RECENT ADVANCES

Recent advances in the genetics of severe childhood obesity

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Abstract

Childhood obesity is becoming a global epidemic. Twin studies suggest a heritability of fat mass, and disorders of energy balance that arise from genetic defects have been identified. In the past three years, five single gene disorders resulting in early onset obesity have been characterised. The discovery of these genetic defects has biological and clinical implications which are greater than the rarity of the individual diseases might suggest.

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Childhood obesity is rapidly emerging as a global epidemic. Its immediate adverse effects include orthopaedic complications, sleep apnoea, and psychosocial disorders.[1] As obese children are more likely to become obese adults,[2] we may expect to see profound public health consequences as a result of the emergence in later life of associated co-morbidities such as non-insulin dependent diabetes mellitus, ischaemic heart disease, and stroke. The true prevalence of obesity in childhood is difficult to determine as there is as yet no internationally accepted definition of pathological adiposity in the paediatric age group. A range of methods are available which allow quite accurate measurement of total body fat; however, none of these are widely available and/or easily applicable to the clinical situation. Body weight is reasonably well correlated with body fat but is also highly correlated with height, and children of the same weight but different heights can have widely differing amounts of adiposity. In adults, BMI (body mass index; weight (kg) divided by height^2 (m^2)) correlates reasonably well with more specific measurements of body fat. In children the relation between BMI and body fat varies considerably with age and with pubertal maturation. However, useful centile charts relating BMI to age have now been published in several countries.[3]

In the 10 years between the National Health and Nutrition Examination Survey (NHANES) II (1976–1980) and NHANES III (1988–1991) the prevalence of overweight in the USA, based on body mass index corrected for age and sex, has increased by approx. 40% (to 11% in the 6–11 year age group).[4] The rising prevalence of obesity can be explained in part by changes in our environment over the last 30 years, in particular the unlimited supply of convenient, highly palatable, energy dense foods, coupled with a lifestyle typified by low physical activity. However, obesity represents the archetypal complex multifactorial disease and arises as a result of behavioural, environmental, and genetic factors which may influence individual responses to diet and physical activity.

Evidence for a genetic influence

Twin studies suggest a heritability of fat mass (fraction of the age adjusted phenotypic variance accounted for by genetic factors) of between 40% and 70% with a concordance of 0.7–0.9 between monozygotic twins compared to 0.35–0.45 between dizygotic twins.[5 6] While these associations may in part be explained by sharing the same childhood environment, a number of studies have described a closer relation between the weights of adoptees and their biological parents rather than their adoptive parents.[7] These genetic influences are not confined to the extremes of obesity, but exert their effect across the whole range of body weight and are consistent with a polygenic inheritance of fat mass.

WHICH GENES?

A number of families with rare pleiotropic obesity syndromes have been studied by linkage analysis and chromosomal loci for Cohen's syndrome,[8] Alström's syndrome,[9] and at least four for Bardet–Biedl syndrome[10–12] have been mapped so far, although the precise molecular defects are not yet known. However, recent studies of genetic syndromes of obesity in rodents have provided several novel insights into molecules which may be involved in energy homoeostasis. The rodent single gene obesities represent complex admixtures of the key mechanisms that are involved in the development of an obese phenotype, namely an increase in energy intake, relative decrease in energy expenditure, or preferential partitioning of ingested energy to fat storage. In the past two years we and others have begun to identify human disorders of energy balance that arise from genetic defects in these or similar

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molecules. These mutations often result in morbid obesity in childhood without the developmental pleiotropic features characteristic of the recognised syndromes of childhood obesity.

Leptin and the leptin receptor

The severely obese *ob*/*ob* mouse, first described by Ingalls *et al* in 1950,[13] inherits its early onset obesity in an autosomal recessive pattern and weighs three times more than normal mice by maturity. A decrease in thermogenesis is the earliest demonstrable defect; hyperphagia is seen after weaning, followed by the development of severe obesity caused by the preferential deposition of fat. The hyperinsulinaemia, fasting hyperglycaemia, infertility, thyroid dysfunction, stunted linear growth, and low sympathetic tone of *ob*/*ob* mice are shared by another strain of severely obese mice, *db*/*db*. In 1994, Friedman and colleagues cloned and characterised the ob gene which is expressed predominantly in white adipose tissue and encodes the 167 amino acid secreted protein, leptin.[14] The ob transcript is mutant in both strains of *ob*/*ob* mice which are leptin deficient as a result. Administration of recombinant leptin completely reverses their phenotypical abnormalities,[15–17] but has no effect in *db*/*db* mice which harbour a mutation in the cytoplasmic domain of the leptin receptor,[18] abundantly expressed in the hypothalamus.

Human congenital leptin deficiency

In man, serum leptin concentrations have been found, in general, to correlate positively with indices of obesity.[19] We have previously identified two cousins within a highly consanguineous family of Pakistani origin with severe obesity of early onset: an 8 year old girl weighing 86 kg and a 2 year old boy weighing 29 kg.[20] These children were noted to be severely hyperphagic, constantly demanding food, with an intense drive to eat which was never satisfied. They did not exhibit any of the clinical features suggestive of the recognised childhood obesity syndromes, had a normal karyotype, thyroid, and adrenal function, but were hyperinsulinaemic and had an advanced bone age. They were found to have undetectable concentrations of serum leptin and were homozygous for a deletion of a single guanine nucleotide at codon 133 which results in a truncated protein. Both sets of parents were heterozygous for this mutation in keeping with an autosomal recessive pattern of inheritance. There was no evidence of substantial impairment in basal or total energy expenditure and body temperature was consistently normal, indicating that leptin may be less central to the regulation of energy expenditure in humans than in mice, although subtle defects of energy expenditure are difficult to measure.

Subsequently Strobel and colleagues have described a Turkish family in which three severely obese siblings were found to be leptin deficient because of a missense mutation in the leptin gene.[21] Additionally, Clement and colleagues identified three morbidly obese sisters with very high serum leptin concentrations who were found to be homozygous for a mutation in a splice donor site of the leptin receptor, which results in loss of the transmembrane and cytoplasmic domains because of exon skipping.[22] There were a number of similarities with the leptin deficient subjects. These sisters were also born of normal birth weight, and exhibited rapid weight gain in the first few months of life, with severe hyperphagia and aggressive behaviour when denied food. Basal temperature and resting metabolic rate were normal. In contrast, they had mild growth retardation in early childhood with impaired basal and stimulated growth hormone secretion and decreased insulin like growth factor 1 (IGF-1) and IGF-BP3 concentrations. There was evidence of hypothalamic hypothyroidism, although as in the leptin deficient subjects, cortisol concentrations were normal and they were normoglycaemic with mildly raised plasma insulins.

Of note, the two Turkish adults with leptin deficiency and the sisters with mutations in the leptin receptor did not undergo pubertal development with biochemical features of hypogonadotropic hypogonadism. In the older of our two patients (a 9 year old girl) it is difficult to confirm hypogonadotropic hypogonadism as she is clinically prepubertal, but a child with a bone age of 12.5 years would usually have started to develop some secondary sexual characteristics. While bone age is frequently advanced in obese children, an advance in excess of three years has rarely been reported.[23] In this instance, advanced bone age could not be attributed to excessive and/or premature secretion of adrenal or ovarian sex steroids as their plasma concentrations were low and the physiological basis for this is not clear.

Morbid obesity was inherited in an autosomal recessive pattern in both leptin and leptin receptor families and the absence of morbid obesity and normal sexual maturation in the heterozygote parents indicates that the lack of one normal allele does not greatly affect weight regulation or neuroendocrine function.

POMC and the melanocortin pathway

The behavioural and neuroendocrine effects of leptin are thought to be mediated through its actions at hypothalamic leptin receptors. The complex neurochemical systems downstream of leptin that regulate appetite and energy expenditure and integrate nutritional and circadian information into endocrine responses, are being dissected. Pro-opiomelanocortin (POMC) is produced by hypothalamic neurones of the arcuate nucleus and is sequentially cleaved by prohormone convertases to yield peptides (including α melanocyte stimulating hormone, αMSH) that have been shown to play a role in feeding behaviour. Forty per cent of POMC neurones in the arcuate nucleus express the mRNA for the long form of the leptin receptor, and POMC expression is regulated positively by leptin.[24] There is clear evidence in rodents that αMSH, a melanocortin peptide produced from POMC, acts as a suppressor of feeding behaviour. The recent description of two unrelated German subjects with mutations in POMC

associated with isolated adrenocorticotropic hormone (ACTH) deficiency, red hair pigmentation, hyperphagia, and severe, early onset obesity confirms the importance of POMC derived peptides in the regulation of body weight in humans.[25] The hair, skin, and adrenal phenotype of these subjects is readily understandable on the basis of the known effects of POMC derived peptides in these tissues. Given the importance of prohormone convertase 1 (PC1) in the proteolytic processing of POMC, it is notable that we have reported a single patient with severe early onset obesity to have compound heterozygote mutations in the gene encoding PC1.[26] In addition to obesity, this patient had primary amenorrhoea caused by hypogonadotropic hypogonadism, massive hyperproinsulinaemia, and impaired adrenal function.[27]

How does the lack of POMC derived ligands lead to obesity? Interestingly, one form of melanocortin receptor (MC4R) is highly expressed in areas of the hypothalamus known to be involved in feeding. Mice in which the MC4 receptor has been disrupted by gene targeting are hyperphagic, becoming severely obese, hyperinsulinaemic, and exhibiting increased linear growth, but show no evidence of reproductive failure or corticosterone excess.[28] We have recently described a father and son with hyperphagia, severe early onset obesity and tall stature, with mutations in MC4R.[29] Both were heterozygous for a four base pair deletion in the region encoding the fifth of seven transmembrane domains, resulting in a truncated protein. Interestingly, both subjects were tall, in keeping with the increased linear growth seen in MC4R knockout mice, but had no other endocrine abnormalities. A French family described by Vaisse and colleagues with obesity associated with a mutation in MC4R have no obvious defect in resting energy expenditure.[30] MC4R, therefore, represents the first locus at which mutations are associated with dominantly inherited morbid obesity in man, a finding that is consistent with the observation that mice heterozygous for a null MC4R allele exhibit weight gain intermediate to that seen in wild type and homozygous mutant littermates. An increasing number of obese families with MC4R mutations are now being described (Gu *et al*,[31] Hinney *et al*,[32] and our unpublished observations) making it the commonest known genetic cause of human obesity.

Conclusions

In the past three years, five single gene disorders resulting in early onset obesity have been characterised. Two of these, leptin receptor and PC1, have been restricted to single families. Three families with mutations in POMC or leptin have been described. Mutations in the MC4R appear to be a more common cause of obesity, perhaps because heterozygotes are clinically affected and therefore only one mutational event is required. Additionally, mutations in leptin, the leptin receptor, and PCI adversely affect reproduction and therefore would be expected to be rapidly bred out. Similarly POMC deficiency is fatal if unrecognised owing to profound cortisol deficiency. In contrast MCR4 deficiency appears to cause a relatively "pure" obesity syndrome with no impairment of early viability or reproductive function.

The discovery of these genetic defects has biological and clinical implications which are greater than the rarity of the individual diseases might suggest. Firstly, at least one disorder, namely leptin deficiency, is amenable to treatment. Such treatment represents the first, rationally based, hormone replacement therapy for any form of human obesity. Secondly, these disorders establish for the first time that human obesity can result from a simple fault in the wiring of the circuits concerned with energy homoeostasis without the need to implicate complex social and environmental factors. We hope that this may help to "destigmatise" obesity and validate it as a medical condition deserving of sympathetic handling and worthy of scientific study. Thirdly, they represent powerful confirmation that the growing body of data on the molecular circuitry controlling appetite and energy balance in rodents is directly relevant to humans, and provides strong support for the benefits of animal research. Fourthly, they provide validation of certain key molecules as potential targets for pharmacological manipulation. Finally, as the loci encompassing these genes have been found to be significantly associated with obesity related phenotypes in genome wide scans, they provide important candidate genes for examination in the more common forms of human obesity.[33 34]

Postscript

The authors welcome enquires regarding biochemical and genetic studies of patients with severe early onset obesity. The criteria for inclusion in these studies is a BMI >4 SD above the age related mean[3] and an onset of obesity before 10 years of age.

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