EJE PRIZE 2012

Obesity: from genes to behaviour

I Sadaf Farooqi

Wellcome Trust – MRC Institute of Metabolic Science, Addenbrooke's Hospital, University of Cambridge Metabolic Research Laboratories, Cambridge, UK

Correspondence
should be addressed
to I S Farooqi
Email
isf20@cam.ac.uk

Abstract

An increase in the consumption of highly palatable foods coupled with a reduction in the amount of voluntary exercise undertaken has contributed to the rising prevalence of obesity. However, despite the obvious environmental influences, there is considerable evidence to support a genetic component to weight gain. In some people, particularly those who are severely obese, genetic factors play a major role in the development of their obesity and associated complications. Studies into the genetic basis of obesity have yielded insights into the mechanisms involved in the regulation of weight. We now understand that weight is regulated by neural mechanisms that regulate appetite and energy expenditure and that disruption of these pathways can result in severe obesity in some patients. These studies provide a starting point for investigating patients with severe obesity and may ultimately guide the development of more rational targeted therapies.

*European Journal of
Endocrinology*
(2014) **171**, R191–R195

Introduction

The rising prevalence of obesity in Europe and worldwide has been driven by changes in the environment over the last 30 years. Considerable epidemiological evidence suggests that over this period of time, major changes have occurred in daily energy expenditure (in particular physical activity conducted during work and leisure time) associated with increased urbanisation. There have also been changes in the amount of food we consume, attributed to the easy availability of cheap, highly palatable foods. However, there is a considerable variation in body weight and BMI within a population that shares the same environment. Moreover, some ethnic groups are particularly prone to

gaining weight, suggesting a genetic predisposition. We have identified a number of genes whose disruption leads to severe obesity that begins in early childhood. The study of these patients has paved the way for understanding the mechanisms involved in energy balance and how these may be disrupted to cause severe obesity in humans.

Hypothalamic pathways involved in weight regulation

The discovery of the hormone leptin in 1994 paved the way for the identification of an entire pathway that regulates

Invited Author's profile

Professor Sadaf Farooqi identified the first single gene defect to cause human obesity in patients with a mutation in the leptin gene and described their dramatic response to leptin therapy, establishing leptin's role in the regulation of eating behaviour, puberty and immune function. As a Wellcome Trust Senior Clinical Fellow at the Institute of Metabolic Science in Cambridge, Professor Farooqi co-ordinates a programme of research into the genetic, molecular and physiological basis of human obesity.

energy balance (1). Leptin is expressed and secreted by adipocytes in a manner that is proportionate to the amount of fat mass (2). As leptin levels rise with obesity, it was initially considered that leptin's primary role was to signal increasing energy stores which should lead to a change in energy intake and expenditure to restore energy balance. However, it is clear that this does not happen and that most people are relatively resistant to rising endogenous, or indeed exogenously administered leptin. Instead, leptin's physiological role appears to be to signal nutritional depletion, such that fasting or weight loss results in a fall in leptin levels, which then triggers a series of changes in energy intake, energy expenditure and neuroendocrine function in order to maintain energy homeostasis (3). Many of the physiological effects of leptin are mediated through neurons in the hypothalamus which express the signalling form of the leptin receptor (4). These primary leptin-responsive neurons project to second-order neurons in the hypothalamus and other brain regions that express the melanocortin 4 receptor (MC4R). These hypothalamic pathways interact with other neural systems to coordinate appetite and modulate efferent signals to the periphery to regulate energy balance in response to nutrients, hormones and other external cues (5).

Mutations in the leptin pathway cause severe human obesity

Although rare (1–5% of severe obesity), the characterisation of genetic disorders involving disruption of the leptin–melanocortin pathway has provided insights into the regulation of body weight in humans. The first gene defect to be identified was congenital leptin deficiency. Homozygous mutations in the gene encoding leptin result in severe obesity from a young age (6, 7). The key clinical features seen in patients are an intense drive to eat (hyperphagia) and impaired satiety, with patients demanding food soon after a meal. We used functional neuroimaging to investigate the neural response to food-related stimuli. Based on the clinical observation that patients with leptin deficiency like all foods and display emotional responses to food, we hypothesised that leptin may play a broader role in mediating aspects of eating behaviour such as the rewarding properties of food. Using functional MRI, we found that leptin-deficient patients showed marked activation of the ventral striatum, an area associated with pleasure and reward, in response to the images of food vs non-food items; even images of bland foods were rewarding and elicited striatal activation in these patients in contrast to healthy volunteers (8).

Patients with mutations in the gene encoding the leptin receptor have very similar clinical features including hyperphagia and severe early-onset obesity (9, 10). Disruption of leptin signalling by mutations in leptin and the leptin receptor are associated with hypogonadotropic hypogonadism and a failure of normal pubertal development. However, there is some evidence for the delayed but spontaneous onset of menses in some leptin receptor-deficient adults (11). One possibility is that excess adipose tissue mass leads to the production of sufficient oestrogen (due to the action of aromatase), to result in uterine development and irregular menses in the absence of fully developed secondary sexual characteristics. Leptin does not appear to have direct effects on gonadotrophin-releasing hormone secretion, but may exert effects on the reproductive system through the neuropeptide kisspeptin, which signals through GPR54.

Although congenital leptin deficiency is rare, we were able to demonstrate that it is entirely treatable with daily s.c. injections of recombinant human leptin with beneficial effects on the degree of hyperphagia, reversal of the immune defects and infection risk seen in leptin-deficient patients and leading to the development of puberty at an appropriate age (Fig. 1) (7, 12). Such treatment is currently available to patients on a named patient basis. We showed that the major effect of leptin administration is on food intake, with normalisation of hyperphagia, enhanced satiety and normalisation of the striatal response to food images. We were unable to demonstrate a major effect of leptin on basal metabolic rate (BMR) or free-living energy expenditure, but, as weight loss by other means is associated with a decrease in BMR (13), the fact that energy expenditure did not fall in leptin-deficient subjects is notable. The administration of leptin permits progression of appropriately timed pubertal development, suggesting that leptin is a permissive factor for the development of puberty in humans.

Central melanocortin pathways

Leptin stimulates the expression of pro-opiomelanocortin (POMC) in primary neurons located in the arcuate nucleus of the hypothalamus. POMC is processed by prohormone convertases to generate the melanocortin peptides which activate melanocortin receptors to modulate diverse functions in the CNS, the adrenal gland and skin (14). The melanocortins are agonists at melanocortin receptors, and activation of the MC4R leads to a reduction in food intake. In addition, leptin inhibits orexigenic pathways mediated by neurons expressing the

Figure 1

Schematic representation of the hypothalamic leptin–melanocortin pathway. POMC, pro-opiomelanocortin; PC1/3, prohormone convertase 1/3; MC4R, melanocortin 4 receptor.

*Indicates molecules disrupted by genetic mutations found in severely obese patients.

melanocortin antagonist agouti-related peptide (AgRP) and neuropeptide Y (NPY); NPY can suppress the expression of POMC. These two sets of primary leptin-responsive neurons project to second-order neurons expressing MC4R (15).

In further studies, we identified mutations in a number of genes involved in pathways that regulate appetite downstream of leptin in patients with severe early-onset obesity. We and others have reported that heterozygous mutations in MC4R are found in 2–3% of children in obesity clinics and up to 5% of patients with severe early-onset obesity, making MC4R deficiency the commonest genetic form of severe obesity (16, 17). As such, assessment of the MC4R gene is increasingly seen as a necessary part of the clinical evaluation of the severely obese child (18). Heterozygous functionally significant MC4R mutations are inherited in a co-dominant manner, with variable penetrance; additionally, homozygous mutations in MC4R have been found in some patients with severe obesity. MC4R mutation carriers are objectively hyperphagic with impaired satiety.

By studying a large number of patients with different MC4R mutations, we found that the severity of receptor dysfunction measured in cells predicted food intake at a test meal, suggesting that signalling through this pathway is a major mechanism for the regulation of appetite (19). As such, a number of drugs that target MC4R are being developed for the potential treatment of severe obesity, initially focusing on this group of patients (20).

We found that MC4R-deficient patients have a lower prevalence of hypertension and lower systolic and diastolic blood pressures when compared with equally obese volunteers (21). We hypothesised that the lower blood pressures seen in MC4R-deficient humans may be explained by altered sympathetic nervous system activation. We measured heart rate variability, which is a widely accepted non-invasive tool that has been validated against more direct pharmacological measurements of sympathetic and parasympathetic activation, and found that sleeping heart rate (mediated predominantly by parasympathetic activation) was similar in

MC4R-deficient subjects and controls. The increase in heart rate upon waking (driven predominantly by sympathetic nervous system (SNS) activation) was reduced in MC4R-deficient subjects. We found that urinary nor-adrenaline excretion was markedly reduced in MC4R deficiency. These findings established the importance of MC4R-mediated signalling in the regulation of blood pressure and suggested that melanocortinergic circuits play a key role in mediating the link between changes in weight and changes in blood pressure.

New obesity genes

To date, all the genetic forms of severe obesity seem to act predominantly by impacting on the regulation of appetite. We recently identified multiple loss of function mutations in the gene encoding kinase suppressor of Ras 2 (KSR2), a cellular scaffolding protein that is involved in the Ras-Raf-MEK signalling pathway (22). In contrast to normal weight and obese healthy volunteers and individuals with other genetic forms of obesity (such as MCR deficiency), we found that BMR was significantly less than predicted in adult KSR2 mutation carriers. In the presence of normal thyroid function and in the absence of other explanations for reduced BMR, our findings indicate that mutations in *KSR2* represent a novel genetic influence on BMR in humans. There was a history of increased food-seeking behaviour in childhood; however, hyperphagia was reported as being less prominent with age and, in adult *KSR2* mutation carriers, measured *ad libitum* energy intake did not differ significantly from obese controls. Further work is needed to understand the mechanisms underlying the clinical features of these patients, but the evidence suggests that *KSR2* has multiple effects on energy balance.

Conclusions

Some individuals are particularly susceptible to the development of severe obesity due to genetic factors. Future strategies to treat and support this group of patients, whose numbers are increasing, will need to consider how specific genes modulate the drive to eat and energy expenditure. Our work has emphasised the need to recognise and characterise the heterogeneity of obesity and to define subgroups of patients at risk of different metabolic and cardiovascular complications who may benefit from targeted preventative and therapeutic strategies.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

The author would like to thank the many colleagues and collaborators who have contributed to this work and in particular to physicians who have referred patients with severe obesity, without whom this work would not have been possible. The author would also like to thank the patients and their families for their active involvement in many years of research for the benefit of others.

References

- 1 Zhang Y, Proenca R, Maffei M, Barone M, Leopold L & Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994 **372** 425–432. (doi:10.1038/372425a0)
- 2 Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, Fei H, Kim S, Lallone R, Ranganathan S *et al.* Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nature Medicine* 1995 **1** 1155–1161. (doi:10.1038/nm1195-1155)
- 3 Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E & Flier JS. Role of leptin in the neuroendocrine response to fasting. *Nature* 1996 **382** 250–252. (doi:10.1038/382250a0)
- 4 Elmquist JK, Bjørbaek C, Ahima RS, Flier JS & Saper CB. Distributions of leptin receptor mRNA isoforms in the rat brain. *Journal of Comparative Neurology* 1998 **395** 535–547. (doi:10.1002/(SICI)1096-9861(19980615)395:4<535::AID-CNE9>3.0.CO;2-2)
- 5 Schwartz MW, Woods SC, Porte D Jr, Seeley RJ & Baskin DG. Central nervous system control of food intake. *Nature* 2000 **404** 661–671. (doi:10.1038/oby.2006.275)
- 6 Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, Sewter CP, Digby JE, Mohammed SN, Hurst JA *et al.* Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* 1997 **387** 903–908. (doi:10.1038/43185)
- 7 Farooqi IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, Prentice AM, Hughes IA, McCamish MA & O'Rahilly S. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *New England Journal of Medicine* 1999 **341** 879–884. (doi:10.1056/NEJM199909163411204)
- 8 Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S & Fletcher PC. Leptin regulates striatal regions and human eating behavior. *Science* 2007 **317** 1355. (doi:10.1126/science.1144599)
- 9 Clément K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, Goumelen M, Dina C, Chambaz J & Lacorte JM. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction [see comments]. *Nature* 1998 **392** 398–401. (doi:10.1038/32911)
- 10 Farooqi IS, Wangenstein T, Collins S, Kimber W, Matarese G, Keogh JM, Lank E, Bottomley B, Lopez-Fernandez J, Ferraz-Amaro I *et al.* Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. *New England Journal of Medicine* 2007 **356** 237–247. (doi:10.1056/NEJMoa063988)
- 11 Ozata M, Ozdemir IC & Licinio J. Human leptin deficiency caused by a missense mutation: multiple endocrine defects, decreased sympathetic

- tone, and immune system dysfunction indicate new targets for leptin action, greater central than peripheral resistance to the effects of leptin, and spontaneous correction of leptin-mediated defects. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 3686–3695. (doi:10.1210/jcem.84.10.5999)
- 12 Farooqi IS, Matarese G, Lord GM, Keogh JM, Lawrence E, Agwu C, Sanna V, Jebb SA, Perna F, Fontana S *et al*. Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *Journal of Clinical Investigation* 2002 **110** 1093–1103. (doi:10.1172/JCI0215693)
 - 13 Galgani JE, Greenway FL, Caglayan S, Wong ML, Licinio J & Ravussin E. Leptin replacement prevents weight loss-induced metabolic adaptation in congenital leptin-deficient patients. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 851–855. (doi:10.1210/jc.2009-1739)
 - 14 Coll AP, Farooqi IS, Challis BG, Yeo GS & O'Rahilly S. Proopiomelanocortin and energy balance: insights from human and murine genetics. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 2557–2562. (doi:10.1210/jc.2004-0428)
 - 15 Huszar D, Lynch CA, Fairchild-Huntress V, Dunmore JH, Fang Q, Berkemeier LR, Gu W, Kesterson RA, Boston BA, Cone RD *et al*. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. *Cell* 1997 **88** 131–141. (doi:10.1016/S0092-8674(00)81865-6)
 - 16 Vaisse C, Clement K, Durand E, Hercberg S, Guy-Grand B & Froguel P. Melanocortin-4 receptor mutations are a frequent and heterogeneous cause of morbid obesity. *Journal of Clinical Investigation* 2000 **106** 253–262. (doi:10.1172/JCI9238)
 - 17 Farooqi IS, Yeo GSH, Keogh JM, Aminian S, Jebb SA, Butler G, Cheetham T & O'Rahilly S. Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency. *Journal of Clinical Investigation* 2000 **106** 271–279. (doi:10.1172/JCI9397)
 - 18 Farooqi IS. The severely obese patient – a genetic work-up. *Nature Clinical Practice. Endocrinology & Metabolism* 2006 **2** 172–177 quiz following 177. (doi:10.1038/ncpendmet0137)
 - 19 Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T & O'Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *New England Journal of Medicine* 2003 **348** 1085–1095. (doi:10.1056/NEJMoa022050)
 - 20 René P, Le Gouill C, Pogozeva ID, Lee G, Mosberg HI, Farooqi IS, Valenzano KJ & Bouvier M. Pharmacological chaperones restore function to MC4R mutants responsible for severe early-onset obesity. *Journal of Pharmacology and Experimental Therapeutics* 2010 **335** 520–532. (doi:10.1124/jpet.110.172098)
 - 21 Greenfield JR, Miller JM, Keogh JW, Henning E, Satterwhite JH, Cameron GS, Astruc B, Mayer JP, Brage S, See TC *et al*. Modulation of blood pressure by central melanocortinergeric pathways. *New England Journal of Medicine* 2009 **360** 44–52. (doi:10.1056/NEJMoa0803085)
 - 22 Pearce LR, Atanassova N, Banton MC, Bottomley B, van der Klaauw AA, Revelli JP, Hendricks A, Keogh JM, Henning E, Doree D *et al*. KSR2 mutations are associated with obesity, insulin resistance, and impaired cellular fuel oxidation. *Cell* 2013 **155** 765–777. (doi:10.1016/j.cell.2013.09.058)

Received 11 August 2014

Accepted 13 August 2014