Human obesity and insulin resistance: lessons from experiments of Nature

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Abstract

Examination of individuals with ‘extreme phenotypes’ has revealed some rare monogenic disorders that were previously unknown. This identification can shed light on physiological pathways that are also important in normal physiology and how their impairment leads to more common, milder, multigenic forms of the disease. Ultimately, this is a potential route to treatment of both disease types. This approach is discussed in relation to Type 2 diabetes, arising from both insufficient insulin production and insulin resistance.

Introduction

One of the principal motivations underlying the biomedical science revolution of the late 20th and early 21st Centuries is the promise that what scientists do in the laboratory will have ultimate benefit to patients. The poet Alexander Pope wrote, “The proper study of mankind is man” [1], and I, as a clinician scientist, have many advantages in being able to study man as an experimental animal. In this short review, I will try to demonstrate how human patients, who tend, self-evidently, to exhibit extreme deviations from normal in their physiology, illuminate normal human physiology and develop models for more common human diseases.

The advantages of using patients to study human physiology include the fact that people with metabolic disorders and other illnesses seek medical attention, and therefore present themselves to trained observers, i.e. doctors, in the clinic. Doctors, with access to the full range of communication technologies, can quickly build up series of patients with similar disorders who originally presented themselves at diverse sites throughout the world. Furthermore, higher cognitive and emotional phenotypes can be assessed and studied very much more easily in humans than in experimental animals, even other mammals.

The arguments for studying not only humans, but also those individuals with extreme physiological abnormalities, are both practical and moral. Practical reasons include the fact that, simply, when an extreme abnormality of this kind does occur, it is quite likely that the disease is monogenic and therefore tractable and easily studied. Finding mutations in single genes is much easier than unravelling the complex interactions between genotype and environment that underlie milder, more common diseases of the same type. Also, although these diseases are rare, they will often provide useful models for these more common diseases.

The moral reason is obvious: such individuals are seriously afflicted, with shortened lifespan and poor quality of life, and compassion dictates that we as physicians should give them disproportionate attention.

A few examples of insights into normal human physiology that have been learned from studies of abnormal phenotypes include the facts that oestrogens, rather than androgens, are responsible for the closure of long-bone growth in both males and females [2], that the growth factor IGF-1 (insulin growth factor 1) is essential for cognitive development [3], and that the WNK [with no K (lysine)] serine/threonine kinases play a central role in renal sodium handling and therefore in the control of blood pressure [4].

Type 2 diabetes, insulin deficiency and obesity

The phenotypes that are studied in my laboratory all relate to Type 2 diabetes in some way. This disorder really consists of two separate, but related, dysfunctions: a dysfunction of the β-cells in the pancreas, leading to insufficient insulin production, and insulin resistance (basically, an impaired response to insulin in its target cell types). Type 2 diabetes occurs when both these phenotypes are combined (Figure 1). The most common cause of insulin resistance is obesity (see, e.g., [5]). We have been studying Type 2 diabetes in my laboratory for 20 years, but in the last 10, I have been focusing particularly on obesity and insulin resistance, and using an extreme phenotype approach to explore some of the molecules that are involved in mediating these disorders in humans [6]. The method that we have used involves selecting cohorts of the most ‘extreme’ individuals with intrinsic...
genetic disorders of insulin action, severe insulin resistance, or obesity – the more extreme and the more phenotypically homogeneous a cohort is, the more likely the individuals in it are to have the same or similar genetic defects.

We have therefore set up two separate cohorts of patients, one exhibiting severe insulin resistance and the other genetically determined obesity. Criteria for inclusion in the insulin-resistance group include the presence of the dermatological disorder acanthosis nigricans, which is caused by elevated levels of insulin and can therefore be taken as a ‘marker’ for insulin resistance, and measured high blood insulin levels. Severely obese individuals are excluded as we are looking for people whose insulin resistance is not caused by excess weight. Those included in the obese cohort must have severe obesity with pre-pubertal onset. As height and weight change proportion rapidly as children grow, the best way of comparing BMI (body mass index) in children of different ages is by quoting standard deviations from the mean. All children included in our study have a BMI at least three standard deviations above the mean, and the average value for the cohort is 4.5 standard deviations above the mean. We have taken a targeted candidate gene analysis approach to exploring the causes of these two phenotypes and have identified a number of genetic defects, including several not observed before [6].

**PPARγ and metabolic disorders**  
**PPARγ** (peroxisome-proliferator-activated receptor γ) is a transcription factor that has been associated with metabolic disorders for some time. Spiegelman and co-workers first observed that PPARγ is required for the differentiation of adipose tissue [7]; it is also known to be the target of the thiazolidinediones, a useful family of insulin-sensitizing drugs. In the late 1990s, I and my colleagues Krishna Chatterjee and Ines Barroso found dominant-negative mutations that proved for the first time the importance of this transcription factor for the control of insulin sensitivity in mammals [8]. There was no mouse model because this protein is essential for placentation so the mouse PPARγ-knockout is embryonic-lethal. The human patients that we found with these mutations shared a phenotype that included severe insulin resistance (progressing to Type 2 diabetes at an early age), high triacylglycerols and low HDL (high-density lipoprotein) cholesterol, hepatic steatosis, hypertension and a marked stereotypical form of partial lipodystrophy characterized by very little fat on the buttocks. This phenotype is so distinct that it has been proved possible to spot the condition, which is known as PPARγ ligand resistance syndrome, on clinical presentation.

Many of the mutations associated with this syndrome are in the receptor ligand-binding domain, so they do not interfere with DNA binding, but rather with the attraction of co-activators and the repulsion of co-repressors. However, other mutations that produce the same phenotype have also been discovered. These include a premature stop mutation that truncates the ligand-binding domain [9]. We are now investigating why mutations like these, which give rise to defective proteins that cannot bind DNA, are nevertheless inherited in the same dominant-negative manner as those in the ligand-binding domain. Research into these single-gene disorders is expected to give rise to important insights into the mechanisms involved in more common, milder, multigenic forms of insulin resistance.

Individuals who do not have dominant-negative PPARγ mutations, but are haploinsufficient in this gene (i.e. they have only one functional copy) are even rarer than those with the dominant-negative genotype. It appears that these individuals can exhibit abnormal metabolic responses to modest weight gain that make them far more likely to develop Type 2 diabetes. This type of mutation can also interact with mutations in other genes, giving rise to more severe phenotypes. In 2002, my colleague David Savage and I, again with Barroso and Chatterjee, described a pedigree that contained five women with acanthosis nigricans and very severe insulin resistance [10]. All the affected individuals were found to have frameshift/premature stop mutations in one copy each of two unlinked genes: PPARγ and regulatory subunit 3 of protein phosphatase 1. This subunit controls glycogen synthase in skeletal muscle and is important for the regulation of glycogen metabolism. Only the five individuals who had inherited both of these mutations exhibited the extreme insulin-resistant phenotype (Figure 2). The latter mutation is present in 1–1.5% of all Caucasians. Alone, it causes impaired glycogen synthesis in skeletal muscle, but affected individuals remain healthy. It is only when it is combined with PPARγ haploinsufficiency that it gives rise to insulin resistance and diabetes. This rare digenic syndrome provides a model for studying interactions between genes with implications for studies of more common metabolic disorders.

**Leptin and obesity**  
Researchers in my laboratory have studied severely obese children with congenital leptin deficiency for many years. We are now working with eight children from five families, all

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**Figure 1** | **Components of Type 2 diabetes**  
Schematic representation of the factors involved in the development of Type 2 diabetes, highlighting the role of obesity in promoting the development of insulin resistance.
Figure 2 | A digenic disorder of insulin action
Plot of fasting insulin level against BMI for a number of individuals with mutations in PPARγ, PPP1R3, neither or both genes. Only those who were double heterozygotes exhibited very high insulin levels that were independent of BMI.

Figure 3 | Schematic representation of common mutations in the MC4 receptor gene
The MC4 receptor gene is found in 0.1% of the Caucasian population and 1% of those with a BMI > 30.

of Pakistani origin, with the same frameshift/premature stop mutation [11], and one Egyptian child with a novel nonsense mutation. Six of these children are now undergoing leptin-replacement therapy, and the others will be starting soon. This therapy results in a dramatic stabilization or even reduction of weight as the children grow, so their BMI is gradually reduced towards normal levels. It is really remarkable that children with what is, initially, often life-threatening obesity can be effectively ‘normalized’ by this simple treatment.

For many years, it was thought that mutations in the leptin receptor were much rarer than those in leptin itself. The first leptin receptor mutation was discovered by Philippe Froguel and Karen Clement in three sisters from a Kabilian family [12]. This mutation caused a truncation at the beginning of the transmembrane domain, resulting in a huge amount of circulating leptin bound to the receptor ligand-binding domain. My colleague Sadaf Farooqi and I have now performed a much more detailed analysis of our obese pedigrees, and we are finding that mutations in this large and rather unwieldy gene are actually more common than those in leptin itself.

However, most people with defects in leptin metabolism have leptin resistance, rather than mutations in either leptin or its receptor. The causes of leptin resistance are very widely discussed, but, as yet, poorly understood. One theory that was published recently suggests that the well-studied C-reactive protein, which is involved in acute inflammation, may bind to leptin and inhibit its action, and that leptin increases the production of this protein by hepatocytes [13]. But this is a very new finding which has not been replicated.

The most important insights in understanding leptin resistance are likely to come from studying the neurochemistry and neurobiology of leptin action in the brain (where the majority of its action is known to take place), and particularly within the hypothalamus. The functions of leptin in the brain are known to include activating the protein POMC (pro-opiomelanocortin) and switching off neuropeptide Y. Humans who lack POMC are severely obese, with adrenal insufficiency, pale skin and reddish-coloured hair [14]. We analysed the pedigree of the one child in our cohort who is POMC-deficient and found that heterozygotes, who carry one abnormal copy of the POMC gene, also appear to be predisposed to obesity. This fits in with some of our earlier work on a mouse POMC-knockout model [15]. We found that mice that were heterozygous at this locus were lean when fed on a normal diet, but had increased appetite, and became obese, when exposed to a 40% fat diet. The POMC-knockout mice seemed to prefer an even higher (65%) fat diet, indicating...
that this protein might be acting within the brain as a 'sensor' for dietary fat content.

These results underline the fact that obesity is not just a metabolic disease, but is a genetically predisposed neuro-behavioural disease. Almost all of the genes that we have found to predispose to obesity in humans are expressed in the hypothalamus and cause changes in appetite and satiety. One of these genes is the MC4 receptor, which is the G-protein-coupled receptor for two peptide derivatives of POMC that are synthesized in the hypothalamus, α-MSH (melanocyte-stimulating hormone) and β-MSH. Mutations in this receptor are very common compared with those causing most monogenic human diseases. They are found in 0.1% of the U.K. population, 1% of all obese individuals (defined as having BMI > 30) and 5.5% of our severe early-onset obesity cohort [16] (Figure 3). Studies in human subjects and mouse models have shown that mutations in the MC4 receptor are associated with decreased satiety and increased food intake [17].

In summary, therefore, examining individuals with phenotypes at the extreme end of continuous distributions, such as BMI, has revealed some rare monogenic disorders that were previously unknown. Insights from these rare diseases can illuminate physiological pathways that are important in normal physiology and impaired in more common, milder, multigenic forms of the same diseases, and can, potentially, lead to treatments for both types of disease.

References

1. Pope, A. (1733) Essay on Man, epistle II

Received 31 August 2006