Monogenic Human Obesity Syndromes

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ABSTRACT

Over the past decade, we have witnessed a major increase in the scale of scientific activity devoted to the study of energy balance and obesity. This explosion of interest has, to a large extent, been driven by the identification of genes responsible for murine obesity syndromes and the novel physiological pathways revealed by those genetic discoveries. We and others recently have identified several single-gene defects causing severe human obesity. Many of these defects have occurred in molecules identical or similar to those identified as a cause of obesity in rodents. This chapter will consider the human monogenic obesity syndromes that have been characterized to date and discuss how far such observations support the physiological role of these molecules in the regulation of human body weight and neuroendocrine function.

I. Introduction

The concept that mammalian body fat mass is likely to be regulated has its underpinning in experimental science going back over 50 years. The adipostatic theory of Kennedy (1953), which emerged in the 1950s, was based on his observations of responses of rodents to perturbations of food intake, together with the hypothalamic lesioning studies of Hetherington (Hetherington and Ranson, 1940) and Anand (Anand and Brobeck, 1951) and the parabiosis experiments of Hervey (1959). The subsequent emergence of several murine genetic models of obesity (Bray and York, 1971) and their study in parabiosis experiments by Coleman (1973) led to the consolidation of the concept that a circulating factor might be involved in mediation of energy homeostasis. However, it was not until the 1990s, when the precise molecular basis for the agouti, ob/ob, db/db, and fat/fat mouse emerged, that the molecular components of an energy balance regulatory network began to be pieced together (Leibel et al., 1997). The use of gene-targeting technology has gone on to demonstrate the critical roles of certain other key molecules in that network, such as the melanocortin 4 receptor (MC4R) (Huszár et al., 1997) and melanin-concentrating hormone (MCH) (Shimada et al., 1998; Chen et al., 2002).
A critical question raised by these discoveries is the extent to which these regulatory pathways are operating to control human body weight. Over the past few years, a number of novel monogenic disorders causing human obesity have emerged (Barsh et al., 2000). In many cases, the mutations are found in components of the regulatory pathways identified in rodents. The importance of these human studies is several-fold. First, they established for the first time that humans can become obese due to a simple inherited defect. Second, it has been notable that in all cases, the principle effect of the genetic mutation has been to disrupt mechanisms regulating food intake. Third, some defects, though rare, are amenable to rational therapy. Fourth, although the physiological consequences of mutations in the same gene in humans and mice are frequently very similar, there are certain key interspecies differences in phenotype.

This review will describe certain recent advances in our understanding of single-gene defects causing human obesity. It will not consider genetic diseases such as Bardet-Biedl, Cohen’s, Alstrom’s, and Prader-Willi, where obesity is only one feature in a complex developmental disorder. Indeed, considerable advances have been made in the identification of genetic defects underlying many of these syndromes. However, in all cases, the link between the molecular defect and the clinical phenotype remains unclear (reviewed in O’Rahilly and Farooqi, “The Genetics of Obesity in Humans,” at www.endotext.org.).

II. Congenital Leptin Deficiency

In 1997, we reported two severely obese cousins from a highly consanguineous family of Pakistani origin (Montague et al., 1997). Both children had undetectable levels of serum leptin and were found to be homozygous for a frameshift mutation in the ob gene (ΔG133), which resulted in a truncated protein that was not secreted (Montague et al., 1997; Rau et al., 1999). We since have identified three more affected individuals from two other families (Farooqi et al., 2002; I.S. Farooqi and S. O’Rahilly, unpublished observations) who are homozygous for the same mutation in the leptin gene. All the families are of Pakistani origin but are not known to be related over five generations. A large Turkish family who carries a homozygous missense mutation also has been described (Strobel et al., 1998). All subjects in these families are characterised by severe, early-onset obesity and intense hyperphagia (Farooqi et al., 1999,2002; Ozata et al., 1999). Hyperinsulinaemia and an advanced bone age are also common features (Farooqi et al., 1999,2002). Some of the Turkish subjects are adults with hypogonadotropic hypogonadism (Ozata et al., 1999). Although normal pubertal development did not occur, there was some evidence of a delayed but spontaneous pubertal development in one person (Ozata et al., 1999).

We demonstrated that children with leptin deficiency had profound abnormalities of T-cell number and function (Farooqi et al., 2002), consistent with
high rates of childhood infection and a high reported rate of childhood mortality from infection in obese Turkish subjects (Ozata et al., 1999). Most of these phenotypes closely parallel those seen in murine leptin deficiency (Table I). However, some phenotypes do not have as clear-cut parallels between human and mouse. Thus, while ob/ob mice are stunted (Dubuc and Carlisle, 1988), it appears that growth retardation is not a feature of human leptin deficiency (Farooqi et al., 1999, 2002), although abnormalities of dynamic growth hormone (GH) secretion have been reported in one human subject (Ozata et al., 1999). ob/ob mice have marked activation of the hypothalamic-pituitary-adrenal axis, with very elevated corticosterone levels (Dubuc, 1977). In humans, abnormalities of cortisol secretion are, if present, much more subtle (Farooqi et al., 2002). The contribution of reduced energy expenditure to the obesity of the ob/ob mouse is reasonably well established (Trayhurn et al., 1977). In leptin-deficient humans, we found no detectable changes in resting or free-living energy expenditure (Farooqi et al., 2002), although it was not possible to examine how such systems adapted to stressors such as cold. Ozata and colleagues reported abnormalities of sympathetic nerve function in leptin-deficient humans, consistent with defects in the efferent sympathetic limb of thermogenesis (Ozata et al., 1999).

III. Response to Leptin Therapy

Recently, we reported the dramatic and beneficial effects of daily subcutaneous injections of leptin for reducing body weight and fat mass in three congenitally leptin-deficient children (Farooqi et al., 2002). We have commenced therapy in two other children and seen comparably beneficial results (I.S. Farooqi and S. O’Rahilly, personal observations). All children showed a response to initial leptin doses that were designed to produce plasma leptin levels at only 10% of those predicted by height and weight (i.e., ≈ 0.01 mg/kg of lean body mass) (Farooqi et al., 2002). The most-dramatic example of leptin’s effects was in a 3-year-old boy, severely disabled by gross obesity (weight, 42 kg), who now weighs 32 kg (75th centile for weight) after 48 months of leptin therapy (Figure 1).

The major effect of leptin was on appetite, with normalisation of hyperphagia. Leptin therapy reduced energy intake during an 18-megajoule (MJ) ad libitum test meal by up to 84% (5 MJ ingested pretreatment vs 0.8 MJ post-treatment in the child with the greatest response) (Farooqi et al., 2002). We were unable to demonstrate a major effect of leptin on basal metabolic rate or free-living energy expenditure (Farooqi et al., 2002). However, as weight loss by other means is associated with a decrease in basal metabolic rate (BMR) (Rosenbaum et al., 2002), the fact that energy expenditure did not fall in our leptin-deficient subjects is notable.
### TABLE I

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>ob/ob</th>
<th>Human leptin deficiency</th>
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<tbody>
<tr>
<td><strong>Total body weight</strong></td>
<td>3X Normal</td>
<td>Mean BMI sds = 6.2</td>
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<tr>
<td><strong>Body composition</strong></td>
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<tr>
<td>Fat mass</td>
<td>&gt; 50%</td>
<td>Mean 57% of body weight</td>
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<tr>
<td>Lean mass</td>
<td>Decreased</td>
<td>Normal for age</td>
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<tr>
<td>Bone mineral content</td>
<td>Decreased</td>
<td>Normal for age</td>
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<tr>
<td><strong>Food intake</strong></td>
<td>Increased meal size</td>
<td>Increased meal size and frequency</td>
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<tr>
<td><strong>Energy expenditure</strong></td>
<td></td>
<td></td>
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<tr>
<td>Body temperature</td>
<td>Decreased in response to cold</td>
<td>Normal in basal state</td>
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<tr>
<td>Basal metabolic rate</td>
<td>Decreased oxygen consumption</td>
<td>Appropriate for body composition</td>
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<td>Physical activity</td>
<td>Reduced</td>
<td>Reduced</td>
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<td>SNS activation</td>
<td>Basal decreased and refractory to cold exposure</td>
<td>Reduced in response to cold</td>
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<td><strong>Metabolic responses</strong></td>
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<td>Diabetes</td>
<td>Fasting hyperglycaemia</td>
<td>Normoglycaemia</td>
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<td>Hyperinsulinaemia</td>
<td>Severe; resistance to exogenous insulin</td>
<td>Appropriate for degree of obesity</td>
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<td>T cell-mediated immunity</td>
<td>Decreased CD4 cells, reduced T-cell proliferation</td>
<td>Decreased CD4 cells, reduced T-cell proliferation</td>
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<td><strong>Neuroendocrine function</strong></td>
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<td>Reproductive</td>
<td>Hypogonadotropic hypogonadism</td>
<td>Hypogonadotropic hypogonadism</td>
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<tr>
<td>Thyroid</td>
<td>Hypothalamic and ?peripheral effects</td>
<td>Mild hypothalamic hypothyroidism</td>
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<td>Growth</td>
<td>Stunted</td>
<td>Normal linear growth and IGF-1 levels</td>
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<tr>
<td>Adrenal</td>
<td>Corticosterone excess</td>
<td>Normal cortisol and ACTH levels</td>
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[Abbreviations: BMI, body mass index; SNS, sympathetic nervous system; IGF-1, insulin-like growth factor-1; ACTH, corticotropin.]
Leptin administration permitted progression of appropriately timed pubertal development in the single child of appropriate age and did not cause the early onset of puberty in the younger children (Farooqi et al., 2002). Free thyroxine and thyroid-stimulating hormone (TSH) levels, although in the normal range before treatment, consistently increased at the earliest post-treatment time point and subsequently stabilized at this elevated level (Farooqi et al., 2002). These findings are consistent with evidence from animal models that leptin influences thyrotropin-releasing hormone (TRH) release from the hypothalamus (Legradi et al., 1997; Nillni et al., 2000; Harris et al., 2001) and from studies illustrating the effect of leptin deficiency on TSH pulsatility in humans (Mantzoros et al., 2001).

Throughout the trial of leptin administration, weight loss continued in all subjects, albeit with refractory periods that were overcome by increases in leptin dose (Farooqi et al., 2002). The families in the United Kingdom harbour a
mutation that leads to a prematurely truncated form of leptin; thus, wild-type (WT) leptin is a novel antigen to them. Thus, all subjects developed antileptin antibodies after \( \approx 6 \) weeks of leptin therapy, which interfered with interpretation of serum leptin levels and, in some cases, were capable of neutralising leptin in a bioassay (Farooqi et al., 2002). These antibodies are the likely cause of refractory periods that occur during therapy. The fluctuating nature of the antibodies probably reflects the complicating factor that leptin deficiency is itself an immunodeficient state (Lord et al., 1998; Matarese, 2000). Leptin administration leads to a change from the secretion of predominantly Th2 to Th1 cytokines, which may directly influence antibody production. Thus far, we have been able to regain control of weight loss by increasing the dose of leptin.

IV. Does a Heterozygous Phenotype Exist?

The major question with respect to the potential therapeutic use of leptin in more-common forms of obesity relates to the shape of the leptin dose/response curve. We have shown clearly that at the lower end of plasma leptin levels, raising leptin levels from undetectable to detectable has profound effects on appetite and weight (Farooqi et al., 2002). Heymsfield and coworkers (1999) administered supraphysiological doses (i.e., 0.1–0.3 mg/kg body weight) of leptin to obese subjects for 28 weeks. On average, subjects lost significant weight, but the extent of weight loss and the intersubject variability has led many to conclude that the leptin resistance of common obesity cannot be usefully overcome by leptin supplementation, at least when administered peripherally. However, on scientific rather than pragmatic grounds, it is of interest that there was a significant effect on weight, suggesting that plasma leptin can continue to have a dose/response effect on energy homeostasis across a wide plasma concentration range.

To test this hypothesis, we studied the heterozygous relatives of our leptin-deficient subjects. Serum leptin levels in the heterozygous subjects were found to be significantly lower than expected for % body fat and they had a higher prevalence of obesity than seen in a control population of similar age, sex, and ethnicity (Farooqi et al., 2001). Additionally, % body fat was higher than predicted from height and weight of the heterozygous subjects, compared to control subjects of the same ethnicity (Farooqi et al., 2001). These findings closely parallel those in heterozygous \( ob/+ \) and \( db/+ \) mice (Coleman, 1979; Chung et al., 1998). These data provide further support for the possibility that leptin can produce a graded response in terms of body composition across a broad range of plasma concentrations.

All heterozygous subjects had normal thyroid function and appropriate gonadotropins, normal development of secondary sexual characteristics, and normal menstrual cycles and fertility, suggesting that low leptin levels are
sufficient to preserve these functions (Farooqi et al., 2001). This is consistent with the data of Ioffe and colleagues, who demonstrated that several of the neuroendocrine features associated with leptin deficiency were abolished in low-level leptin transgenic mice, which were fertile with normal corticosterone levels (Ioffe et al., 1998). However, these low-level leptin transgenic mice still exhibited abnormal thermoregulation in response to cold exposure and had mildly elevated plasma insulin concentrations, suggesting that different thresholds exist for the various biological responses elicited by changes in serum leptin concentration and that these could be reversed by leptin administration (Ioffe et al., 1998).

Our findings in the heterozygous individuals have implications for treating common forms of obesity. While serum leptin concentrations correlate positively with fat mass, considerable interindividual variation exists at any particular fat mass. Leptin is inappropriately low in some obese individuals. The relative hypoleptinemia in these subjects may be contributing actively to their obesity and may be responsive to leptin therapy (Ravussin et al., 1997). Heymsfield and colleagues (1999) found no relationship between baseline plasma leptin levels and therapeutic response. However, study subjects were not preselected for relative hypoleptinemia. A therapeutic trial in a subgroup of subjects selected for disproportionately low circulating leptin levels would be of great interest.

V. Leptin Receptor Deficiency

A mutation in the leptin receptor has been reported in one consanguineous family with three affected subjects (Clement et al., 1998). Affected individuals were found to be homozygous for a mutation that truncates the receptor before the transmembrane domain. The mutant receptor ectodomain is shed from cells and circulates bound to leptin. The phenotype has similarities to leptin deficiency. Leptin receptor-deficient subjects were of normal birthweight but exhibited rapid weight gain in the first few months of life, with severe hyperphagia and aggressive behaviour when food was denied (Clement et al., 1998). Basal temperature and resting metabolic rate were normal, cortisol levels were in the normal range, and all individuals were normoglycaemic, with mildly elevated plasma insulin similar to leptin-deficient subjects. Leptin receptor-deficient subjects had some unique neuroendocrine features not seen with leptin deficiency. Evidence of mild growth retardation in early childhood, with impaired basal and stimulated GH secretion and decreased insulin-like growth factor (IGF)-1 and IGF-binding protein (BP)3 levels, alongside features of hypothalamic hypothyroidism in these subjects, suggest that loss of the leptin receptor results in a more-severe neuroendocrine phenotype than loss of leptin itself (Clement et al., 1998). The most-likely explanation for this is that the leptin
VI. Pro-opiomelanocortin

Two unrelated obese German children have been reported with homozygous or compound heterozygous mutations in pro-opiomelanocortin (POMC) (Krude et al., 1998). Both children were hyperphagic and developed early-onset obesity, presumably due to impaired melanocortin signaling in the hypothalamus (Krude et al., 1998). Presentation was in neonatal life, with adrenal crisis due to isolated corticotrophin (ACTH) deficiency. (POMC is a precursor of ACTH in the pituitary.) The children had pale skin and red hair from the lack of MSH function at MC1Rs in the skin (Krude et al., 1998). Three additional subjects with homozygous or compound heterozygous complete loss-of-function mutations of the POMC gene have been described (Krude and Gruters, 2000). Recently, several groups have identified a heterozygous missense mutation (Arg236Gly) in POMC that disrupts the dibasic amino acid processing site between β-MSH and β-endorphin (Echwald et al., 1999; Del Giudice, 2001a; Challis et al., 2002). This results in an aberrant β-MSH/β-endorphin fusion peptide, which binds to MC4R with an affinity identical to that of α- and β-MSH but has a markedly reduced ability to activate the receptor (Challis et al., 2002). Therefore, this cleavage site mutation in POMC may confer susceptibility to obesity through a novel molecular mechanism. Mutations affecting this processing site have been reported in obese children from several different populations and therefore may be a relatively common contributor to early-onset obesity.

VII. Prohormone Convertase 1 Deficiency

Further evidence for the role of the melanocortin system in human body weight regulation comes from the description of a 47-year-old woman with severe childhood obesity, abnormal glucose homeostasis, very low plasma insulin, but elevated levels of proinsulin, hypogonadotropic hypogonadism, and hypocortisolaemia associated with increased levels of POMC (Jackson et al., 1997). She was found to be a compound heterozygote for mutations in prohormone convertase 1 (PC1), which cleaves prohormones at pairs of basic amino acids, leaving C-terminal basic residues that are excised by carboxypeptidase E (CPE) (Jackson et al., 1997). We recently identified a child with severe early-onset obesity who was compound heterozygote for complete loss-of-function mutations in PC1 (Jackson et al., 2003). Although inability to cleave POMC is a likely mechanism for obesity in these patients, PC1 cleaves a number of other neuropeptides in the hypothalamus, including glucagon-like-peptide 1, which may influence feeding behaviour. The phenotype of these subjects is very similar
to that of the CPE-deficient fat/fat mouse (Naggert et al., 1995), implying that this part of the pathway may be important in controlling body weight in humans. To date, however, no humans with CPE defects have been described.

VIII. Human MC4R Deficiency

Of the five known melanocortin receptors, MC4R has been most-closely linked to control of energy balance in rodents (Yeo et al., 2000). Mice homozygous for a deleted MC4R become severely obese; heterozygotes have body weights intermediate between WT and homozygote null animals (Huszar et al., 1997). In 1998, two groups reported heterozygous MC4R mutations in humans that were associated with dominantly inherited obesity (Vaisse et al., 1998; Yeo et al., 1998). Since then, heterozygous mutations in MC4R have been reported in obese humans from various ethnic groups (Hinney et al., 1999; Farooqi et al., 2000; Vaisse et al., 2000).

We have studied over 500 severely obese probands and found that $\approx 5\text{--}6\%$ have pathogenic MC4R mutations that are nonconservative in nature, not found in control subjects from the background population, and that co-segregate with obesity in families (Farooqi et al., 2003). MC4R deficiency represents the most-commonly known monogenic cause of human obesity. Some studies have observed a lower prevalence, which may be explained by the differing prevalence in certain ethnic groups. However, it is more likely to reflect the later onset and reduced severity of obesity of the subjects in these studies (Jacobson et al., 2002). While we found a 100% penetrance of early-onset obesity in heterozygous probands, others have described obligate carriers who were not obese (Vaisse et al., 2000). Given the large number of potential influences on body weight, it perhaps is not surprising that both genetic and environmental modifiers will have important effects in some pedigrees. Indeed, we have now studied six families in which the probands were homozygotes. In all of these, the homozygotes were more obese than the heterozygotes (Farooqi et al., 2003). Interestingly, in these families, some heterozygous carriers were not obese. This may reflect ethnic-specific effects, as all these families were of Indo origin. Taking into account all these observations, co-dominance, with modulation of expressivity and penetrance of the phenotype, is the most-appropriate descriptor for the mode of inheritance. This finding is supported by the pattern of inheritance of obesity seen in heterozygous and homozygous MC4R knockout (KO) mice (Huszar et al., 1997).

We now have studied over 70 MC4R mutant carriers in our Clinical Research Facility. In addition to increased fat mass, MC4R mutant subjects have increased lean mass that is not seen in leptin deficiency (Farooqi et al., 2003). Linear growth of these subjects is striking, with affected children having a height standard deviation score (SDS) of $+2$, compared to population standards (mean
height SDS of other obese children in our cohort = + 0.5) (Farooqi et al., 2003). MC4R-deficient subjects also have higher levels of fasting insulin than age, sex, and BMI SDS-matched children (Farooqi et al., 2003). The accelerated linear growth and disproportionate early hyperinsulinaemia are consistent with observations in the MC4R KO mouse (Fan et al., 2000).

Affected subjects are objectively hyperphagic but not as severely as seen with leptin deficiency (Farooqi et al., 2003). Of particular note is the finding that the severity of receptor dysfunction seen in in vitro assays can predict the amount of food ingested at a test meal by the subject harbouring that particular mutation (Figure 2). One notable feature of this syndrome is that the severity of many of the phenotypic features appears to partially ameliorate with time. Thus, obese adult mutation carriers report less-intense feelings of hunger and are less hyperinsulinaemic than children with the same mutation (I.S. Farooqi and S. O’Rahilly, personal observations). We have studied in detail the signaling properties of many of these mutant receptors. This information should help advance the understanding of structure/function relationships within the receptor (Yeo et al., 2003). Importantly, we have been unable to discover evidence for dominant negativity associated with these mutants, which suggests that MC4R mutations are more likely to result in a phenotype through haploinsufficiency (Yeo et al., 2003).

MC4R mutations appear to be the most-common monogenic cause of obesity thus far described in humans. Maintenance of this reasonably high disease frequency is likely to be due partly to the fact that obesity is expressed in heterozygotes and no evidence exists of any apparent effect of the mutations on reproductive function.

IX. Other Possible Monogenic Syndromes

Identification of a leptin-regulated melanocortin pathway has provided a molecular and neuroanatomical link between peripheral signals and central nervous system (CNS) circuits but leaves open the question of how these melanocortin signals produce downstream effects on appetite, energy expenditure, and neuroendocrine function. Mutations in a number of other genes have been found in association with severe obesity in a small number of individuals; however, the significance of these findings often remains unclear.

Two groups have found missense mutations in the cocaine- and amphetamine-regulated transcript (CART), a neuropeptide implicated in the control of feeding behaviour in rodents. We identified a Ser66Thr mutation in heterozygous form in two unrelated U.K. probands. However, this did not co-segregate with obesity in family studies (Challis et al., 2000). In an Italian study, the Leu34Phe CART mutation was identified in the heterozygous state in a 10-year-old obese
FIG. 2. Genotype-phenotype correlations in human melanocortin 4 receptor (MC4R) deficiency. (A) Cyclic adenosine monophosphate (cAMP) response to alpha-melanocyte-stimulating hormone (α-MSH) in transiently transfected human embryonic kidney (HEK)293 cells for mutant MC4Rs, indicating complete (left panel) or partial (right panel) loss of function in vitro. (B) Ad libitum food intake at an 18-megajoule (MJ) test meal for leptin-deficient subjects and for MC4R-deficient subjects with complete/partial loss-of-function mutations.
boy and a number of obese family members but no functional data were provided (del Giudice et al., 2001b).

Holder and colleagues (2000) studied a girl with early-onset obesity and a balanced translocation between 1p22.1 and 6q16.2. The child displayed an aggressive, voracious appetite. The obesity was thought to be due to increased energy intake, as measured energy expenditure was normal. The translocation did not appear to affect any transcription unit on 1p but it disrupted the SIM1 gene on 6q (Holder et al., 2000). The *Drosophila* single-minded (sim) gene is a regulator of fruit fly neurogenesis. In the mouse, Sim1 is expressed in the developing kidney and CNS and is essential for formation of the supraoptic and paraventricular (PVN) nuclei, which express the MC4R (Michaud et al., 2001). It thus could be hypothesized that haploinsufficiency of SIM1, possibly acting upstream or downstream of MC4R in the PVN, was responsible for severe obesity in this patient.

It is of note that in all the genetic syndromes thus far described, the major physiological perturbance appears to be in appetite and energy intake. One possible exception is the description of three German subjects with mutations in the N terminus of the nuclear hormone receptor peroxisome proliferator-activated receptor gamma (PPARγ), an important determinant of adipogenesis (Ristow et al., 1998). Receptors containing this mutation are more-powerful inducers of adipogenesis when transfected into cultured cells. Unfortunately, however, no information is available regarding the co-segregation of this mutation with obesity in pedigrees. Since this mutation appears to be unique to the original population, it has not been possible to test this issue in independent families.

X. Summary

Several monogenic forms of human obesity have been identified by searching for mutations homologous to those causing obesity in mice. Although such monogenic obesity syndromes are rare, the successful use of murine models to study human obesity indicates that substantial homology exists across mammalian species in the functional organisation of the weight regulatory system. More importantly, identification of molecules that control food intake has generated new targets for drug development in the treatment of obesity and related disorders. These considerations indicate that an expanded ability to diagnose the pathophysiological basis of human obesity will have direct applications to its treatment. A more-detailed understanding of the molecular pathogenesis of human obesity ultimately may guide treatment of affected individuals.
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