamping’ experiments of Leibel *et al*. (8), subjects who after a period of overfeeding maintained their body weight at a level of 10% above their usual weight showed an increase in daily EE (+15%; ~400 kcal d⁻¹) beyond that predicted from changes in body weight and body composition; the daily EE being measured in a respiratory chamber by indirect calorimetry and/or by the doubly labelled water (DLW) technique. Conversely, subjects who after a period of underfeeding maintained body weight at a level of 10 or 20% below their usual weight showed a decrease in daily EE (~15% or 300 kcal d⁻¹) beyond that predicted from the losses of body weight and lean tissues, and which were also shown to persist in subjects who have sustained weight loss for long periods of time ranging from months to years (8,9). These compensatory increases or decreases in mass-adjusted EE (~15% above or below predicted values) are thought to reflect changes in metabolic efficiency that oppose the maintenance of a body weight that is different from the usual body weight; the magnitude of these adjustments in EE being found to be similar in the non-obese and obese subjects as well as in men and women.

**Inter-individual variability**

A closer inspection of data from these ‘weight-clamping’ experiments (8,9) reveals that there is a large inter-individual variability in the changes in mass-adjusted daily EE, with some individuals showing little or no evidence for altered metabolic efficiency, while others showed marked changes in metabolic efficiency in a direction that opposes the weight change. Indeed, the most striking feature of human studies of experimental overfeeding (lasting from a

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**Figure 1** Day-to-day fluctuations in body weight over a 4-year period in a healthy young adult man of normal body mass index (BMI = 22.4 kg m⁻²). The frequency distribution on the right hand side indicates the number of times (counts) that subject’s body weight was between 71.5 and 77.5 kg, with weight intervals of 0.5 kg. Adapted from Schutz and Garrow (5).
few weeks to a few months) is the wide range of individual variability in the amount of weight gain for the same excess energy consumed. Some of these differences in the efficiency (or energy cost) of weight gain can be attributed to individual variability in the gain of lean mass relative to fat mass (i.e., variability in the composition of weight gain), but the possibility also arises that part of the variability also resides in converting excess calories to heat, i.e., in diet-induced thermogenesis (DIT). In a reanalysis of data from some 150 human beings participating in the various ‘gluttony’ experiments conducted between 1965 and 1999, Stock (10) estimated DIT as the energy cost of weight gain above a theoretical maximum energy cost of 45 MJ kg⁻¹, and argued that at least 40% of these overfed subjects must have exhibited an increase in DIT, albeit to varying degrees. That genes play an important role in such variability in weight gain has in fact been established from the long-term overfeeding experiment of Bouchard et al. (11) in identical twins, with similarity within pairs of twins clearly indicating that genetic factors are involved in the partitioning between lean and fat tissue deposition and in the EE response. Conversely, a role for genotype in human variability in the composition of weight loss (i.e., ratio of lean to fat tissue) and in the estimated increase in metabolic efficiency during weight loss has been suggested from studies of Hainer et al. (12), in which identical twins underwent slimming therapy on a very-low-calorie diet. Taken together, these studies suggest that in addition to the control of food intake, the partitioning of weight change between lean and fat tissues as well as changes in metabolic efficiency play an important role in the regulation of body weight and body composition, and that the magnitudes of these adaptive responses to limit weight loss or weight gain are strongly influenced by the genetic make-up of the individual.

**Controversies**

However, considerable uncertainties and controversies exist about the quantitative importance of the altered metabolic efficiency in these responses to under- or overfeeding, amidst variable definitions, methodological and analytical approaches that are used to attribute or deny changes in EE to adaptive thermogenesis. In the analysis of the factors that contribute to these controversies, it is therefore important to first discuss what could constitute adaptive thermogenesis when examining changes in the various compartments of daily EE.

**What constitutes adaptive thermogenesis?**

Figure 2 shows a schematic presentation of daily EE divided into the various compartments and sub-compartments that are generally measured or estimated in studies investigating metabolic adaptation resulting from adaptive thermogenesis. To note that in this review, the

![Figure 2](http://doc.rero.ch)
term basal metabolic rate (BMR) is used interchangeably with resting EE measured after an overnight fast. Furthermore, fat-free mass (FFM), the difference between body weight and fat mass (ether extractable), is used interchangeably with lean body mass (LBM), which is the difference between body weight and adipose mass.

Adaptive thermogenesis in resting state

As depicted in Fig. 2, EE measured at rest in the post-absorptive state whether as BMR or sleeping EE reflects the production (or generation) of heat, i.e. thermogenesis. In response to overnutrition or undernutrition, the changes in mass-adjusted BMR (i.e. changes in BMR beyond that predicted by changes in FFM and fat mass) can be quantified by applying regression models to calculate residuals; such deviations from predicted values are considered to reflect changes in metabolic efficiency and hence in adaptive thermogenesis. Decreases in mass-adjusted BMR in response to starvation or hypocaloric dieting (13–18) as well as increases in mass-adjusted BMR in response to overfeeding (19–25) have often been reported in humans, and could reflect the operation of adaptive thermogenesis in the compartment of resting EE. In the classic longitudinal Minnesota Experiment (13) where normal weight volunteers went through phases of semi-starvation, restricted refeeding, and subsequently ad libitum refeeding (Fig. 3), adaptive thermogenesis in the BMR compartment could thus be inferred from mass-adjusted BMR decreasing during the course of weight loss and remaining low during the period of restricted refeeding (15,26), but also increasing during the hyperphagic phase of ad libitum refeeding and remaining high even after hyperphagia was no longer evident (27); the large inter-individual variability in adaptive thermogenesis at each of these time points is shown in Fig. 4. Further evidence for the existence of adaptive thermogenesis in the BMR compartment can also be derived from the studies of Blundell and Cooling (28), showing elevated BMR in some habitually high-fat consumers maintaining similarly normal BMI and body composition on a higher energy intake than habitually low-fat consumers, as well as from the meta-analysis of Astrup et al. (29) showing a lower mass-adjusted BMR or resting EE in post-obese subjects than in never-obese controls.

Thermic effect of food

EE in the postprandial state is quantified as the thermic effect of food (TEF); it is also referred to as the specific dynamic action, postprandial thermogenesis, or DIT, and can amount between 5 and 15% of daily metabolizable
energy intake (30). It is generally measured at rest and is divided into an obligatory component related to the energy costs of digestion, absorption, and metabolic processing of nutrients for storage, and a facultative component which in part results from the sensory aspects of foods and in part from stimulation of the sympathetic nervous system. TEF assessed at rest may be considered as a proxy for exploring the net efficiency of exogenous macronutrient utilization. Although it is unclear whether TEF (as a % of meal calories) is altered in response to experimental overfeeding or underfeeding (30–32), and whether its impairment contributes to the pathogenesis of obesity (33,34), reports of a lower TEF in post-obese subjects than in the never-obese controls (35–38) may also be suggestive of adaptive thermogenesis in this compartment of EE (generally measured at rest) in response to weight loss.

Adaptive thermogenesis in non-resting state

The adaptive changes in heat production from what is generally clustered under non-resting EE or activity EE are more difficult to assess as they consist of several overlapping sub-compartments (Fig. 2). In interpreting the energy cost of physical activity, it is important to point out that physical activity is often used synonymously with ‘work’ which has a strict definition in physics, namely work performed on the environment, i.e. force \times distance. The efficiency of muscular work during dynamic exercise is low (~25%), but that of spontaneous physical activity (SPA) – such as muscle tone and posture maintenance, fidgeting and non-specific ambulatory behaviour such as pacing – is even lower because these essentially involuntary (subconscious) activities comprise a larger proportion of isometric work. Because no physical work is done in the strict physical sense, isometric work per se is considered to be simply thermogenic. Thus, as actual work done on the environment during SPA is very small compared to the total energy spent on such activities, the energy cost associated with SPA has been referred to as movement-associated thermogenesis or SPA-associated thermogenesis. As SPA is essentially a biologically driven (subconscious) behaviour, a change in the level or amount of SPA in a direction that defends body weight also constitutes autoregulatory adjustment in EE. In this context, an increase in the amount of SPA in response to overfeeding, or a decrease during undernutrition, also constitutes adaptive changes in thermogenesis (Fig. 2).

Spontaneous physical activity thermogenesis

To date, the most direct evidence that changes in SPA, as assessed by radar motion detectors in respiratory chambers, contribute to autoregulatory changes in EE in humans is derived from data (39) obtained from the eight men and women who were participating in the Biosphere 2 experiment, a self-contained ecologic ‘miniworld’ and prototype planetary habitat built in Arizona. As a result of unexpected shortage of food, their losses in body weight (~15%) over a 2-year period were found to be accompanied by a markedly lower SPA, which, like their reduced daily EE, persisted several months after the onset of weight recovery and could be implicated in their disproportionate recovery of fat mass relative to lean mass. Whether inter-individual variability in the amount of SPA contributes to variability in resistance or susceptibility to obesity has also been the focus of a few human studies. The potential importance of SPA-associated thermogenesis in human weight regulation was in fact underscored by the findings of Ravussin et al (40) that even under conditions where subjects are confined to a respiratory chamber, SPA accounted for 8–15% of daily EE varying between 100 and 680 kcal d$^{-1}$. Subsequent studies indicated that SPA is a familial trait and a predictor of subsequent weight gain over a 3-year follow-up (41). In fact, a main conclusion of the early overfeeding experiments of Miller et al. (42) was that resistance to obesity in some of the individuals could not be accounted by an increase in EE at rest (BMR or TEF), and was postulated to reside in an increased EE associated with simple low-level activities of everyday life. This notion has gained support from the
report of Levine et al. (43) that >60% of the increase in daily EE in response to overfeeding could be attributed to changes in activity EE which they referred to as non-exercise activity thermogenesis (NEAT), and which they showed to be the most significant predictor of fat gain in their overfed subjects. As the subjects did not engage in exercise (i.e. structured physical activity) and no changes in overt physical activity could be detected by accelerometers in response to overfeeding, Levine et al. (43) attributed the increases in NEAT to an increase in low-level SPA. One could, however, also attribute these increases in NEAT to decreases in the efficiency of muscular work, whether voluntary or spontaneous.

Efficiency of muscle work

Indeed, in the previously mentioned ‘weight-clamping’ experiments of Leibel et al. (8), the autoregulatory increases or decreases in non-resting EE could not be explained by changes in the amount of time spent in physical activity. Instead, muscle work efficiency during low-intensity cycle ergometry was found to be decreased by 18% or increased by 26% during such forced weight maintenance at 10% above or below the usual body weight, respectively (44); such changes in muscle efficiency at altered body weight could account for about a third of the change in daily energy expended in the non-resting state (i.e. associated with physical activity). The finding of an adaptive decrease in thermogenesis, as judged by the lower (net) energy cost of exercise when body weight is reduced, is consistent with other reports of an increase in skeletal muscle work efficiency after weight reduction in lean and obese subjects (45,46), in non-obese female dieters exercising at different workloads (47), and in chronically undernourished subjects in India (48).

Adaptive thermogenesis in overlapping energy expenditure compartments

While some of the most compelling evidence in support of adaptive thermogenesis attempts to quantify its relative importance in the resting vs. non-resting compartments of daily EE, it must be emphasized, however, that this division of EE into resting and non-resting EE is artificial. The possibility of overlaps and interactions across these compartments and sub-compartments of EE are also illustrated in Fig. 2, and discussed below.

First, sleep EE, which is generally nested under ‘resting’ EE, may also comprise a ‘non-resting’ component due to spontaneous movement or SPA occurring during sleep (e.g. rollovers, posture alterations), the frequency of which is highly variable between individuals (49).

Second, BMR might be confounded by the long-lasting effect of a large evening meal whereby TEF might be incomplete by the time BMR is assessed in the morning.

Third, non-resting EE could also include heat production resulting from the impact of physical activity (exercise or SPA) on the TEF or postprandial thermogenesis. There is in fact some evidence for interactions between acute exercise and food on EE, with both high- and low-intensity physical activity leading to a potentiation of TEF (50–53). Schutz (54) has proposed that as feeding and exercise performance have opposite effects on metabolic flux, with feeding inducing macronutrient substrate storage in the postprandial phase whereas the performance of exercise results in endogenous macronutrient mobilization, the simultaneous operation of both processes increases macronutrient utilization and substrate turnover, resulting in enhanced TEF – by analogy to the concept of increased postprandial substrate cycling, referred to (inappropriately) as ‘futile’ cycling.

Fourth, the effect of exercise and physical activity on EE can persist well after the period of the physical activity (post-exercise or post-SPA stimulation of thermogenesis) whether in the post-absorptive or postprandial state (55,56). For example, in the study by Broeder et al. (56) in which men performed low-intensity vs. high-intensity exercise with and without a meal in the post-exercise period, the thermogenic response was higher in the high-intensity group (+14%) than in the low-intensity group (+6%) in the post-exercise period. In a more recent study of tightly controlled physical activity in a respiratory chamber (57), vigorous exercise at 75% of VO2max for 45 min resulted in a significant elevation in post-exercise EE that persisted for 14 h. The approximately 190 kcal expended after exercise above resting levels represented an additional 37% to the net energy expended during the 45-min cycling bout. Such interactions between food and physical activity persisting after the cessation of physical activity have not been studied in response to experimental perturbations of energy balance and weight changes, and their contributions to adaptive thermogenesis cannot be disregarded.

Limitations and issues in quantifying adaptive thermogenesis

Despite the many lines of evidence previously mentioned in support for the existence of adaptive thermogenesis in both resting and non-resting compartments of EE in humans, they are nonetheless fragmentary as the measures have most often been made in different studies. Few studies have attempted to simultaneously and independently measure most of the components of EE in response to energy imbalance and weight perturbations. Furthermore, there are potentially large technical errors in assessing non-resting EE and in the determination of body composition, and these will impact upon estimates of mass-adjusted EE and hence in the quantification of adaptive thermogenesis. Last, but not least, the very definition of adaptive thermogenesis
remains somehow obscure and hotly debated among many investigators, mostly because it has not been clearly mathematically defined (ideally by a straight equation). These limitations have served to fuel the controversy (58,59) about the importance of adaptive thermogenesis, with some attributing its role as minor in weight regulation and others actually considering the phenomenon as irrelevant to human weight homeostasis. Some of the most important methodological, technical and biological issues in the interpretation of adaptive thermogenesis are discussed below.

**Dietary intake assessment**

Dietary compliance is often pinpointed as an important factor in explaining lower-than-predicted weight changes in response to dieting or overfeeding. In performing human studies, the degree of compliance to the diet, and above all, the maintenance of adherence to the prescribed diet over time is indeed a difficult task (60), in particular since it is not constant in a given individual and may change over time. However, well-controlled studies conducted under metabolic ward conditions have also reported large variability in weight gain/loss in response to overfeeding/dieting. It could also be argued that such differences in weight gain/loss may be explained by our inability to accurately assess weight maintenance energy requirements and therefore the actual energy excess or energy deficit. In particular, Stubbs and Tolkamp (61) have argued that the magnitude of inter-individual differences in DIT may not be as great as suggested by Stock (10), as a main criticism in estimating DIT from most of these studies resides in the general failure of most human overfeeding studies to characterize the habitual energy requirements of subjects. An estimate of energy requirements is usually made as a standardized multiple of BMR (e.g. 1.6 \times BMR), which therefore does not account for inter-individual differences in baseline physical activity. By assuming that all subjects have a similar sedentary EE when expressed as a multiple of BMR, any difference in physical activity would translate into an estimate of DIT. Uncertainties about the assessment of energy requirements during weight maintenance were more recently underscored by Westerterp (62) who has challenged some of the conclusions of studies (63), investigating the effect of overfeeding diets varying in protein content on the composition of weight gain, on the grounds that an underestimation of energy requirement for weight maintenance in the group overfed with a low-protein diet resulted in an overestimation of the energy overfed in this group. Furthermore, errors also occur in the calculation of the energy deficit and hence in predicted or target weight loss, particularly in the estimation of daily energy requirement for weight maintenance before weight loss interventions. As underlined by Heymsfield et al. (64), if the estimated baseline energy requirement of an obese person is 100–200 kcal d\(^{-1}\) higher or lower than measured, then even perfect adherence to a diet will result in an error of 2–4 kg in predicted weight change over a year.

**Body composition assessment**

In assessing adaptive thermogenesis as greater-than-predicted changes in EE in response to altered energy balance, the data on EE as resting EE, BMR, or as total daily EE are adjusted for changes in FFM, the most important predictor of EE at rest, but with the inherent assumption that the composition of FFM remains constant. However, FFM can be divided into several constituents with very different specific metabolic rates. In particular, brain, heart, kidneys and liver that represent \(<10\%\) of body mass contribute \(>60\%\) of BMR (65). In contrast, skeletal muscle represents 35–40\% of body mass (and 50\% of FFM), but its contribution to BMR is only 20–25\%. Consequently, given that the contribution of the organ mass to BMR is disproportionately greater than skeletal muscle mass (60–80\% vs. 20–25\%), and that for most individuals in our mechanized societies, BMR is the major component of daily EE, the possibility arises that relatively small changes in the proportion of organ mass to muscle mass in response to weight perturbations can impact significantly on EE. Hence, this could account for some of the unexplained variance in changes in EE and thereby the estimation of adaptive thermogenesis. New technologies such as computed tomography (CT) scanning and magnetic resonance imaging (MRI) are increasingly being applied to estimate organ size in the evaluation of inter-individual variability in resting EE (66,67), in body composition phenotyping in general (68), and in explaining ethnic differences in EE (68). To date, however, only a few studies have provided insights into this issue of composition of FFM or LBM pertaining to altered EE in response to dietary-induced weight loss or weight gain, and these are discussed below.

**Organ size**

First, in contrast to the increases in the size of heart, liver and kidney observed during the development of spontaneous obesity (68,69), the increased LBM during weight gain in response to a 100-d overfeeding study in 22 young men was not found to be accompanied by detectable increases in organ size (70). Indeed, using CT scanning to assess the changes in adipose tissue mass, skeletal muscle mass, and non-muscular LBM in relation to the changes in BMR, Dérait et al. (70) found that increases in LBM occurred in skeletal muscle but not in non-muscle FFM, such that the prediction of resting EE by the LBM or skeletal muscle mass could not be improved by introducing the non-muscular-LBM components (organs, bones). The implica-
tion of these findings is that the contribution of the LBM or FFM gain to the increase in BMR would be overestimated, leading to an underestimation of mass-adjusted BMR and hence an underestimation (or failure to detect) of adaptive increases in thermogenesis in response to such overfeeding.

Second, in a recent study by Bosy-Westphal et al. (71), which was conducted in 45 overweight and obese women who have lost weight in response to a low-calorie diet for 3 months, body composition was determined by MRI, dual-energy X-ray absorptiometry, and a four-compartment model in order to assess the contribution of loss in individual organ mass to the weight loss-associated decline in resting EE. By comparing resting EE measured by indirect calorimetry with that calculated from detailed body composition analysis with the use of specific organ metabolic rates, they found that almost 50% of the decrease in measured resting EE after a mean 10-kg weight loss was explained by losses in FFM and fat mass, and that the variability in measured resting EE explained by body composition increased to 60% by also considering the weight of individual organs. This still leaves, albeit theoretically, about 40% of the decline in resting EE attributed to adaptive thermogenesis. It should be noted that the latter value must be an overestimation, because it is illusory to expect that 100% of the variability could be explained given the fact that the technical error of measurement is included in the total variability and that the intra-individual variability is not zero and is inflating the total inter-individual variability. At least, under conditions of this experiment in overweight and obese subjects, the estimation of adaptive thermogenesis is only modestly overestimated if the composition of FFM is not taken into account.

Third, in a subsequent weight loss/regain study, Bosy-Westphal et al. (72) showed that after weight loss, a reduced resting EE adjusted for changes in FFM and fat mass, as well as for changes in organ/tissue masses, persisted during weight regain; these findings being consistent with the notion derived from reanalysis of the Minnesota Experiment, indicating that adaptive suppression of thermogenesis persists during weight regain and drives the accelerated rate of fat recovery or catch-up fat (15,26).

Fat-free mass hydration
It should also be emphasized that in studies of underfeeding and overfeeding, particularly where the magnitude of changes in body weight is small (a few kg), the exact size of the change in energy storage is difficult to assess with great accuracy given the imprecision of body composition measurements (73,74), thereby introducing uncertainties and potentially large errors in the assessment of body composition, with disproportionate changes in body water influencing the composition of FFM. More recent applications of the four-compartment model to assess body composition have revealed a relative overhydration of FFM in response to acute overfeeding in young men (75), as well as in obese subjects who have lost >18 kg in response to dieting and who maintained their post-obese weight for 2–16 years (76). These observations are also important in interpreting the relationship between changes in EE and body composition. An overhydration of FFM (and hence an overestimation of metabolically active cell mass) will lead to underestimation of adaptive thermogenesis in response to overfeeding-induced weight gain and its overestimation in response to underfeeding-induced weight loss.

Energy expenditure assessments
Most studies investigating adaptive thermogenesis have measured EE over a small part of the day, namely as BMR and TEF (one test-meal response), and thus might have missed adaptive thermogenesis occurring over the rest of the day. These limitations of short-term EE measurements can be avoided by two other approaches: respiratory chamber and DLW. Both approaches are thought to enable quantitative assessment of the changes in EE due to altered thermogenesis because any adaptive thermogenesis in the various compartments of EE would cumulate into the total daily EE. The 24-h respiratory chamber measurements can reach the highest accuracy and precision (Table 1). Furthermore, confining the subject in a respiratory chamber is important for maintaining strict experimental conditions, and allows measurements of total EE and its components: BMR, sleeping EE, radar-monitored physical activity, and

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Estimation of relative errors in energy expenditure assessments assessed in appropriate conditions by a hood system (BMR and TEF), by a large size respiratory chamber (24-h EE) or by doubly labelled water (at least 1 week average energy expenditure)</th>
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<tr>
<td>BMR</td>
<td>Technical Accuracy (%)</td>
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<tr>
<td>TEF</td>
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<td>24-h EE</td>
<td>Respiration chamber</td>
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<td>Doubly labelled water TEE</td>
<td>3–10</td>
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<td>Doubly labelled water PAL</td>
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BMR, basal metabolic rate; EE, energy expenditure; PAL, physical activity level; TEE, total energy expenditure; TEF, thermic effect of food.
TEF integrated over 24 h. Respiratory chambers are however not suited to explore behavioural changes in physical activity because the variety, types and intensity of activities are largely limited by the size of the chamber. Consequently, altered thermogenesis in the non-resting compartment is likely to be underestimated. The application of the DLW method for assessing daily EE under free-living conditions (typically over 1–2 weeks) would seem to obviate this limitation, as it provides a means for assessing quantitatively the contribution of physical activity to daily EE, with physical activity level (PAL) estimated from the ratio of 24 h EE to BMR. Furthermore, if volitional activity is held constant over two periods (e.g. baseline vs. underfeeding or overfeeding) and verified with the use of activity monitors, the energy expended in SPA can be inferred by comparing the calculated differences between total EE and BMR plus TEF; a procedure that led Levine et al. (43) to suggest that variability in NEAT predicts susceptibility to fatness in response to overfeeding.

The application of DLW to studies of experimental underfeeding or therapeutic dieting has shown that the reduction in daily EE is importantly contributed by reductions in non-resting EE (77,78), thereby suggesting a decrease in habitual (voluntary and/or spontaneous) physical activity. By contrast, several investigations that have used the DLW method to measure total daily EE and PAL in response to overfeeding have yielded contradictory results (58,77; for review). Most report that the increases in total EE during overfeeding are small, the increases in resting EE assessed as BMR could be accounted for by increases in FFM, while the increases in TEF could be explained by the expected increase in the obligatory cost of storing the extra energy from the larger meals. Furthermore, the increase in non-resting EE referred to as NEAT by Levine et al. (43), which was indirectly calculated, was not found to be a common feature of human overfeeding studies. All other studies that utilized DLW to assess EE responses to overfeeding failed to find a significant increase in non-resting EE or PAL when NEAT was tracked objectively (58,77). Furthermore, studies conducted in respiratory chambers equipped with radar motion detectors most frequently did not find a reduction in SPA in response to caloric restriction, and the use of accelerometry has not consistently explained the reduced activity EE observed under free-living conditions in response to caloric restriction in non-obese humans participating in the CALERIE study (78). The overall conclusion is that undernutrition and caloric restriction seem to result in decreased habitual or voluntary physical activity, but an increase in energy intake does not result in a substantial increase in total EE nor in EE associated with body movements, at least in acute conditions. Such conclusions and discrepancies across studies must however be weighed against considerable limitations in the interpretation of data from DLW, and in teasing out the adaptive thermogenesis component from the non-resting EE compartments.

Technical limitations
Measuring the accuracy of a method is most important for cross-sectional studies, whereas precision is the key factor for a prospective intervention study where the net changes are of great interest, each subject being his/her own control. One technical limitation of the indirect calorimetry chamber is that its accuracy is difficult to assess properly because it relies on a system either based on combustion of a gas (ethanol, butane, etc.) using basic biochemical stoichiometry equations, or a system based on an infusion of a mixture of pure gas, one containing CO₂ and the other an inert dilution gas (typically N₂), in order to produce (by gas dilution) a pseudo-O₂ consumption. In the former case, the combustion never reaches 100% so that real accuracy is difficult to track, and in the latter case, we entirely rely on the purity of certified gases (rarely a strong issue) and above all on the accuracy of the rate of gas infusion (always a strong issue). For the DLW approach, which measures CO₂ production (VCO₂) and not EE, the true accuracy is even more difficult to track. We know that total EE accuracy must be much lower than VCO₂ accuracy since it depends upon an adequate value for selecting the energy equivalent of VCO₂, which varies substantially and which depends upon the respiratory quotient (RQ), the latter being unknown. A proxy for approaching a reasonable RQ value is the use of the food quotient, which is calculated from the proportion of fat vs. carbohydrate vs. protein in the normal habitual diet.

Some of the discrepancies across studies may therefore be attributed to potentially large errors in assessing total EE by DLW, at least in some individuals, and also to artefacts introduced in determining the non-resting component of EE by difference, since the errors in measuring total EE, BMR or TEF are accumulated in the calculations of non-resting EE and PAL (Table 1). In a review of studies with two or more repeat DLW measurements of EE and PAL, Black and Cole (79) found that the pooled mean intra-individual coefficient of variability (CV) derived from 21 studies for EE and PAL was 12%, with wide variability both in EE (range 6.5–22.6%) and PAL (range 2.3–24.3%); these values of intra-individual variability were surprisingly found to be greater than inter-individual CV that was 11 and 7% for EE and PAL, respectively. It is true that, under field conditions, precision is lost due to errors that include those due to changes in background isotope levels, errors in dosing, or the handling and analysis of urine samples and inherent biological variation apart from that due specifically to physical activity. However, in establishing precision of the DLW technique itself by undertaking repeat measurements on six young men who were confined to a metabolic facility, fed a constant weight maintenance diet and
required to be totally sedentary (physical movement being limited to that necessary for personal care and hygiene), Goran et al. (80) found the total intra-individual variability to be 8.4%. Analytic variation was estimated from propagation of error analysis to be 6%, and thus the inherent biological variation was calculated to be 6% (square root of \(8.4^2 - 6^2\)). Similarly, Schoeller and Henlicka (81) made repeat measurements on six free-living female nutritionists 6 months apart, and found intra-individual CV to be 8% on average, and inherent biological variation estimated as 6.4%; they also reviewed the within-subject variation in 15 other studies and calculated the inherent biological variation to average 8%. Although variation that included changes in weight, season and activity augmented with increased time between measurements to about 15% at a time span of 12 months, values of 9–13% have also been reported for time span as short as 3–8 weeks for both EE and PAL (79), the time necessary to wash out the stable isotopes from the body.

Finally, as an estimate of physical activity (PAL) is calculated as the total EE (measured by DLW over, say, 1 week) divided by BMR (measured over only 30 min in steady state by indirect calorimetry), one wonders whether the PAL error may primarily stem from the subject’s sensitive value of BMR, in particular if it is a ‘snap shot’ measure on one single occasion (whose reproducibility can be poor in some subjects). Ideally, BMR should be replicated several times to bracket the DLW time window. Overall, the errors in assessing EE by DLW are large enough to cast shadows on the interpretation of DLW studies about magnitude of adaptive thermogenesis.

**Biological limitations**

The evaluation of what constitutes adaptive thermogenesis in the component of non-resting EE is perhaps the most challenging task. As discussed earlier, changes in the level of subconscious SPA activity (within the NEAT compartment) may be considered by some as adaptive thermogenesis and hence part of the autoregulatory adjustments in EE in response to under- or overfeeding. However, the calculated non-resting EE only provides a crude estimate of physical activity but does not identify the types of activities. Although accelerometers and activity monitors provide some qualification, the detection of SPA behaviours *per se* remains a daunting task (82,83), because as underscored by Garland et al. (84), voluntary exercise, SPA and sedentary behaviours do not necessarily lie along a single continuum or axis of variation. There is considerable evidence suggesting that what is often considered as ‘voluntary’ exercise or movement may also be under substantial biological control. The motivation for exercise can be multifactorial, exceedingly complex and related to major personality traits as it can also be rewarding (i.e. psychologically and/or physically) and even addictive (84). Furthermore, what is referred to as NEAT also poses a problem as it has been estimated in a variety of ways, corresponding to different definitions. Although initially equated with SPA by Levine et al. (43), NEAT has been subsequently extended by the same author to include most of our daily tasks such as walking, talking, reading and gardening (85). Under this sort of very broad definition, the NEAT concept can be of voluntary nature and even encompass what is commonly viewed as exercise (86). Furthermore, TEF is not considered in the NEAT concept when NEAT is calculated above the resting EE measured without an overnight fast and hence generally includes a component of TEF. The hypothesis that NEAT does not potentiate TEF, however, does not take into consideration different physical activity circumstances. Irrespective of how broadly one defines NEAT, it is clear that there is a large grey area between voluntary (or planned) exercise and SPA. To quote Garland et al. (84): ‘How should play behaviour, which occurs commonly in the young, and sometimes in the adults, be classified?’ Furthermore as most of these ‘reliable’ DLW studies to assess EE in response to overfeeding were conducted with subjects living in research institute and metabolic ward conditions where the opportunity for both voluntary and SPA is curtailed, the expression of adaptive thermogenesis in the non-resting compartment of EE is also limited by such experimental constraints.

**The meaningless mean**

The human population has a wide genetic variation and our ability to construct experimental groups of similar individuals is severely limited. It is possible to exclude outlying data on statistical grounds by applying the Chauvenet criterion, but philosophically and clinically we are also interested in the performance of individuals as the laws of thermodynamics must apply to them also. This brings us to the problem of human experiments: if a predisposition to obesity or leanness is genetically determined as strongly as it is in animals, but undetectable in advance, it is inevitable that the literature on adaptation to energy intake will be contradictory (87). It is an individual and not a general phenomenon. In any population sample under investigation, the existence of a high capacity for adaptive thermogenesis in some individuals may be masked by focusing only on the mean values if this population sample consists mostly of individuals showing little or no adaptive thermogenesis. This is well illustrated in the overfeeding study of Siervo et al. (75) in which total EE and body composition changes in response to a highly standardized 17-week protocol involving progressive overfeeding in a metabolic suite were assessed in six lean men using state-of-the-art measurement methods. A novel and interesting feature of this study is that it utilized a design with recurrent periods of overeating that characterize the weight history of the vast
majority of overweight subjects. This design is therefore unlike previous longer-term overeating studies that have used a single (generally severe) level of overfeeding that may overwhelm the homeostatic processes and obscure more subtle changes that may be effective in modulating energy balance during naturally occurring episodic periods of marginal excess consumption. This contention is supported by the demonstration from an 8-week sustained overfeeding study that increases in BMR during the first few weeks attenuate over subsequent weeks (25).

The study of Siervo et al. (75) started with a baseline period of 3 weeks during which the dietary intake provided was adjusted to maintain body weight. Subjects were then challenged with 3-week stepwise overfeeding phases (+20, +40 and +60% increases above the baseline energy intakes) separated by intermittent ad libitum phases. Body composition was assessed by a four-compartment model using dual-energy X-ray absorptiometry, deuterium dilution and plethysmography. Energy intake was assessed throughout, EE and substrate oxidation rates were measured repeatedly by whole body calorimetry in a respiratory chamber, and free-living EE was measured by DLW at baseline and after 60% overfeeding. At the end of 60% overfeeding, total daily EE assessed in the respirometry chamber and by DLW had increased by 11 and 16%, respectively. Body weight and body fat had increased by 6 and 3.3 kg, respectively, such that fat gain and FFM gain accounted for 55 and 45% of the weight gain, respectively. The computed energy cost of tissue accretion was found to differ from the excess ingested by only 12–13%, indicating an absence of effective dissipative mechanisms. The authors concluded that elevations in total EE provide very limited autoregulatory capacity in body weight regulation (75).

While this conclusion based on mean values seems sound, a more detailed examination of individual responses to the overfeeding challenge nonetheless reveals large interindividual differences in the measured or calculated parameters for EE and body composition, such that the five (out of six) individuals who completed the entire study can be phenotyped into those showing low or high partitioning (HP) of weight gain towards FFM and by whole body calorimetry in a respiratory chamber, and free-living EE was measured by DLW at baseline and after 60% overfeeding. At the end of 60% overfeeding, total daily EE assessed in the respirometry chamber and by DLW had increased by 11 and 16%, respectively. Body weight and body fat had increased by 6 and 3.3 kg, respectively, such that fat gain and FFM gain accounted for 55 and 45% of the weight gain, respectively. The computed energy cost of tissue accretion was found to differ from the excess ingested by only 12–13%, indicating an absence of effective dissipative mechanisms. The authors concluded that elevations in total EE provide very limited autoregulatory capacity in body weight regulation (75).

In discussions about the relevance of adaptive thermogenesis to the aetiology of obesity, to the lower-than-predicted weight loss in response to dieting/exercise interventions, and to the inability to sustain weight loss after slimming therapy, it is argued that the changes in EE that are considered to be ‘adaptive’ are often no more than a few percent of daily EE and hence unimportant for weight homoeostasis. But as obesity is the result of energy intake that exceeds EE for long periods, it needs to be emphasized that even a small positive energy balance on a daily basis can lead to a significant weight gain over years. Such small positive energy imbalances of the order of 200–1,000 kJ d⁻¹ may result from the normal variation in mass-adjusted resting EE among individuals with an intersubject CV of 6% or less (91–93). Thus, for the same energy intake, a lower resting EE in an average adult female would result in a positive energy balance of >630 kJ d⁻¹ for about two-thirds of the population who happens to fall below the mean. It could also result from a lower TEF as has been reported in obese and post-obese states (37,38,94), which would result in a positive energy balance of the order of 100–400 kJ d⁻¹. Using previously reported data in women on body composition, resting EE and the energy cost of tissue deposition, Weinsier et al. (95) have used mathematical models to predict the theoretical effect of a persistent reduction in daily EE on long-term weight gain assuming no adaptation in energy intake, and based on reduction in daily EE in the above-mentioned range of 200–800 kJ d⁻¹, as might be expected from reported inter-individual variations in resting EE, TEF or routine physical activity. As shown in Fig. 6, a decrease in EE that results in an initial
daily positive energy balance of 419 kJ (100 kcal) in a lean individual of 50 kg and 22% fat mass with a constant PAL of 1.4 would result in a weight gain of 6.4 kg (representing 56% fat mass and 44% FFM) before energy equilibrium is re-established. In contrast, an already obese person of 100 kg and 46% fat mass would have to gain almost 50% more weight, i.e. 9.3 kg (representing 83% fat mass and 17% FFM) to offset the same positive energy balance, since the increase in weight is largely fat, which is less metabolically active than FFM. Thus, resting EE rises more slowly with increasing degrees of obesity due to a declining proportion of the more metabolically active FFM. For the same positive initial energy imbalance, a significantly greater weight gain is expected for obese than for lean women before energy equilibrium is re-established, thus tending to perpetuate obesity further. Due to the greater energy density of adipose tissue, the time course of weight gain to achieve energy balance is longer for obese subjects: in general, this is approximately 5 years for lean women and 10 years for obese women.

Based on these calculations and mathematical models, Weinsier et al. (95) concluded that the magnitude of weight gain of lean women in response to a small reduction in EE of 200–800 kJ d⁻¹ would be about 3–15 kg, amounts of weight gain that they consider would be insufficient to explain severe obesity. It is however emphasized here that these amounts of weight gain are sufficient to explain the transition of lean people with a HP of weight gain to FFM (i.e. the HP phenotype) to the overweight category, and those with a LP (the LP phenotype) to the obese category. Thus, the prediction of weight gain resulting from daily EE being lower than energy intake by as little as 100 kcal d⁻¹

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leads to an amount of weight gained that is dependent on lean: fat partitioning characteristic of the individual. The amount and length of time of the weight gain would be considerably greater for a person who is already obese as well as for a lean person (never obese or post-obese) with a LP phenotype than for a lean individual (never obese or post-obese) with a HP phenotype.

Thus, adaptive thermogenesis, even of the order of only a few percent of daily EE, can be of importance for long-term weight homoeostasis. It is relevant as much to the aetiology of obesity as to the inability to sustain weight loss after slimming therapy (96), to catch-up fat during weight regain, and to how dieting makes some fatter (97).

Conclusions

Today, the accuracy and precision with which we can measure the various compartments of EE, energy intake and body composition are still poor relative to the potential long-term impact of small changes in energy imbalance on body weight and body composition. As adaptive thermogenesis is calculated from the parameters of energy balance and body composition, with each parameter’s error accumulating in this calculation, it is understandable that the quantification of adaptive thermogenesis is prone to large errors. In this context alone, it remains more of a concept than a strictly ‘quantifiable’ entity. Nonetheless, the concept of adaptive thermogenesis has evolved considerably over the past century from ‘luxuskonsumption’ to one centred on a fine-tuning system in the long-term regulation of body weight and body composition, most often operating amidst a fluctuating body weight. There is considerable inter-individual variability in the capacity for adaptive thermogenesis, and in addition, there seems to be considerable inter-individual heterogeneity concerning the compartments and sub-compartments of EE in which adaptive thermogenesis might be occurring. Hence, there may be considerable inter-individual differences in metabolic strategies to conserve energy through suppressed thermogenesis or to dissipate excess energy through DIT. Finally, over these past decades, the concept of adaptive thermogenesis in human weight regulation has been a major driving force for research that has led to major advances in our understanding of many facets of human metabolism, including the importance of genetics in human susceptibility to obesity and resistance to slimming (11,12), in establishing fundamental mechanistic links between diet, weight dynamics, and disease entities of the metabolic syndrome (98,99), and last, but not least, in opening new avenues for exciting research into pharmaceutical and nutraceutical approaches for the management of obesity and its associated chronic diseases (100–103).

Conflict of interest statement

The authors declare no conflict of interest.

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