Mechanisms of weight gain in humans

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Introduction

Throughout evolution, animals and humans have developed redundant mechanisms that promote the accumulation of fat tissue during periods of “feast” to survive periods of “famine”. However, in the current “obesigenic” environment of readily available high fat foods and little need for physical activity, what once was an asset has become a liability. As a consequence, obesity has reached epidemic proportions in both industrialized countries and in urbanized populations around the world.

In the United States in the late 1990’s one out of 2 adult Americans were overweight or obese. More alarming, the prevalence of obesity is drastically increasing among children. The World Health Organization has identified obesity as one of the major emerging chronic diseases. Obesity increases the risk for a number of non-communicable diseases (i.e., type 2 diabetes, hypertension, dyslipidemias) and reduces life expectancy. In the United States alone, the annual cost of obesity to the public health system is estimated to be close to $100 billion. This represents between 5 and 10% of the US health care budget.

Heritability of Obesity

Numerous observations have shown that obesity aggregates in families. However, family members share genes as well as common dietary habits, cultural background and many other aspects of lifestyle. To assess the relative contributions of genes and environment to the interindividual variability of body mass index (BMI, kg/m²) studies have been conducted in twins, adoptees, and family members. The most convincing evidence that obesity is largely a genetic disease comes from studies of monozygotic twins reared apart. These studies are based on the assumption that when genetically identical individuals are separated at a young age and assigned randomly to different families, their shared environment is no larger than in the general population. Under these conditions the degree of correlation of the BMI between individuals represents an estimate of the heritability of obesity (heritability being defined as the proportion of between person phenotypic variance that is attributable to between person genotypic variance). Studies in populations of twins from Europe, Asia and the US indicate that as much as 60-70% of the intraindividual variability in BMI is determined by a common genetic background. In Pima Indians, a population with one of the highest reported prevalence rates of obesity, family studies confirmed this estimate.

Therefore, our studies concerning the mechanisms of weight gain in humans have been based on 2 main assumptions:

a) the variability in BMI among individuals from the same population who have uniform access to food and similar requirements for physical activity is largely determined by genes (Figure 1);

b) because obesity is the result of a chronic energy imbalance between energy intake and expenditure, it is likely that genes control both aspects of the energy balance equation, i.e., energy intake and energy expenditure (Figure 2).
Figure 1. Studies in twins, adoptees and family members indicate that approximately 70% of the interindividual variability in BMI is attributable to genetic factors.

Figure 2. Obesity is the results of a chronic imbalance between energy intake and energy expenditure. Obesity susceptibility genes and their interaction with the ‘obesogenic’ environment are likely to control both sides of the energy balance equation, i.e., energy intake and energy expenditure.
Metabolic Risk Factors of Weight Gain

The introduction of indirect calorimetry and the technological advancement of methodologies that measure respiratory gases to estimate energy expenditure have allowed an extensive understanding of the regulation of energy metabolism in humans. We have used indirect calorimetry to estimate resting (respiratory chamber) and total (doubly labeled water) energy expenditure and identify heritable metabolic risk factors of weight gain in Pima Indians, a population with a very high propensity for obesity and type 2 diabetes.

Metabolic rate

Resting metabolic rate (RMR), the amount of energy that the human body requires at rest, is largely determined by the size and composition of the metabolically active tissues in the body. RMR is a familial trait in Pimas as well as other populations. Because obesity is associated with high absolute metabolic rate, both in resting conditions and over 24-hours, it cannot be caused by a low absolute metabolic rate, as is often proposed. Many investigators have suggested that in the absence of a clear defect in energy expenditure in obese subjects, obesity can only be the result of excessive energy intake. However, the scatter around the regression line between metabolic rate and body size indicates that, at any given body size, individuals can have a “high”, “normal”, or “low” relative metabolic rate. This concept is expressed graphically in Figure 3. From our own studies in adult non-diabetic Pima Indians, we found that a low relative metabolic rate (resting and 24-hour) adjusted for differences in fat-free mass, fat-mass, age and sex was a risk factor for body weight gain.

After 4 years of follow-up, the risk of gaining 10 kg was approximately 8 times greater in subjects with the lowest RMR (lower tertile) than those with the highest RMR (higher tertile) (Figure 4).

Nevertheless, these results in Pimas need to be interpreted with caution. First, in our studies the variability of baseline energy expenditure accounted for only 15% of the variability of weight gain. Secondly, theoretical estimates suggest that only 30-40% of the increase in body energy stores in people who gained weight can be attributed to the baseline deficit in energy expenditure. Finally, relatively low energy expenditure does not seem to be a predictor of weight gain in other adult populations.

Respiratory quotient

The respiratory quotient is an index of the ratio of carbohydrate to fat oxidation. It ranges from a value of about 0.80 after an overnight fast when fat is the main oxidative substrate to values close to 1.00 after a large carbohydrate meal when glucose is the major

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Figure 3. Relationship between 24-h energy expenditure and fat-free mass derived from a large population. This figure represents values for different subjects. In terms of the absolute 24-h energy expenditure, lean person A has a low value while obese person B has a high value. In terms of relative 24-h energy expenditure, both A and B fall on the regression line and are normal. Subjects C and D are of similar body size, but C has a relatively low metabolic rate and subject D has a relatively high metabolic rate. Subject C is at the greatest risk of developing obesity, but upon gaining weight, the low relative metabolic rate becomes normalized (arrow).
In addition to the effect of diet composition, the respiratory quotient is also influenced by recent energy balance (negative balance increasing fat oxidation), sex (females tend to have reduced fat oxidation), adiposity (higher fat mass leads to higher fat oxidation), and family membership, suggesting genetic determinants.

Toubro et al. confirmed that substrate oxidation rates, measured by respiratory quotient, after adjustment for energy balance, sex, and age, exhibit familial aggregation. In a Prospective study in Pima Indians, a high 24-hour respiratory quotient predicted weight gain. Those in the 90th percentile for respiratory quotient (“low fat oxidizers”) had a 2.5 times greater risk of gaining 5 kg or more body weight than those in the 10th percentile (“high fat oxidizers”). This effect was independent of a relatively low or high 24-hour metabolic rate. However, respiratory quotient at baseline explained only 5-6% of the variability of subsequent weight gain. Similar results were found in Caucasian volunteers participating in the Baltimore Longitudinal Study on Aging. In support of these observations, others have demonstrated that post-obese volunteers have high respiratory quotients, i.e., low rates of fat oxidation, and those who are able to maintain weight loss have lower respiratory quotients compared to those experiencing weight relapse.

### Physical activity

Spontaneous physical activity (SPA), a component of 24-hour energy expenditure which accounts for 8-15% of total daily expenditure, has shown the highest degree of familiality among the metabolic risk factors identified in Pima Indians. Consistent with the cross-sectional observation of a decrease in SPA in obese subjects, our prospective studies showed that even in the confined environment of a respiratory chamber, low levels of SPA are associated with subsequent weight gain in males, but not in females. A recent study found that resistance to weight gain might be due to the ability of increasing SPA in response to overfeeding. Of course, prospective studies in which free-living physical activity is measured (doubly labeled water technique) are needed to objectively assess what most scientists believe, i.e., that a low level of physical activity is a major predisposing factor for weight gain in individuals and in populations.

### Relative Role of Energy Expenditure and Energy Intake

Our studies on the regulation of energy expenditure in Pima Indians have provided evidence that energy expenditure and nutrient partitioning play a role in the pathogenesis of weight gain.
human obesity. However, even if we use our less conservative estimates of the proportion of the interindividual variability of body weight gain that can be attributed to familial traits such as resting energy expenditure (10-15%), respiratory quotient (5%), and spontaneous physical activity (10%), we have to conclude that a large proportion of the genetic variance of BMI is due to the effect of genes on factors not measured in our studies, i.e., an inherited tendency to overeat (hyperphagia) and/or inherited tendency to inactivity in free-living conditions (Figure 5).

In contrast to animal models of obesity, it has been very difficult to study the molecular mechanisms and resulting behaviors that underlie excessive energy intake in humans. Nevertheless, the identification of severe hyperphagia in individuals with mutations of the leptin, leptin receptor, and MC4-receptor genes leaves little doubt that energy intake is as highly regulated at the molecular levels in humans as it is in animals. Furthermore, based on the results that have emerged from the recent use of new techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), it seems likely that the level of complexity of the neuroanatomical correlates of eating behavior in humans could be much higher than it is in rodents. Using PET, we have recently shown that in response to a single meal neuronal activity increases in the prefrontal cortex and decreases in the hypothalamus, thalamus, insular cortex, orbitofrontal cortex, and hippocampal formation in the brain of healthy men. An inhibition of neuronal activity in the hypothalamic region following a meal was confirmed in a second study using fMRI. Most importantly, preliminary data suggest that brain responses to a meal may be substantially different between lean and obese subjects. Such techniques applied to post-obese subjects as well as subjects suffering from eating disorders may help identify the neurological pathways responsible for hyperphagia and obesity.

Past difficulties in measuring habitual physical activity in humans have largely been alleviated by the advent of the doubly labeled water technique. Thus, in the near future it should be possible to better understand the interaction between the energy expended in daily physical activities and the development of obesity in children and adults.

A greater knowledge of the physiology of obesity will ultimately come from the current efforts to isolate the genes related to weight gain and its metabolic causes. Over the past five years, genetic linkage studies have increasingly focused on complex traits such as obesity. Genome-wide scans have been com-
pleted in Mexican Americans\textsuperscript{35}, in Pima Indians\textsuperscript{36,37}, in a diverse population of whites and blacks\textsuperscript{38}, in French-Canadian families\textsuperscript{39} and in French families\textsuperscript{40}. 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 are currently under intense investigation as they may lead to the cloning of obesity susceptibility genes.

**Conclusion**

Obesity is a chronic disease, which is quickly reaching epidemic proportions, and which increases the risk for other non-communicable diseases, thus reducing life expectancy. Obesity is heritable and genes controlling BMI are likely to do so by affecting both energy intake and energy expenditure. While the exact etiology of obesity remains unknown, our own studies suggest that a low RMR, a high RQ, and a low SPA explain very little of the heritability of obesity. Thus, our current conclusion is that an inherited hyperphagia (and/or an inherited tendency to inactivity) is a major cause of obesity in humans.

**References**


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