Energy balance and weight regulation: genetics versus environment

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The prevalence of obesity is reaching epidemic proportions in many industrialized countries. There is growing evidence that, even if the trigger of this epidemic is found in changes in the environment, genes are interacting with the environment to cause weight gain. Studies of twins reared apart indicate that approximately two-thirds of the variability in BMI is attributed to genetic factors. From prospective studies in Pima Indians we can ascribe 12% of the variability in BMI to metabolic rate, 5% to fat oxidation, and another probable 10% to the level of spontaneous physical activity. These data indicate that at least 40% of the variability in BMI is related to genetic factors involved in the regulation of food intake and/or volitional activity. This indicates that the most likely successful therapy for obesity may target pathways of the regulation of food intake. Similarly, an environment favouring engagement in physical activity should be promoted.


Throughout the world, in parallel with industrialization, the prevalence of obesity is increasing dramatically. It is estimated that one in two Americans is overweight or obese (Flegal et al. 1998). Between the late 1970s and the early 1990s, the prevalence of overweight subjects (BMI > 25.0 kg/m²) increased moderately from 46 to 54% in the USA. However, during the same period the prevalence of obesity (BMI > 30.0 kg/m²) increased from 14.5 to 22.5%. The economic burden of obesity was estimated at US$99 billion in 1995, including US$52 billion in direct medical costs (Wolf & Colditz, 1998).

Obesity results from a chronic disruption of energy balance. The energy balance equation states that energy stores are a reflection of the difference between energy intake and energy expenditure. Energy intake consists of food and drink consumption. Total energy expenditure can be divided into three major components: resting metabolic rate, thermic effect of food, and the energy cost of physical activity. While food intake has been difficult to measure in humans (Lichtman et al. 1992), all components of energy expenditure can be measured accurately in a respiratory chamber (Ravussin et al. 1986) and free-living physical activity can be assessed by using the doubly labelled water technique (Schoeller & Field, 1991).

Although the pathogenesis of obesity is not completely understood (Ravussin & Swinburn, 1992; Rosenbaum et al. 1997), in most cases excessive accumulation of fat is probably due to the interaction between genetic factors and environmental conditions. Studies of energy intake and expenditure in humans have shown that obesity is not only the result of bad behaviour, or so-called ‘sloth and gluttony’. In most cases inherited metabolic characteristics, combined with unfavourable environmental conditions such as constant access to energy-dense food and minimal physical demands of daily living, cause the development of obesity. We have previously described our present westernized environment as a ‘pathoenvironment’ (Ravussin, 1995), whereas Egger & Swinburn (1997) have introduced the concept of an ‘obesigenic environment’. This provocative concept seems to call for a cure of the environment rather than the people living in it. However, even in this environment, so favourable to weight gain, there are many people who do not gain weight, perhaps due to a constant struggle against their nature or because of a genetic make-up that is protective against obesity.

Genetics of obesity

Studies of adoptees and twins clearly indicate that a large part of the variability in body size and body composition is attributable to genetic factors (Bouchard, 1994). In contrast, migration studies indicate an important role of the environment. Taken together these studies suggest that among different populations the prevalence of obesity is largely determined by environmental factors. However, among individuals from the same population, living in a given environment, the variability in body size and body composition is mostly related to genetically determined response to that environment. Studies of twins reared apart indicate that approximately two-thirds of the variability in

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BMI can be attributed to genetic factors (Table 1, Fig. 1; Stunkard et al. 1990; Price & Gottesman, 1991; Allison et al. 1996). However, some have argued that the role of genes in determining BMI may be inflated in these studies, as the data were collected in developed countries where the environmental influences are likely to be consistent. Assuming that two-thirds of the variability in BMI is genetically determined, it is now important to determine how much of the genetic predisposition (or resistance) to obesity is related to energy metabolism (metabolic rate, spontaneous physical activity and fat oxidation) and how much is related to food intake.

**Metabolic predictors of weight gain**

The Pima Indians were studied in order to identify metabolic predictors of body weight gain and diabetes (Ravussin & Swinburn, 1993). In these prospective studies body composition was assessed by hydrodensitometry, and measurements of energy metabolism were performed after a minimum of 3 d on a weight-maintenance diet provided at a clinical research centre. Total energy expenditure, 24 h respiratory quotient (RQ) and spontaneous physical activity were all simultaneously measured in a respiratory chamber as described previously (Ravussin et al. 1986). In both men and women, total energy expenditure increases with body weight, although at any given weight the variability in energy expenditure is 500–700 kcal/d. After adjustment for differences in fat-free mass, fat mass, age and sex, most of the variance was found to aggregate in families, indicating a genetic determinant of metabolic rate. Furthermore, the variability in metabolic rate is associated with such biological factors as body temperature (Rising et al. 1995) and the activity of the sympathetic nervous system (Spraul et al. 1993). Most importantly, after adjustment for the above covariates a low relative metabolic rate was associated with body-weight gain over a 3–4-year period of follow-up. The inverse relationship between weight change and adjusted 24 h energy expenditure had a coefficient of determination ($R^2$) = 0.16 indicating that 16 % of the variability in weight change was related to the variability in metabolic rate. However, as described below, part of this 16 % may be related to variability in spontaneous physical activity. One can safely conclude that at least 12 % of the variability in weight is caused by the variability in metabolic rate. We have previously emphasized that only prospective studies can identify metabolic predictors of weight gain, since there is a normalization of these factors in response to the development of obesity. Obesity is the price to pay for re-establishing an equilibrium (Ravussin & Gautier, 1999).

The RQ is used to determine the relative amount of energy derived from carbohydrate and fat (Zurlo et al. 1990; Seidell et al. 1992). In studies of weight gain in Pima Indians over a period of 3 years, individuals with a high RQ were more likely to gain weight than those with a low RQ. The coefficient of determination of this relationship indicated that 5 % of the variability in weight gain was related to the variability in RQ, adjusted for energy balance and percentage body fat. Respiratory quotient was also found to be a familial trait, and is probably, like metabolic rate, genetically determined (Zurlo et al. 1990). As with metabolic rate, the RQ is also related to such biological factors as the activity of the sympathetic nervous system. Similar results of high RQ predicting weight gain were

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of pairs</th>
<th>Heritability ($h^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stunkard et al. (1990)</td>
<td>93</td>
<td>0.66f, 0.77m</td>
</tr>
<tr>
<td>Price &amp; Gottesman (1991)</td>
<td>34</td>
<td>0.61</td>
</tr>
<tr>
<td>Allison et al. (1996)</td>
<td></td>
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<tr>
<td>Finnish</td>
<td>17</td>
<td>0.65</td>
</tr>
<tr>
<td>Japanese</td>
<td>10</td>
<td>0.73</td>
</tr>
<tr>
<td>American</td>
<td>26</td>
<td>0.85</td>
</tr>
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Fig. 1. (a) Studies of monozygotic twins reared apart (see Table 1) indicate that approximately one-third of the variability in BMI is attributable to non-genetic factors and two-thirds to genetic factors. (b) Breakdown of the genetic part of the variability in BMI into effects of metabolic rate (MR), respiratory quotient (RQ), spontaneous physical activity (fidgeting) and hyperphagia. Values for MR, RQ and fidgeting were obtained from prospective studies conducted among the Pima Indians of Arizona.
obtained in older subjects (Seidell et al. 1992). In a dietary
type model of obesity, Pagliassotti et al. (1997) showed that,
when placed on a high-fat diet, obesity-prone rats had a
higher RQ than obesity-resistant rats. The authors observed
that a high RQ is the major link with increased energy intake
when animals are placed on a high-fat diet. Taken together,
these results indicate that metabolic rate and RQ are two
genetically determined traits which affect weight regulation
in Pima Indians and probably in other populations.

Another component of 24 h energy expenditure is the
energy cost of spontaneous physical activity which accounts for
8–15 % of daily energy expenditure (Ravussin et al.
1986). Some of the 24 h energy expenditure variability is
due to variability in the level of spontaneous physical activity
(Ravussin et al. 1986; Zurlo et al. 1992). Most
cross-sectional studies have shown a decrease in sponta-
aneous physical activity in obese subjects. In longitudinal
studies in Pima Indians, even in the confined environment of
a respiratory chamber, spontaneous physical activity is a
familial trait, and a low level of spontaneous physical activity was associated with subsequent weight gain in
males (Zurlo et al. 1992). Consistent with these data, a
recent overfeeding study found that a gain in fat mass was
inversely related to the level of spontaneous physical activity (Levine et al. 1999). The authors call this activity
non-exercise activity thermogenesis (NEAT).

Factors underlying variability in body weight

With the knowledge that approximately two-thirds of var-
ance in BMI is genetically determined (Table 1; the
remainder is due to ‘sloth and gluttony’), we can divide the
67 % into 12 % for metabolic rate, 5 % for RQ and an
estimated 10 % for spontaneous physical activity. This
leaves another 40 % related to factors not measured in
these studies, i.e. food intake. The latter has been very
difficult to measure in humans. One can use precise methods
in a laboratory setting, but results are not reflective of
everyday life, or crude methods under free-living conditions
that are not accurate enough. Therefore new techniques,
such as positron emission tomography or functional mag-
netic resonance imaging (MRI), will help to uncover the
genetic components underlying hyperphagia. In a recent
study (Tataranni et al. 1999) we showed that in healthy men
neuronal activity increases in the prefrontal cortex and
decreases in the hypothalamus, insular cortex, orbital frontal
cortex, thalamus and hippocampal formation, in response to
a single meal. Another study using functional MRI con-
firmed that lean subjects demonstrate an inhibition of
signals in the area of the paraventricular and ventromedial
nuclei of the hypothalamus (Matsuda et al. 1999). Impor-
tantly, these authors showed that this inhibitory response
was markedly attenuated and delayed in obese subjects
when compared with lean volunteers. Using PET scans,
one of our most recent studies raises the possibility that the
brain’s responses to a meal in pre-frontal areas (often
associated with the inhibition of inappropriate response
tendencies) and in limbic/paralimbic areas (commonly
associated with the regulation of emotions) may reflect
changes in the central autonomic network, which may be
different between obese and lean subjects (Gautier et al.
1999, unpublished results). Such techniques, applied to
post-obese subjects as well as patients suffering from
eating disorders, will help identify the neurological
pathways involved in hyperphagia, often found in obese
subjects.

The search for obesity genes

Over the past 5 years genetic linkage studies have focused
increasingly on complex traits such as obesity. Genome-
wide scans have been completed in Mexican Americans
(Comuzzie et al. 1997); Pima Indians (Hanson et al. 1998;
Norman et al. 1998); a diverse population of whites and
blacks (Lee et al. 1999); French Canadian families (Pérusse
et al. 1999); and French families (Hager et al. 1998). From
all these studies, major loci linked to obesity have been
found on chromosomes 2, 5, 10, 11 and 20. Those areas of
the genome will be studied further to possibly clone obesity
susceptibility genes.

The Québec group (Pérusse et al. 1999) provides an
annual update of the human obesity gene map. From
association and linkage studies, the authors claim that
putative loci affecting obesity-related phenotypes are
found on all except chromosome Y of the human genome.
It also seems that the number of genes and other markers
that have been associated or linked with human obesity is
increasing very rapidly, and now approaches 200.

With the upcoming partial publication of the Human
Genome, it is likely that our understanding of the genetic
basis and the identification of novel genes involved in obesity
will be greatly improved. New pathways in the etiology of
obesity will be uncovered, and in the more distant future
individual identification of genetic variants will be possible,
making individually targeted therapies available.

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