

Fat: an evolving issue

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Summary

Work on obesity is evolving, and obesity is a consequence of our evolutionary history. In the space of 50 years, we have become an obese species. The reasons why can be addressed at a number of different levels. These include separating between whether the primary cause lies on the food intake or energy expenditure side of the energy balance equation, and determining how genetic and environmental effects contribute to weight variation between individuals. Opinion on whether increased food intake or decreased energy expenditure drives the obesity epidemic is still divided, but recent evidence favours the idea that food intake, rather than altered expenditure, is most important. There is more of a consensus that genetics explains most (probably around 65%) of weight variation between individuals. Recent advances in genome-wide association studies have identified many polymorphisms that are linked to obesity, yet much of the genetic variance remains unexplained. Finding the causes of this unexplained variation will be an impetus of genetic and epigenetic research on obesity over the next decade. Many environmental factors – including gut microbiota, stress and endocrine disruptors – have been linked to the risk of developing obesity. A better understanding of gene-by-environment interactions will also be key to understanding obesity in the years to come.

Introduction

We are currently in the middle of a worldwide pandemic of obesity. By the latest available estimates (2010), there are ~700 million obese people worldwide, and another ~2 billion who are overweight, as defined by the WHO categories based on body mass index (BMI). For the first time in human history, there are more obese and overweight people on the planet than people suffering from malnutrition. In the space of just 50 years, we have become an obese species. Why? Generally, an answer to this question is normally given in terms of energy balance. We get fat because our intake of energy exceeds our expenditure – that is, the proximate cause of obesity is positive energy balance. This seems to be a consensus agreed by everyone within the field (Hall et al., 2012). In terms of an ultimate explanation, however, this really only moves the question to a different level. We all agree on the cause of obesity, but what is the reason that large numbers of us are in positive energy balance?

A question of balance: an evolving picture

Part of the answer to this question has revolved around which side of the equation contributes most to the imbalance. Opinion on this matter has been divided. In the 1970s and 1980s it was widely thought that the key issue was food intake. This was based on the simple fact that if the number of calories in food is compared with the number of calories burned by exercise, then it would seem much easier for a person to eat their way to excess body fatness than drive themselves into positive energy balance by becoming less active. However, during the 1990s, the tide turned. Several publications showed, using dietary questionnaires, that levels of food intake had in fact been effectively unchanged since the 1960s (Prentice and Jebb, 1995). If anything, they were actually declining. By contrast, the anecdotal evidence suggesting a decline in physical activity levels was overwhelming. Compared with life in the 1950s, life in the 1990s involved owning more cars, TVs and computers; we had invented automatic washing machines and vacuum cleaners; and we did our shopping in supermarkets rather than walking around multiple small local shops carrying shopping bags. By the mid-2000s, the idea that obesity was primarily due to lowered activity levels was dominant.

However, wrinkles in the argument began to appear. First, direct measures of energy expenditure using the doubly labelled water method showed that, since the 1980s, our expenditure has been stable (Westerterp and Speakman, 2008), despite the anecdotal ‘evidence’ to the contrary. Second, several studies showed that cross-sectional variation in activity did not necessarily predict subsequent variation in weight gain (Tataranni et al., 2003; Luke et al., 2009). Third, models of energy balance suggested that the change in obesity levels over the time course of the epidemic can be accounted for by increases in food supply (Swinburn et al., 2009). Fourth, it was shown that the tools used to quantify food intake (based on dietary questionnaires and subject recall) are prone to subjects misreporting their intake (Bandini et al., 1990; Black et al., 1993). Consequently, the data suggesting that intakes have not changed over time are not as robust as they first appeared. Therefore, the field is currently split, and papers on both sides of the argument are appearing regularly (e.g. Church et al., 2011; Hall et al., 2012).

One reason why individual differences in activity are not closely linked to obesity is because activity might stimulate appetite. Studies of this link have produced equivocal results, but those studies that observed people over longer periods of time tend to support the idea that exercise stimulates an increase in food intake. As Blundell and colleagues point out in this issue of *Disease Models & Mechanisms* (Blundell et al., 2012), this finding actually returns us to an idea from the 1950s that energy intake is regulated by energy demand. Of course, if increased expenditure stimulates food intake then, theoretically, excess intake might stimulate expenditure. The idea that individual differences in the efficiency of such a response might underpin our individual susceptibility to obesity on a background of generally elevated food intake has become popular. In particular, this idea is in line with the discovery of functionally

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active brown adipose tissue (BAT) in adult humans (Nedergaard et al., 2007) and the finding that differences in the levels of activity of BAT are inversely correlated with obesity levels (Cypess et al., 2009).

Evaluating environmental and genetic effects

Regardless of whether increased intake or reduced activity is the primary cause, the factors driving positive energy balance can be generally divided into genetic factors and environmental factors. The relative importance of these factors can be established by looking at studies of the heritability of obesity from parents to their offspring, and the similarity in body weight between monozygotic and dizygotic twins. The answers vary between different studies, but a consensus value is that ~65% of the variation in obesity is genetic (Segal and Allison, 2002), with the balance of the variance attributed to environmental factors. The actual numbers are probably less important than the recognition that both genes and the environment conspire to create obese people. Indeed, what is most important is the gene-by-environment interaction (Speakman et al., 2011).

Knowing that the cause of obesity has a large genetic component leads naturally to the question: which genes are involved? In the last 20 years, our understanding of the genetics of obesity has taken some giant steps forward. This was stimulated principally by the identification of the leptin gene in 1994 (Zhang et al., 1994), and the recognition that the leptin feedback system was present in humans (Considine et al., 1996). Moreover, studies clearly showed that humans with mutations that resulted in them producing leptin that was unable to bind to its receptor, or in receptors that were unable to bind to native leptin, became massively obese (Farooqi et al., 1999; Farooqi et al., 2001). Similarly, mice with defects in the same system also become obese (Zhang et al., 1994). The progressive elucidation at the turn of the millennium of the complex leptin signalling system and how additional signals from the periphery interact in the brain (Friedman, 1998; Cowley et al., 1999; Schwartz et al., 2000) were major advances in understanding the cause of obesity. Although it became clear that people with major genetic defects in this system were few and far between (Maffei et al., 1996), other genetic studies that were focussed on determining polymorphic variation in the genes involved in this pathway suggested that genetic variation in some of these key regulators of food intake and energy balance [notably the melanocortin 4 receptor gene (*MC4R*)] were linked to variability in body weight in humans (Farooqi and O'Rahilly, 2008; Loos et al., 2008).

Surprises at the sequence level

Since the middle of the last decade, the biggest contribution to this field has been the advent of genome-wide association studies (GWAS). The results of these studies have been surprising. The first surprise was that the genetic polymorphisms that have been linked to obesity (with a few notable exceptions such as those in the *MC4R* gene) have almost universally been in or close to genes that a priori nobody would have pointed the finger at as likely candidates. Indeed, for most of these genes revealed by GWAS, we are still in the dark about their functions and how they cause obesity – although for the ones with the largest effects, such as *FTO* (Frayling et al., 2007), some details are emerging (Gerken et al., 2007; Fredriksson et al., 2008; Fischer et al., 2009). The second

surprise was that the effect sizes for these genes were all rather small, and the accumulated amount of variance they explained was very minor relative to the estimated 65% of variance that we believe is due to genetic effects. The largest of these studies to date (Speliotes et al., 2010) involved 249,796 subjects and identified 18 genes, variants in which together explain less than 4% of the variation in BMI.

Although surprising at the time, such a structure for the genetic architecture of obesity is exactly in line with a theoretical genetic model derived for polygenic continuous traits almost 100 years ago – called the infinitesimal model (Fisher, 1918). The infinitesimal model predicts a negative exponential between effect size and frequency such that all polygenic traits are ultimately defined by hundreds if not thousands of genes, each with vanishingly small effects. If this model is correct then where we go from here in genetic research for obesity is an interesting question. However, an alternative model is that the balance of the variation is not accounted for by common genes of smaller and smaller effect size, but by a mixture of rare variants (population frequency of 0.001 or less) that have strong effects, and low frequency variants (population frequency 0.01 or less) that have intermediate effects. The plummeting costs of whole-genome and whole-exome sequencing mean that we will soon be able to begin addressing this alternative hypothesis, rather than simply speculating about competing models for the inherited susceptibility to obesity.

Evolutionary background

Another set of questions regarding the genetics of obesity is related not to the identity of the genes, but rather why obesity-associated genetic polymorphisms were selected. This is an interesting issue because obesity seems to bring with it a host of negative consequences: obese people have a greater risk of many other disorders, including insulin resistance, type 2 diabetes, fatty liver disease, hypertension and some forms of cancer (Pi-Sunyer, 1993; Prospective Studies Collaboration et al., 2009). Our understanding of evolution by natural selection is that evolution favours genes that give us advantages, not disadvantages, so how did this situation arise? How is it possible for us to become an obese species, if obesity is a negative trait? Surely natural selection should have wiped us out – or at least wiped out the obese, along with their predisposing polymorphisms?

Perhaps an important point to raise here is that we are not the only species that becomes obese. Many animals deposit body fat in amounts that would be considered obesity in humans. Hibernating animals deposit enormous fat stores before entering hibernation. Migrating birds deposit similar stores before embarking on migrational journeys. Maybe these other situations can give us clues about positive selection for obesity in humans. It is quite clear that these situations of 'natural obesity' in the animal kingdom involve animals depositing fat in anticipation of a future shortfall of energy. The hibernating animal will be unable to feed in winter, the migrating bird will be similarly unable to feed while flying at altitude, or over oceans devoid of food. Might human obesity have been selected for a similar reason? Maybe humans deposited fat to get through similar periods of shortfall in food supply?

This type of adaptive story-telling as an explanation for all things biological was extremely popular in the 1960s, so it is unsurprising that such explanations for the genetic contribution to obesity first

emerged in the early 1960s (Neel, 1962). The argument was that humans have 'thrifty genes' (more strictly, 'thrifty alleles') that help us deposit fat between periods of famine. People with these alleles would deposit fat and survive the next famine, passing their advantageous thrifty alleles onto their offspring. What is more surprising is that, despite many influential critiques of 'the adaptionist programme' (e.g. Gould and Lewontin, 1979) and the fact that such adaptive stories have been largely abandoned among scientists studying evolution, this adaptive idea for the evolution of obesity has survived and continues to be reiterated right up to the present day.

The 'thrifty gene' hypothesis for the evolution of obesity based on famine survival, or more latterly famine effects on fertility (Prentice et al., 2008), has some major problems. These problems have been presented in detail elsewhere (Benyshek and Watson, 2006; Speakman, 2007; Speakman, 2008), so we concentrate here on just one of the problems – namely the idea that obesity is an adaptive response to famine, analogous to fat storage observed in other animals in preparation for periods of food scarcity or high demand. The problem is that closer inspection reveals that the phenomenon of human obesity does not have much in common with the phenomenon of natural fattening that occurs in other animals to survive periods of food shortage. This is because in all of the animal examples, such as hibernation and migration, the entire population becomes obese. The reason is clear – if a migrating bird does not deposit enough fat to migrate across the ocean (e.g. Piersma, 2011), it plunges into the ocean short of its destination and, along with its inferior fat storage alleles, becomes fish food. The selection pressure is strong, and the alleles favouring fat storage spread through the entire population and, consequently, all of the birds in the population get fat. If the same selection pressure was driving obesity in humans, then the same would be true – that is, between famines, we would all get fat. Yet, despite 60 years of plentiful food supplies, about 70% of the population of the USA remain stubbornly not obese, and 20% have not even managed to put on enough weight to be classified as overweight (Flegal et al., 2010). In almost all other societies, the percentage of people that are lean is even higher. Clearly something else is going on. As suggested by Wells (Wells, 2012), we really need to get past this adaptive response to famine idea. There are probably many other scenarios worth pursuing to understand the genetic architecture of the epidemic, some of which are based on non-adaptive processes such as genetic drift (Speakman, 2007; Speakman, 2008).

Epigenetics

At least some of the 'genetic' variation in obesity might actually reflect epigenetic effects – that is, effects that are programmed by early-life experiences. These effects first came to light when it was shown that birth weight was a strong predictor of risk for the development of non-communicable diseases in later life (Hales et al., 1991). In particular, low birth weight children had large increases in the risk of subsequent type 2 diabetes. The effect of in utero nutrition on subsequent disease risk was shown by elegant follow-up studies of children conceived or born during periods of famine: risk of diabetes was again linked with low birth weight and famine exposure during the period in utero; however, the effects on obesity risk, although statistically significant, were relatively small and gender dependent (Ravelli et al., 1999; Stein et al., 2009). Indeed,

fetal undernutrition has proved to be less of an issue for obesity risk than fetal overnutrition – which does seem to be a significant risk factor for obesity development in later life (Symonds et al., 2009; Symonds et al., 2011; Rooney and Ozanne, 2011; Slomko et al., 2012). Because a female fetus already contains all of the eggs that will be used for reproduction in its adult life, such influences might not be restricted to a single generation. This suggests that, if a person becomes obese, it might be partly due to factors that were experienced by their mother's grandmother when she was pregnant or breastfeeding. Clearly, retrospectively or prospectively establishing the importance of such effects is not easy.

Environmental factors

When it comes to environmental effects that might have contributed to individual variation in energy imbalance and hence stimulated the obesity epidemic, there are many to choose from (e.g. Keith et al., 2006). Most factors are subject to debate regarding their importance and the mechanism by which they might precipitate an effect. For example, the time spent viewing television seems to be associated with obesity in children (Robinson, 1999; Robinson, 2001), but, surprisingly, this is not linked to greater time spent inactive or lower energy expenditure (Jackson et al., 2009). Rather, we get fat watching TV either because of the snack food we consume while watching, or because of exposure to advertisements that prompt increased intake after TV watching ends. What might at first seem a straightforward cause-and-effect relationship is, on further investigation, much more complex – and this pattern is typical for many studies of the causes of obesity.

Many reviews have been written summarising the evidence for and against different environmental factors in obesity. Three controversial suggestions that have emerged in the last decade are the potential roles of the gut microbiome, stress and endocrine-disrupting chemicals. Studies showing differences in the populations of bacteria in the guts of obese and lean subjects have appeared only during the last decade (Turnbaugh et al., 2006). These studies have been enormously facilitated by technological advances that allow unbiased screening of gut bacterial populations by sequencing their DNA. However, the associations with obesity remain controversial because they are not always observed (e.g. Duncan et al., 2008) and it is also unclear whether the differences are secondary to or causative of the obesity. Moreover, a mechanism is elusive because the differences in gut microbiota do not seem to be strongly and consistently linked to differences in, for example, the efficiency of digestion (a potential route by which gut bacteria might have their impact).

Second, there is the tricky issue of stress. It is widely agreed that stress levels are elevated in modern society. Isolating an effect of stress on obesity, however, is complicated because the manner in which we respond to stress differs between individuals – some gain weight, others lose weight and yet others are robust to the effects of stress. Thus, a general role for stress in the obesity epidemic might be hard to establish. Nevertheless, animal studies involving social defeat paradigms clearly show that there is an interaction between chronic social stress in rodents and their responses to high-fat diets. Animals that were dominant in interactions were generally in negative energy balance and were protected from obesity, whereas those that were subordinate were in positive energy balance and gained weight (Bartolomucci et al., 2009).

Finally, the invention of plastics in the 1950s resulted in the production of many compounds that now contaminate our environment at chronic low levels. We are all exposed to these compounds at different levels, depending on where we live. Several of these compounds have been shown to have endocrine-disrupting activity in vertebrates that can lead to severe impacts on, for example, reproductive biology in fish and amphibians. Similar effects on reproductive biology in humans have also been reported (Diamanti-Kandarakis et al., 2009). The potential that these compounds also lead to obesity and diabetes has been suggested (Newbold et al., 2008). In favour of such an effect is the fact that their production coincides temporally with the onset of the epidemic. In addition, the distribution of obesity in the United States can be linked geographically to variations in the contamination levels of the environment. However, a survey of exposure to bisphenol A (the most often-cited endocrine-disrupting chemical potentially linked to energy imbalance) showed significant links between its levels in urine and cardiovascular disease and diabetes, but not obesity (Lang et al., 2008). Moreover, if the causal factor is low-level environmental contamination, it is pertinent to ask why other mammals living in these contaminated areas have not also become 'obese species' like us.

Conclusion

The question of why have we become an obese species has many diverse answers, some of which are supported by articles in this special issue of *Disease Models & Mechanisms* (<http://dmm.biologists.org/content/5/5.toc>). Ideas about the causality of obesity and the legacy of our evolutionary past are constantly evolving. However, there is probably one thing on which all the contributors to this issue concur, and that is that obesity is a complex multi-factorial problem. As the veteran obesity researcher George Bray once said, "Obesity isn't rocket science. It's much more complicated". We agree.

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