

CHAPTER 1

Energy Balance and Body Weight Homeostasis

Key points

- Energy intake is highly variable, and mechanisms to defend a “set point” in energy stores appear to have evolved.
- Energy is spent doing useful physical, chemical, and electrical work and also producing heat (thermogenesis) as a by-product of these activities.
- Thermogenesis is subject to regulation and may be adapted to prevailing energy balance.
- Basal metabolic rate (BMR) increases predominantly in proportion to lean body mass and is higher in the obese. Its fall with caloric restriction may present a barrier to long-term weight loss.
- Energy is also spent in voluntary (exercise) and other non-exercise activity thermogenesis (NEAT).
- Spontaneous physical activity (SPA) is a major component of NEAT and is regulated by the sympathetic nervous system (SNS), and its fall with caloric restriction may present a barrier to successful weight loss.
- Genetic and acquired variations in the amount and efficiency of these largely unconscious processes may explain some inter- and intra-individual variability in energy metabolism and thus predisposition toward obesity.
- Food (energy) intake is subject to complex regulation by circulating and gut-derived signals which include leptin.
- In addition to its effects on energy intake, leptin has the ability to stimulate adaptive thermogenesis via SPA, uncoupling of oxidative phosphorylation, and possibly via futile cycling. Many of these effects depend on the SNS.
- Leptin deficiency or receptor mutations are a very rare cause of human obesity. Nevertheless, relative defects in leptin action may (at least in theory) influence body weight homeostasis and are the subject of current research.
- Brown adipose tissue (BAT) exists in adults; it is regulated by the SNS and contributes to thermogenesis. Stimulating its differentiation and activation is a target of current research.

CASE STUDIES

Case study 1

CF is a 24-year-old woman with a body mass index (BMI) of 32 kg/m². She describes an apparently healthy diet which she considers to be no higher in calories than that taken by many of her friends and family who do not have weight problems. She also walks regularly. She feels immensely frustrated over her seeming inability to achieve or maintain an ideal body weight despite good habits and is starting to feel like giving up.

Comment: You explore her concerns and find that she is certain that she has an undiagnosed metabolic problem leading to a slow metabolism, a problem she feels runs in her family despite repeatedly normal tests of thyroid function. You explain that the body does adapt over time to a change in weight and the new higher or lower weight tends to be opposed by changes in metabolic rate and overall energy expenditure which can make the achievement and maintenance of weight loss progressively harder. You arrange to measure her resting metabolic rate principally to demonstrate to her that it lies in the range expected for body composition, age, and sex. You explain how SPA may lessen over time in people who are losing weight and discuss ways of maintaining this, for example, walking to the shops, taking stairs rather than escalators, and measuring the number of daily footsteps with a pedometer. You also explain that periods of weight maintenance are perfectly logical (and successful) as part of a long-term program of weight control and may permit the body to acclimatize and form a new set point—the only outcome that represents failure is to give up and regain any weight lost. She finds sufficient motivation in these concepts to re-energize herself in her weight loss goals.

Case study 2

LW, an obese 58-year-old man, has been very gradually but successfully reducing his weight with your support over the past year. However, his weight loss trajectory has stopped over the past month and he has begun to regain weight.

Comment: You enquire about changes in his circumstances and discover that his primary care physician recently started him on a beta-blocker following possible, although incompletely ascertained, intolerance of first-line drug therapy for his hypertension. You explain that beta-blockers inhibit the actions of the SNS. This could affect his overall energy balance in several ways, including reduced lipolysis (and possibly therefore reduced futile cycling of fatty acids between free and esterified forms) and reductions in thermogenesis, SPA, and in overall metabolic rate. Furthermore, beta-blockers may also reduce exercise capacity and cause fatigue, all of which may counter attempted weight loss. Although the magnitude of these effects is small (typically 1–2 kg, 2.2–4.4 lb), it is possible that some individuals may be affected more than this. Older “non-selective” beta-blockers appear to be more problematic than newer “cardioselective” agents. On discussing this, together with possible adverse effects on insulin sensitivity, you agree to try an angiotensin receptor blocking agent.

Introduction

In most individuals, body weight remains relatively stable over years to decades despite wide variations in energy intake and expenditure. This would seem to suggest that body weight is rigorously defended by homeostatic

mechanisms. However, whilst a useful defense against the development of obesity, any tendency to defend a set point once obesity is established may act as a barrier to the achievement and maintenance of planned weight loss.

Many individuals seeking professional help in relation to their own obesity become confused or frustrated by what appears to be inability to lose weight (or a tendency to gain weight) despite behaviors that might appear no less healthy than other individuals who do not appear to have a weight problem. Some will have developed counterproductive health beliefs that may act as barriers to weight loss (e.g., that they must have a slow metabolism and that this is genetically programmed or is the result of some undiagnosed metabolic disorder and therefore beyond their control). These misunderstandings can rapidly evolve into a sense of “learned helplessness” and all too often result in disengagement and failure to achieve goals.

Clear and accurate explanations of the complexities of energy balance regulation are often of practical help, particularly where such frustration or despondency exists.

Basic concepts and principles in human energetics

Energy balance and laws of thermodynamics

According to the *first law of thermodynamics*,

Energy intake = Energy expenditure + Change (Δ) in energy stores

The chemical energy obtained from food is used to perform a variety of work, such as

- synthesis of new macromolecules (*chemical work*)
- muscular contraction (*mechanical work*)
- maintenance of ionic gradients across membranes (*electrical work*)

Thus, if the total energy contained in the body (in the form of fat, protein, and glycogen) of a given individual is not altered (i.e., Δ energy stores = 0), then energy expenditure must be equal to energy intake and the individual is said to be in a state of *energy balance*.

If the intake and expenditure of energy are not equal, then a change in body energy content will occur, with *negative energy balance* resulting in the degradation of the body's energy stores (glycogen, fat, and protein) or *positive energy balance* resulting in an increase in body energy stores, primarily as fat.

The *second law of thermodynamics* makes a distinction between the potential energy of food, useful work, and heat. It states essentially that

Energy expenditure = Work done + Heat generated

and describes the fact that when food is utilized in the body, these processes must be accompanied inevitably by some loss of heat. In other words, the conversion of available food energy is not a perfectly efficient process: about

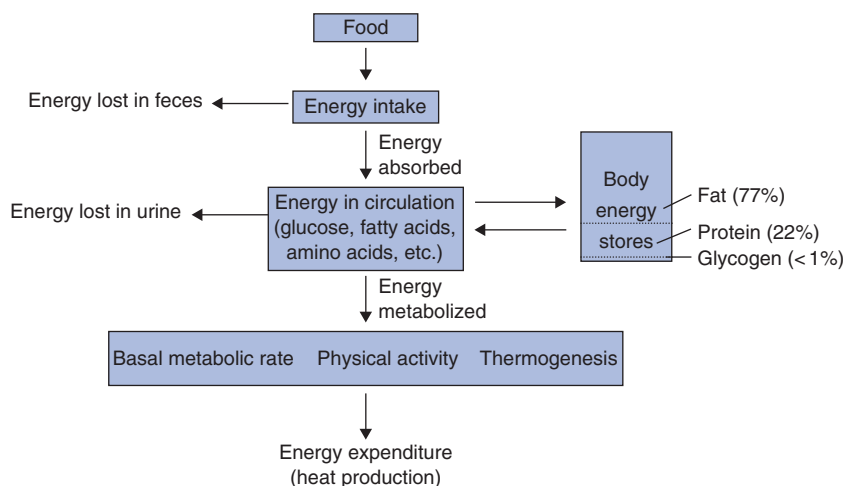


Figure 1.1 Principles of energy balance within a schematic framework that depicts the transformation of energy from food to heat throughout the body. Note that on diets typically consumed in developed countries, the total energy losses in feces and urine are small (about 5%) so that the metabolizable energy available from these diets is around 95%. Reproduced from Kopelman *et al.* (eds). *Clinical Obesity in Adults and Children*, 3rd edn, Blackwell Publishing, Oxford, 2010, with permission from Blackwell Publishing.

75% of the chemical energy contained in foods may be ultimately dissipated as heat because of the inefficiency of intermediary metabolism. The energy “wasted” as heat may be calculated as the sum of BMR and adaptive thermogenesis. Adaptive thermogenesis refers to the increase in resting energy expenditure in response to stimuli such as food intake, cold, stress, and drugs.

Components of energy expenditure

It is customary to consider human energy expenditure as being made up of three components:

- Energy spent on basal metabolism (BMR)
- Energy spent on physical activity (work done plus exercise- or non-exercise-associated thermogenesis)
- The increase in resting energy expenditure in response to stimuli such as food, cold, stress, and drugs (adaptive thermogenesis).

These three components are depicted in Figure 1.1 and are described in the following text.

Basal (or resting) metabolic rate (BMR)

This is the largest component of energy expenditure for most individuals. Typically, BMR accounts for 60–75% of daily energy expenditure. It is

measured under standardized conditions, that is, in an awake subject lying in the supine position, in a state of physical and mental rest in a comfortable warm environment, and in the morning in the post-absorptive state, usually 10–12 h after the last meal.

By far the most important determinant of BMR is body size, in particular lean (fat-free) body mass which is influenced by weight, height, age, and gender. Lean body mass is increased in obese individuals, although to a lesser extent than fat mass. This means that, counter to many obese subject's expectations, their BMR is almost certainly higher than that of their lean counterparts, and a low BMR is, with the debatable exception of hypothyroidism, virtually never a direct cause of obesity. On the contrary, a higher BMR in obese subjects tends to oppose further weight gain, although its fall with weight loss may act as a barrier to successful weight management.

Measurement of BMR by indirect calorimetry is a non-invasive test used in a number of obesity clinics often as a means of demonstrating to an individual that their BMR lies within the range expected for body composition, age, and sex.

In addition to increasing BMR, there appears to be a decrease in metabolic efficiency in obese subjects, which also acts to favor a return to the previous "set point." Subjects made under experimental conditions to maintain body weight at a level 10% above their initial body weight show a compensatory change in resting energy expenditure (approximately 15%), which reflects changes in metabolic efficiency that oppose the maintenance of a body weight that is above or below the set or preferred body weight.

Energy expenditure due to physical activity

Physical activity can represent up to 70% of daily energy expenditure in an individual involved in heavy manual work or competition athletics, although values of 10–25% are more usual in modern Westernized civilizations.

Energy expended in physical activity may be thought of as being spent either on deliberate "exercise" or on all other "non-exercise" activities. Non-exercise activities may be deliberate and consciously modifiable (e.g., daily tasks such as work, shopping, cooking), may be related to posture and balance, or may be involuntary purposeless movements (e.g., fidgeting, movements during sleep), the latter being termed spontaneous physical activity (SPA). The energy dissipated as heat through such forms of "non-exercise" activities is called non-exercise activity thermogenesis (NEAT).

Levels of SPA are regulated in part by the SNS. Losses in body weight are accompanied by a major reduction in SPA, which can persist for several months after weight recovery and favor disproportionate recovery of fat mass. Twenty-four-hour energy expenditure attributed to SPA may vary

between 100 and 700kcal/day between individuals and can predict subsequent weight gain after a period of caloric restriction. In one study, more than 60% of the increase in total daily energy expenditure in response to overfeeding could be attributed to SPA, variability of which was the best predictor of individual weight gain.

Other components of NEAT also differ between obese and lean individuals. One study showed that obese participants were seated, on average, for 2 h longer per day than lean participants. This difference (corresponding to about 350kcal/day) was not altered after weight gain in lean individuals or weight loss in obese individuals, suggesting that it might be biologically determined. Increased skeletal muscle work efficiency after experimentally induced weight loss has also been reported.

It seems likely that such mechanisms form a barrier to the effectiveness of planned weight loss regimens and are subject to as yet largely unknown genetic influences.

Energy expenditure in response to various thermogenic stimuli

Exertion, whether as exercise or as NEAT, generates heat as a by-product and contributes to thermogenesis. However, several non-exertional thermogenic stimuli with relevance to body weight regulation also exist. These include the following.

Diet-induced thermogenesis or the “thermic effect of food”

The thermic effect of food refers to heat production due to the mechanical and chemical consequences of food ingestion. This process dissipates some 7–9% of the energy content of a typical mixed meal and is affected by meal size, meal composition, meal frequency, thermogenic ingredients such as caffeine, and the individual subject’s insulin sensitivity.

Psychological thermogenesis

Psychological thermogenesis refers to heat dissipation over baseline in response to states such as anxiety or stress. Thermogenesis in this setting may depend on both changes in physical activity (e.g., SPA) and via central (e.g., endocrine) mechanisms.

Cold-induced thermogenesis

Energy is spent on maintaining temperature homeostasis through “shivering” (muscular activity) and “non-shivering” (SNS activity, partly via BAT) responses to cold. The extent to which maintenance of warm environments through modern central heating may contribute to obesity is at present unknown, although average temperature settings continue to rise steadily and there is some evidence that a lack of need to respond to “mild thermogenic stress” may lead to a long-term loss of BAT.

Drug-induced thermogenesis

Caffeine, alcohol, nicotine, and other prescription or “recreational” drugs may stimulate the dissipation of energy as heat. Of these, the most clinically relevant is probably the effect of smoking cessation on body weight with some 7 kg (15.4 lb) weight gained on average, partly through changes in food intake and partly through a reduction in thermogenesis. Discouraging the abuse of tobacco for weight control purposes remains a considerable practical challenge for clinicians.

Mechanisms of thermogenesis

The SNS, through its neurotransmitter norepinephrine (NE), acts via α - and β -adrenoceptors to influence heat production by either increasing the use of ATP (e.g., ion pumping and substrate cycling) or by reducing the efficiency of ATP synthesis. These actions induce metabolic inefficiency, which has the potential to oppose any change from the body weight set point.

The recent realization that brown fat exists in adult humans has rekindled interest in pharmacologic activation of BAT in anti-obesity therapy.

Leptin is a cytokine whose principal role is thought to be to defend minimum fat stores in the longer term. As fat stores fall, leptin levels also fall, with the net result being that of reduced thermogenesis and increased metabolic efficiency. This action is an example of a “lipostatic” model of weight defense: the set point is for body fat stores, and homeostatic regulation (e.g., by leptin pathways) acts to defend this set point (Box 1.1).

Inter-individual variability in metabolic adaptation

A striking feature of virtually all experiments of human overfeeding (lasting from a few weeks to a few months) is the wide range of individual variability in the amount of weight gain per unit of excess energy consumed. Some of

Box 1.1 Leptin effects on thermogenesis.

- Diminished skeletal muscle work efficiency
- Increased SPA
- Thermogenic action of leptin via the SNS on BAT and skeletal muscle
- Central effects on SPA-associated thermogenesis
- Regulation of reward signals, motivated behaviors that influence appetite, and locomotor activity
- Direct action on skeletal muscle, possibly through stimulation of “futile” substrate cycling between *de novo* lipogenesis and lipid oxidation

these differences in the efficiency of weight gain could be attributed to inter-individual variability in the gain of lean tissue relative to fat tissue (i.e., variability in the composition of weight gain), but mostly lie in the ability to convert excess calories to heat, that is, in the large inter-individual capacity for diet-induced (and other forms of adaptive) thermogenesis.

Over- and under-feeding experiments suggest that in addition to the control of food intake, changes in the composition of weight (via partitioning between lean and fat tissues) and in metabolic efficiency (via adaptive thermogenesis) both play an important role in the regulation of body weight and body composition. Evidence from identical-twin studies suggests that the magnitude of these adaptive changes is strongly influenced by the genetic makeup of the individual.

Current evidence suggests the existence of two distinct but overlapping control systems underlying adaptive thermogenesis.

One control system responds rapidly to attenuate the impact of changes in food intake on changes in body weight through alterations in the activity of the SNS which is suppressed during starvation and increased during overfeeding.

The other control system, exemplified by leptin, has a slower time-constant since it operates as a feedback loop between the size of the fat stores and thermogenesis. Its suppression during weight (and fat) losses serves to restore body fat to its set or preferred level.

These autoregulatory control systems operating through adjustments in heat production or thermogenesis play a crucial role in attenuating and correcting deviations of body weight from its set or preferred value. The extent to which these adjustments through adaptive thermogenesis are brought about is dependent upon the environment (e.g., diet composition) and is highly variable from one individual to another. In societies where food is plentiful all year round and physical activity demands are low, the resultant subtle variations among individuals in adaptive thermogenesis can, in dynamic systems and over the long term, be important in determining long-term constancy of body weight in some and in provoking the drift toward obesity in others.

Pitfalls

- Significant weight loss is followed by metabolic adaptation which tends to oppose it. This includes reduced SPA, increased metabolic efficiency, reduced resting metabolic rate, and increased skeletal work efficiency. Losing weight in the short term is often achievable with relative ease. Difficulties presented by defense of a set point are a common reason for failure to maintain weight loss in the longer term, and explanations may help keep the patient engaged.
- Metabolic rate is higher in the obese and correlates best with lean body mass which is also higher in them. However, many obese people consider that they have an

undiagnosed metabolic problem and may lose confidence if this belief is not sympathetically addressed.

- Energy may be spent by increasing NEAT, for example, taking stairs, not using a car to travel short distances, cycling to work, and so on.
- Periods of weight maintenance may be an effective strategy to permit adaptation to a newly reduced body weight and is certainly better than giving up. The only completely failed weight loss episode is one where weight is initially lost but regained after despondency sets in, the episode concluding with acquisition of a new weight higher than that at the start.
- Not exploring a patient's belief that because they find weight loss harder than others, they are unable to do it. There is no doubt that some people and some lifestyles do present challenges, but they can be overcome.
- Diets that are difficult to digest, require energy to obtain and chew, and that are low in calorie density may help with weight loss. Compare, for example, walking to a market to buy fresh carrots or growing one's own (and perhaps eating them raw) with snacking on crisps or biscuits kept in the house.
- Not appreciating sympathetically the degree to which the thermogenic and appetite-reducing effects of tobacco consumption may be used by some patients as an adjunct to weight control.

Key web links

Weight Control Information Network (National Institute of Diabetes and Digestive and Kidney Diseases). <http://win.niddk.nih.gov/resources/> [accessed on December 29, 2012].

Association for the Study of Obesity. <http://www.aso.org.uk/> [accessed on December 29, 2012].

National Institutes of Health. <http://health.nih.gov/topic/Obesity> [accessed on December 29, 2012].

Further reading

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