

Energy balance in obesity

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The current epidemic of human obesity implies that whilst energy balance appears to be regulated, the extent of this regulatory process is being overwhelmed in large numbers of the population by environmental changes. Clearly, the shift towards positive energy balance reflects both alterations in energy intake and decreases in physical activity. Increased energy intake and, in particular, the rising proportion of energy from fat is linked with obesity. However, on a population level reduced levels of activity probably play the predominant role. It is apparent that individual susceptibility to weight gain varies enormously. The factors underlying this susceptibility are an area of intense research interest. Variations in BMR from that predicted appear to be linked to the propensity to gain weight. The genes responsible for this variation may include uncoupling proteins-2 and -3, with a number of studies showing a link with obesity. However, *in vivo* studies of these proteins have not yet demonstrated a physiological role for them that would explain the link with obesity. Non-exercise activity thermogenesis may also protect from weight gain, but the regulation of this type of thermogenesis is unclear, although the sympathetic nervous system may be important. A profusion of hormones, cytokines and neurotransmitters is involved in regulating energy intake, but whilst mutations in leptin and the melanocortin-3 receptor are responsible for rare monogenic forms of obesity, their wider role in common polygenic obesity is not known. Much current work is directed at examining the interplay between genetic background and environmental factors, in particular diet, that both lead to positive energy balance and seem to make it so hard for many obese subjects to lose weight.

Obesity: Energy balance: Underfeeding: Overfeeding: Genetic susceptibility

The growing incidence of obesity and the reasons why some individuals appear to gain weight so easily is a much-debated topic. When asked about why they are obese, many obese subjects will say that it is something to do with their genes, or that they must have an abnormal metabolism. However, most scientific research clearly demonstrates the importance of the environment, in particular the dominant contributions of food intake and physical inactivity to weight gain (French *et al.* 2001). It is now clear that the responses, in terms of weight changes, to the alterations in the environment are highly variable both between individuals and between different racial groups. Some individuals appear much more susceptible than others to weight gain. Whatever the causes of obesity and of maintenance of the obese state, there is no doubt that the majority of obese subjects find it very difficult to lose weight and even more challenging to keep off any weight that they are able to lose.

Environmental factors and energy balance

The current epidemic of human obesity implies that whilst energy balance appears to be regulated, the extent of this regulatory process is being overwhelmed in large numbers of the population by environmental changes. This shift towards positive energy balance reflects both alterations in energy intake and decreases in physical activity. A number of environmental factors have been identified as favouring weight gain in the population (French *et al.* 2001). In terms of the factors promoting energy intake these include the large diversity, high palatability and widespread availability of food, snacking rather than meal eating, fast rates of eating, high-energy-density diets (i.e. high-fat diet) and eating outside the home. On the activity front, increased television watching (giving rise to both reduced activity and being exposed to the pressure of food advertising), technological developments (e.g. washing machines, improved heating within the home), reduced physical

Abbreviation: REE, resting energy expenditure.

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activity level and urbanisation (with less need to walk) all contribute.

There is debate about the relative importance of changes in activity and diet. Parallels have been drawn between indices of inactivity (car ownership and the number of hours spent watching television) and the increasing prevalence of obesity in the UK, and the lack of such relationships when it comes to energy intake (Prentice & Jebb, 1995). However, the accuracy of food survey data has been called into question, with snacking in particular being underreported (Poppitt *et al.* 1998). The close relationship between obesity rates and increased energy intake and the proportion of energy from fat supports a major role for dietary changes (Bolton-Smith & Woodward, 1994). In addition, in experimental settings covert manipulation of the diet leading to varied fat content leads to a positive energy balance when higher proportions of fat are introduced into the diet (Stubbs *et al.* 1995).

The activity levels of the population have decreased dramatically over the last century. One study in Australia used triaxial accelerometers to compare activity in a group of sedentary office workers compared with actors in a theme park playing the role of early settlers to Australia (Egger *et al.* 2001). Those in the historical group were at least twice as active as the office workers, and this difference in activity accounted for the equivalent of walking up to 16 km more each day.

Reduced activity energy expenditure may account for the majority of weight gain in many subjects. Free-living energy expenditure measured using doubly-labelled water was compared in women successful and unsuccessful (>10% weight gain) in maintaining a normal body weight over 1 year (Weinsier *et al.* 2002). No differences were found between the groups in terms of sleeping energy expenditure or substrate utilisation, but those who gained weight had much lower activity levels. Lower activity energy expenditure accounted for 77% of the weight gain, without having to look further into genetic variations in resting energy expenditure (REE), substrate utilisation or the energy costs of activity.

How well regulated is body weight?

The current epidemic of obesity appears to demonstrate a lack of regulatory processes when it comes to human body weight. However, body weight does not appear to vary that much in most subjects, at least over short time periods. Over longer periods more marked variations occur. The average fluctuation in body weight over 18 years in men participating in the Framingham study was 10 kg (Lissner *et al.* 1991). The content of weight loss or gain is on average 75% fat and 25% lean tissue (Heitmann & Garby, 2002). The energy content of body fat is approximately 36 MJ/kg, whilst fat-free mass (a large amount of which is muscle) contains only 4.2 MJ/kg; protein and carbohydrate represent only about 16.7 kJ/g and are stored in association with water, so further reducing the energy density. The energy density of this weight is thus approximately 29 MJ/kg. Energy stores therefore vary by about 290 MJ over this time period in the average person. A system that allows an error in energy balance of 290 MJ, or the energy intake for about

1 month, is not very precise. On the other hand, over 18 years the average participant in the Framingham study had an energy intake of about 62 700 MJ, so an error of 290 MJ is <0.5% of the turnover, which in many contexts would be described as precise regulation.

An individual weighing 70 kg with a BMI of 22 kg/m² would need to gain 25 kg to reach a BMI of 30 kg/m². Of this gain, approximately 18.8 kg will be fat and 6.2 kg fat-free mass, giving a total energy gain of >732 MJ. If energy intake exceeded expenditure by 836 kJ/d, it would take 2.5 years for this weight gain to occur. In most cases of obesity developing in adulthood the rate of weight gain is much slower, thus small inaccuracies in day-to-day energy balance can have large long-term repercussions.

In many individuals it is perhaps surprising that fairly stable weights are maintained, given the environmental stresses on the system. This stability is achieved through control of food intake and REE, and through voluntary or involuntary effects on physical activity. Obesity develops when one or more of these controls are ineffective. In animals hypothalamic control of energy intake and expenditure is of major importance in weight regulation and it may also play a role in man. That some individuals do not put on even more weight than they do already, given current energy intakes and expenditure levels, may indicate the presence of other regulatory mechanisms. Only a small proportion of the excess ingested energy is stored. One reason for this small proportion is that not all the excess weight is stored as triacylglycerol. Both intra- and extracellular fluid content also increases, and muscle mass increases to support the increase in body weight. However, the relatively small weight gains observed, in the presence of a large excess of intake over expenditure, suggests the existence of increased metabolic inefficiency. This topic has been further studied using underfeeding and overfeeding paradigms, and examining the metabolic predictors of weight gain.

Predictors of susceptibility to weight gain

It is apparent that individual susceptibility to weight gain varies enormously. The factors underlying this susceptibility are an area of intense research interest. Variations in BMR from that predicted appear to be linked to the propensity to gain weight (Ravussin *et al.* 1988). Relatively low rates of fat oxidation may also predispose to weight gain, with those individuals with a high RQ having a 2.5-fold increased risk of weight gain (Zurlo *et al.* 1990).

Underfeeding studies

Whilst many obese subjects are able to lose some weight, at least in the short term, most obese subjects find it hard to sustain such weight loss. Underfeeding studies have helped to characterise the metabolic changes that accompany dietary restriction and weight loss and that appear to predispose to relapse. There appear to be three components to the observed decrease in energy expenditure during underfeeding (Leibel *et al.* 1995). Since energy intake is reduced, dietary-induced thermogenesis falls (it normally approximates to 10% of the energy intake). The decrease in metabolic rate is also related to the weight of metabolically-active tissue lost (about

42 kJ/d per kg body weight lost). There is also a variable adaptive decrease in metabolic rate (5–8%). Thus, if a subject is able to reduce their weight from 100 to 70 kg (30% weight reduction) it is expected that there will be a 15% reduction in their energy requirements for weight maintenance.

A further indication of the magnitude of the changes seen in energy expenditure during weight loss comes from studies by Doucet *et al.* (2001). Thirty-five obese subjects underwent a 15-week weight-loss programme. At baseline their predicted energy expenditure (based on their measured body composition and on regression equations derived from a local population) did not differ from their measured energy expenditure. After weight loss their REE fell by about 500 kJ/d more than that predicted from changes in their body composition. These changes were maintained even during a period of weight stability at the end of the intervention.

The adaptations seen during underfeeding may be secondary to alterations in sympathetic nervous system activity and also to changes in leptin. Urinary noradrenaline excretion falls during and after weight loss and increases during and after weight gain (Rosenbaum *et al.* 2000). Leptin concentrations fall during a weight-loss programme and are closely related to falls in REE and fat oxidation (Doucet *et al.* 2000). In animal models leptin secretion and sympathetic activity are linked, although this relationship has not been demonstrated as clearly in man. In addition, the low fat oxidation rates and low leptin concentrations seen in post-obese individuals are likely to predispose to weight relapse (Filozof *et al.* 2000).

Overfeeding studies

Weight gain is associated with increases in energy expenditure due to increases in dietary-induced thermogenesis and in the metabolic costs incurred, associated with the synthesis of glycogen, protein and fat in the tissues deposited. In response to experimental weight gain these changes are greater than those predicted for the body composition changes, indicating presumed metabolic adaptations that may oppose further weight changes. These adaptations may be mediated by the sympathetic nervous system (Rosenbaum *et al.* 2000). Eventually, with weight gain a new equilibrium will occur. For example, if intake is increased by 836 kJ/d, with weight gain and changes in thermogenesis a new equilibrium will occur after about a 12 kg weight gain (energy requirements for weight maintenance change by about 58 kJ/d per kg weight change; Leibel *et al.* 1995).

There is great variability in both weight gain and the metabolic response to weight gain during overfeeding. Studies with twins illustrate the importance of genetic factors in this variation (Bouchard *et al.* 1990). Twelve pairs of monozygotic twins were overfed by 4.2 MJ/d for 100 d. Weight gain on this regimen varied from 4 to 13 kg, and within-pair variation was small compared with that observed between pairs. On average 220 MJ was gained as fat, 11 MJ as fat-free mass and 121 MJ (35% of the extra energy) was dissipated in some way. In the subject gaining the most weight (13 kg) most of the excess was retained as fat tissue.

More recent work has tried to identify the causes of the variability in the response to overfeeding. One candidate for

this variability is non-exercise activity thermogenesis, which has been described as the thermogenesis accompanying physical activities other than volitional exercise, such as activities of daily living, fidgeting, spontaneous muscle contractions and maintaining posture (Levine *et al.* 1999). During overfeeding by about 4.2 MJ/d for 8 weeks, it was found that non-exercise activity thermogenesis (derived from measurements of total energy expenditure by the doubly-labelled-water method and from measurements of REE and dietary-induced thermogenesis using indirect calorimetry) accounted for the 10-fold differences in fat storage that occurred during the study. A subsequent study found that the thermogenic potential of fidgeting-like activities was sufficiently great to contribute to energy balance (Levine *et al.* 2000). The regulation of this type of thermogenesis remains unclear, although the sympathetic nervous system may be important (Van Itallie, 2001).

Outside the controlled world of metabolic overfeeding studies there also appear to be adaptive changes that accompany long-term weight changes. A 4-year retrospective analysis of 102 Pima Indians aged between 18 and 50 years was carried out with measurements made of daily energy expenditure and RQ, body weight and body composition (Weyer *et al.* 2000). A 15 kg weight gain over this time period was associated with an increase in total energy expenditure of 1020 kJ. When this data is compared with cross-sectional data on 24 h energy expenditure and body weight, an 882 kJ change is seen for a 15 kg change in weight. Thus, the 'adaptation' against further weight gain is 138 kJ/d. For a change in fat oxidation the increase seen for a 15 kg weight gain was 222 kJ greater than that predicted from cross-sectional data. Adaptations in energy expenditure and fat oxidation to resist weight gain are present, but are relatively weak and easy to offset by increases in energy intake.

Susceptibility to weight gain

One clear message from all the studies that have examined the influence of environmental changes on body weight is the importance of inter-individual variation. With underfeeding there are larger falls in energy expenditure (greater than those predicted from changes in body composition) in some obese subjects compared with others, potentially giving continued susceptibility to weight gain. The genes and gene–environment interactions governing this susceptibility are gradually being elucidated. However, in many cases the relationship between the genetic polymorphisms identified as occurring at a higher prevalence in those individuals with obesity and with a physiological alteration leading to obesity is not well worked out.

For the majority of cases of human obesity single gene mutations on their own seem unlikely to be the answer. Studies need to look at several genes, together with the environment in which they operate. For example, the Pima Indians in Arizona have high incidences of obesity and have low levels of physical activity and access to the whole range of foods available in the USA. In contrast, a genetically almost identical Pima Indian population in Mexico is predominantly non-obese. This latter population comprises subsistence farmers, with a bland diet and high levels of physical activity (Ravussin *et al.* 1994). Pima Indians

clearly develop obesity when presented with an environment in which physical activity is low and high-fat and energy-dense foods are readily available. Within this environment they develop obesity at a much higher rate than white Caucasians with a similar lifestyle. Studies in this group of Pima Indians and in other obese cohorts are attempting to identify genetic polymorphisms that are associated with the development of obesity in such an environment.

Much initial interest centred on genes related to the effector part of the sympathetic nervous system. Thus, it is known that low REE predisposes to weight gain (Ravussin *et al.* 1988), and that the sympathetic nervous system has an important part to play in energy expenditure. A number of mutations in β -adrenoceptors, particularly the β_3 -adrenoceptor, have been identified as being associated with obesity in population studies, but these findings have not always been replicated (Arner & Hoffstedt, 1999).

Low rates of energy expenditure have also been linked with uncoupling protein polymorphisms (Walder *et al.* 1998). A number of studies have linked polymorphisms of uncoupling protein-2 and -3 with obesity, but at present *in vivo* studies of these proteins have not demonstrated a physiological role for them that would explain this link. At this time it seems that in man uncoupling protein-3 is more likely to have a role in fat oxidation than in energy expenditure (Dulloo *et al.* 2001). The connection between such findings and the observed low rates of fat oxidation in some subjects susceptible to weight gain (Zurlo *et al.* 1990) and weight regain (Filozof *et al.* 2000) is not known.

A profusion of hormones, cytokines and neurotransmitters is involved in regulating energy intake in animals and genetic variations in some of these systems may be important in human appetite regulation (e.g. leptin, neuropeptide-Y, melanocortin-4 receptor polymorphisms; Froguel & Boutin, 2001). Indeed, the rare cases so far discovered of monogenic human obesity all relate to abnormalities of energy intake rather than of energy expenditure. Mutations in the leptin gene are associated with severe early-onset obesity in man, mainly attributable to hyperphagia (Montague *et al.* 1997). There is a dramatic response to recombinant leptin treatment in terms of reducing intake and causing weight loss (Farooqi *et al.* 1999). However, the wider role of leptin in common polygenic obesity remains to be clarified. Mutations in the melanocortin-4 receptor appear to account for up to 5% of childhood-onset morbid obesity (Barsh *et al.* 2000), but again there is uncertainty about the wider applicability of this finding.

Conclusions

At present, environmental factors are leading to a positive energy balance in large numbers of the population. Individual variations in the responses to the changed environment indicate the presence of underlying susceptibility factors. A number of candidate genes are being identified, which should enable early identification of susceptible individuals, with the targeting of preventive measures and the possible development of therapeutic approaches. The interplay between genetic background and the environmental factors that lead to positive energy

balance and seem to make it so hard for many obese subjects to lose weight is an important area for future studies.

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