Obesity hypoventilation syndrome

# Leptin and the obesity hypoventilation syndrome: a leap of faith?

**M Fitzpatrick**

## A possible role for leptin or its analogues in the treatment of the obesity hypoventilation syndrome

The discovery of the anti-obesity hormone leptin (the name is derived from the Greek "leptos" meaning "thin"), the product of the *ob* gene,[1] has fuelled a recent surge of interest in the mechanisms regulating mammalian fat stores. Leptin, a 16 kD protein of 167 amino acids with a similar crystal structure to cytokines,[2] is produced primarily by white adipose tissue.[3] The hormone elicits appetite suppression and weight loss.[4 5] Leptin circulates in the plasma in the free and protein bound forms. Circulating plasma leptin levels reflect the amount of energy storage in adipose tissue and increase exponentially with increasing fat mass.[6] Plasma leptin levels also respond to short term energy imbalance, increasing during periods of overfeeding and decreasing with fasting.[7 8] The hormone activates specific receptors[9] located at several sites throughout the brain, but plays a key role at the hypothalamus, in particular, where it alters the expression of several hypothalamic neuropeptides.[10 11] One of these, neuropeptide Y (NPY), is a potent stimulator of food intake and activator of the hypothalamic-pituitary-gonadal axis. Leptin inhibits synthesis of hypothalamic NPY and downregulation of NPY is associated with appetite suppression, increased sympathetic nervous system outflow, and increased energy expenditure.[12] Increasing leptin levels activate the thyroid hormone, gonadal, and growth hormone axes and suppress the pituitary-adrenal axis.[13] It must be emphasised that human obesity is a complex disorder, probably resulting from both multigenetic and environmental predispositions, and that leptin deficiency is a very rare cause of human obesity.[14] Indeed, circulating leptin levels are typically higher than normal in human obesity, indicating that it is a leptin resistant state.[15] Even within the hypothalamus the NPY axis is clearly not a final common pathway for appetite control as the appetite stimulating orexins can induce feeding despite blockade of the NPY axis.[16]

### REGULATION OF LEPTIN PRODUCTION

Leptin production is regulated by several factors.[17 18] Insulin and glucocorticoids act directly on adipocytes to increase leptin production, and chronic hyperinsulinaemia and increased cortisol turnover may underlie the increase in leptin expression observed in obesity. Similarly, the observed increase in serum leptin levels 4–7 hours after meals is probably related to increased circulating insulin in concert with the permissive effects of cortisol. Fasting results in decreased serum leptin levels—probably through falling insulin levels and the ability of catecholamines to decrease leptin expression (isoproterenol and $\beta_3$ adrenergic receptor agonists reduce leptin production by adipocytes). Women have been noted to have higher serum leptin levels than men, and this could relate to a difference in body fat composition between the sexes or the permissive effects of oestrogen and progesterone on leptin production. Under conditions of constant enteral feeding, circulating leptin levels are higher at night than during the day; in addition to a small circadian influence, sleep is associated with an increase in plasma leptin levels in normal subjects.[19]

### EFFECTS OF LEPTIN ON RESPIRATION

Apart from its anti-obesity effects, leptin exerts important physiological effects on the control of respiration.[20] Ob/ob mice, which lack the gene responsible for production of leptin, demonstrate hypoventilation in addition to marked obesity ($Paco_2$ on average 1.5 kPa higher than wild type mice during wakefulness).[21] Furthermore, these animals have an impaired hypercapnic ventilatory response (HCVR) during both wakefulness and sleep. During REM sleep the HCVR is absent in ob/ob mice. This impairment of the HCVR in ob/ob mice relative to wild type mice cannot be attributed to the mechanical effects of obesity as it precedes the development of the latter.[20] Furthermore, leptin replacement studies in ob/ob mice have shown improvements in baseline minute ventilation and HCVR during wakefulness and sleep under experimental conditions which prevented a concomitant weight change in the animal.[21 22]

### ROLE OF LEPTIN IN OSA

The high prevalence of obstructive sleep apnoea (OSA) in obese humans[23] and the established role of leptin as a respiratory stimulant and appetite suppressant in the mouse raised the possibility that sleep apnoea could be a leptin deficient state. Several groups have shown, however, that patients with OSA have even higher circulating leptin levels (approximately 50%) than subjects without OSA matched for age and body mass index.[24–26] This finding suggests that, independent of the known relationship between obesity and increased circulating leptin levels, OSA could represent a leptin *resistant* state. Two groups have shown that treatment of OSA with nasal continuous positive airway pressure (NCPAP) for 6 months is associated with a reduction in circulating leptin to a level similar to individuals without OSA.[24 26] The physiological explanation for the fall in circulating leptin levels in patients with OSA treated with NCPAP has not been fully elucidated, but some plausible explanations include a reduction in visceral fat accumulation,[27] reduction in muscle sympathetic nerve activity,[28] reduced level of stress,[29] and a change in insulin responsiveness[30] with NCPAP treatment. The fact that circulating leptin levels fall with NCPAP treatment of OSA, however, suggests that OSA may be a stimulant of leptin production rather than a consequence of the action of leptin.

> "A profound degree of leptin resistance may underpin the development of the obesity hypoventilation syndrome"

The obesity hypoventilation syndrome (OHS) is characterised by obesity and hypercapnia while awake in the absence of an alternative neuromuscular, mechanical, or metabolic explanation for hypoventilation. Most patients with OHS suffer from OSA and in many (but not all) cases treatment of OSA with NCPAP restores daytime eucapnia.[31 32] In some patients OHS cannot be explained on the basis of OSA,[33] and daytime hypercapnia appears to result from inadequate physiological compensation for the development of obesity alone. This condition remains an enigma. Why do certain obese individuals hypoventilate during wakefulness while others with similar or greater levels of obesity do not? Could leptin be the key to understanding this conundrum?

The paper by Phipps and colleagues[34] in this issue of *Thorax* contributes an interesting additional piece of information. The authors discovered that the mean serum leptin level was twice as high in a group of 12 hypercapnic obese humans as in a group of 44 eucapnic individuals with a similar percentage of body fat. Both groups had a mean apnoea-hypopnoea index in the severe OSA range but were not significantly different from each other. This finding raises the intriguing possibility that a profound degree of leptin resistance (more than that observed with eucapnic obesity or OSA alone) underpins the development of OHS. If this is the case, then leptin or analogues of leptin could have a role in the treatment of OHS. However, this preliminary finding by Phipps and colleagues will require further exploration to determine whether the marked increase in serum leptin levels found in patients with OHS truly signals a causative mechanism or whether it is simply an epiphenomenon of the condition. In particular, it would be interesting to know whether serum leptin levels are raised in patients with OHS but without significant OSA compared with patients with a similar level of simple obesity, whether leptin levels are increased in non-obese patients with hypoventilation, and whether the serum leptin level in patients with OHS reverts with treatment to the level observed in simple obesity, as might be expected if the increased serum leptin levels are a consequence rather than a causative factor in OHS. These questions and others with regard to the potential respiratory modulating role of leptin in humans, an exciting new research area, will probably find an answer within the next few years.

*Thorax* 2002;**57**:1–2

**Author's affiliation**
**M Fitzpatrick,** Division of Respiratory and Critical Care Medicine, Queen's University, Kingston, Ontario K7L 3N6, Canada

Correspondence to: Dr M Fitzpatrick; mf19@post.qeensu.ca

## REFERENCES

1 **Zhang Y**, Proenca R, Maffei M, *et al*. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994;**372**:425–32.
2 **Zhang F**, Babinski MB, Beals JM, *et al*. Crystal structure of the obese protein leptin-E100. *Nature* 1997;**387**:206–9.
3 **Klein S**, Coppack SW, Mohamed-Ali V, *et al*. Adipose tissue leptin production and plasma leptin kinetics in humans. *Diabetes* 1996;**45**:984–7.
4 **Halaas JL**, Gajiwala KS, Maffei M, *et al*. Weight-reducing effects of the plasma protein encoded by the obese gene. *Science* 1995;**269**:543–6.
5 **Pelleymounter MA**, Cullen MJ, Baker MB, *et al*. Effects of the obese gene product on weight regulation in ob/ob mice. *Science* 1995;**269**:540–3.
6 **Considine RV**, Sinha MK, Heiman ML, *et al*. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 1996;**334**:292–5.
7 **Kolaczynski JW**, Considine RV, Ohannesian J, *et al*. Responses of leptin to short-term fasting and refeeding in humans. *Diabetes* 1996;**45**:1511–5.
8 **Kolaczynski JW**, Ohannesian JP, Considine RV, *et al*. Response of leptin to short-term and prolonged overfeeding in humans. *J Clin Endocrinol Metab* 1996;**81**:4162–5.
9 **Tartaglia L**. The leptin receptor. *J Biol Chem* 1997;**272**:6093–6.
10 **Flier JS**, Maratos-Flier E. Obesity and the hypothalamus: novel peptides for new pathways. *Cell* 1998;**92**:437–40.
11 **Mantzoros CS**. Leptin and the hypothalamus: neuroendocrine control of food intake. *Mol Psychiatry* 1999;**4**:8–12.
12 **Schwartz MW**, Seeley RJ. Seminars in medicine of the Beth Israel Deaconess Medical Center. Neuroendocrine responses to starvation and weight loss. *N Engl J Med* 1997;**336**:1803–11.
13 **Tritos N**, Mantzoros CS. Leptin: its role in obesity and beyond. *Diabetologia* 1997;**40**:1371–9.
14 **Montague CT**, Farooqi IS, Whitehead JP, *et al*. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* 1997;**387**:903–8.
15 **Caro JH**, Sinha MK, Kolaczynski JW, *et al*. Leptin: the tale of an obesity gene. *Diabetes* 1996;**45**:1455–62.
16 **Willie JT**, Chemelli RM, Sinton CM, *et al*. To eat or to sleep ? Orexin in the regulation of feeding and wakefulness. *Annu Rev Neurosci* 2001;**24**:429–58.
17 **Fried SK**, Ricci MR, Russell CD, *et al*. Regulation of leptin production in humans. *J Nutr* 2000;**130**:3127–31S.
18 **Mantzoros CS**. The role of leptin in human obesity and disease: a review of current evidence. *Ann Intern Med* 1999;**130**:671–80.
19 **Simon C**, Gronfier C, Schlienger JL, *et al*. Circadian and ultradian variations of leptin in normal man under continuous enteral nutrition: Relationship to sleep and body temperature. *J Clin Endocrinol Metab* 1998;**83**:1893–9.
20 **Tankersley CG**, Kleeberger S, Russ B, *et al*. Modified control of breathing in genetically obese (ob/ob) mice. *J Appl Physiol* 1996;**81**:716–23.
21 **O'Donnell CP**, Schaub CD, Haines AS, *et al*. Leptin prevents respiratory depression in obesity. *Am J Respir Crit Care Med* 1999;**159**:1477–84.
22 **Tankersley CG**, O'Donnell C, Daood MJ. Leptin attenuates respiratory complications associated with the obese phenotype. *J Appl Physiol* 1998;**85**:2261–9.
23 **Young T**, Palta M, Dempsey J, *et al*. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;**328**:1230–5.
24 **Vgontas AN**, Papanicolaou DA, Bixler EO, *et al*. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab* 2000;**85**:1151–8.
25 **Phillips BG**, Kato M, Narkiewicz K, *et al*. Increases in leptin levels, sympethetic drive, and weight gain in obstructive sleep apnea. *Am J Physiol Heart Circ Physiol* 2000;**279**: H234–7.
26 **Ip MSM**, Lam KSL, Ho C, *et al*. Serum leptin and vascular risk factors in obstructive sleep apnea. *Chest* 2000;**118**:580–6.
27 **Chin K**, Shimizu K, Nakamura T, *et al*. Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. *Circulation* 1999;**100**:706–12.
28 **Snitker S**, Pratley RE, Nicolson M, *et al*. Relationship between muscle sympathetic nerve activity and plasma leptin concentration. *Obes Res* 1997;**5**:338–40.
29 **Heiman MI**, Ahima LS, Craft B, *et al*. Leptin inhibition of the hypothalamic-pituitary-adrenal axis in response to stress. *Endocrinology* 1997;**138**:3859–63.
30 **Brooks B**, Cistulli PA, Borkman M, *et al*. Obstructive sleep apnea in obese noninsulin-dependent diabetic patients: effect of continuous positive airway pressure treatment on insulin responsiveness. *J Clin Endocrinol Metab* 1994;**79**:1681–5.
31 **Sullivan CE**, Berthon-Jones M, Issa F. Remission of severe obesity hypoventilation syndrome after short term treatment during sleep with continuous positive airway pressure. *Am Rev Respir Dis* 1983;**128**:177–81.
32 **Berthon-Jones M**, Sullivan CE. Time course of change in ventilatory response to $CO_2$ in long-term CPAP treatment for obstructive sleep apnea. *Am Rev Respir Dis* 1987;**135**:144–7.
33 **Jokic R**, Zintel T, Gallagher CG, *et al*. Ventilatory chemoresponsiveness in relatives of patients with obesity hypoventilation syndrome and normal subjects. *Thorax* 2000;**55**:940–5.
34 **Phipps PR**, Starritt E, Caterson I, *et al*. Association of serum leptin with hypoventilation in human obesity. *Thorax* 2001;**57**:75–6.