EDITORIAL

# Leptin, obesity and sleep disordered breathing

**J. C. Suri**

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See end of article for authors affiliations

Address for correspondence:
J. C. Suri, Head of the Department, Department of Pulmonary, Critical Care & Sleep Medicine, Vardhaman Mahavir Medical College & Safdarjang Hospital, New Delhi
jcsuri@del3.vsnl.net.in

## Introduction

The term leptin was coined by Zhang and colleagues after they cloned the ob/ob gene and was derived from the Greek word 'Leptis' meaning thin (1). It is a 16 KD, 167 amino acid protein hormone which is produced primarily by white adipose tissue under the influence of adipose-specific ob gene (1,2). It circulates in the plasma as free and protein–bound form and its levels reflect the amount of energy stored in the adipose tissue and body mass index (BMI) (3). It activates specific receptors located at various locations in the central nervous system but plays a vital role at hypothalamus, where it inhibits the production of neuropeptide Y (NPY), which is a potent stimulator of food intake and activator of hypothalamic-pituitary-gonadal axes (4,5,6).

A rapidly growing literature about leptin, highlights its broad and pleiotropic effects on human physiology. The important physiological effects include appetite suppression; increased energy expenditure and weight loss (7); an increased sympathetic nervous system outflow (8,9). It also activates thyroid, gonadal and growth hormone axes and suppresses pituitary-adrenal axis (10). Recently, its deficiency has been associated with hypothalamic amenorrhea (11).

## Regulation of leptin production

Amongst the important factors which influence the levels of leptin in the blood are insulin and glucocorticoids which act directly on adipose tissue to increase leptin production. The observed increase in leptin levels 4-6 hours after food intake is probably indirectly through the release of insulin. Fasting on the other hand is associated with decrease serum leptin levels. This could probably be either due to falling insulin levels or excess release of catacholamines which in turn suppress the expression of leptin from adipocytes. Women in general have higher leptin levels than men for the same degree of adiposity and this could be responsible for the difference in the fat distribution, i.e. visceral versus subcutaneous, between the sexes. Oestrogen and progesterone may have a permissive effect on leptin production in women (12,13).

## Effect of Leptin on Respiration

Besides other effects leptin has been found to have an important role on the control of breathing (14). The early studies using the rodent models highlighted the possible role of leptin in the disorders of ventilation. The ob/ob mice, which lack the gene responsible for the production of leptin and developed as a spontaneous

mutation from the Jackson laboratories in 1950s, exhibited pronounced degree of obesity and hypoventilation (15). The mutant mice had a significantly elevated partial pressure of carbon dioxide in arterial blood ($PaCo_2$) compared with wild-type mice during wakefulness (16,17). Furthermore these animals had an impaired hypercapnic ventilatory response (HCVR) during both wakefulness and sleep (17). The respiratory depression of ob/ob mice was worst during REM sleep during which time they were unable to mount any significant ventilatory response to hypercapnic challenge (17). The other significant finding of this study was that depressed HCVR in ob/ob mice relative to wild type mice was present even before the onset of obesity, indicating that leptin produced impairment in respiratory control independent of mechanical effects of obesity (17). Leptin deficiency along with obesity resulted in significant alterations in lung mechanics. For example, there was 50% reduction in total lung capacity (TLC) and compliance in ob/ob mice compared to wild type mice. In addition, structural changes in diaphragm were noticed. There was an increase in the proportion of diaphragmatic myosin heavy chain (MHC) type I fibers and decrease in MHC II b fibers in ob/ob mice relative to wild type mice. This change helps the diaphragm to overcome the fatigue associated with changed breathing pattern of ob/ob mice (18).

When exogenous leptin was administered to ob/ob mice for a period of three days, it resulted in significant increase in baseline minute ventilation compared with control, and this increase was seen during wakefulness, NREM & REM sleep. Leptin replacement also caused increase in HCVR across all levels of inspired $CO_2$ during both REM and NREM sleep but this effect was not visible during wakefulness (18,19). This acute replacement of leptin was done in experimental conditions which prevented the concomitant alterations in the weight and thus avoiding the confounding effect of weight on respiration. Chronic leptin replacement for a period of six week resulted in 40% increase in total lung capacity (TLC) and lung compliance; a significant reduction in MHC type I and increase in MHC type II b fibers (18).

Thus the above findings of leptin replacement in ob/ob mice resulting in augmentation of baseline ventilation and increased chemosensitivity in sleep states, suggest its stimulatory role on the central respiratory control mechanisms. Recently leptin receptors have been identified in the nucleus of the tractus solitarius and reticular activating system (20,21). These are the specific regions which are shown to affect respiratory control and sleep-wake state.

## Role of leptin on respiratory control of diet induced obese mice

From the observations made in the ob/ob mice it was learned that ventilation increased in proportion to increasing leptin levels. To test this hypothesis, respiratory control was studied in a group of wild type mice exhibiting diet induced obesity. When wild type mice were fed on a high fat diet (50% calories derived from fat) for a period of 16 weeks, there was an almost 50% increase in their body weight compared with age matched wild type mice maintained on regular diet. As was expected the serum leptin levels rose by 15 times i.e. to 30 ng/ml in diet-induced obese mice compared with 2ng/ml in the wild type mice on regular diet. There was also a 50-100% increase in the baseline ventilation across all the sleep/ wake states without any decrease in the HCVR during NREM & REM sleep, except during wakefulness, when it was reduced but maintained at the levels of the lean wildtype mice during NREM & REM sleep. There was no evidence of hypoventilation in the diet induced obese wild type mice. These results suggest that if obesity is associated with appropriate elevation in the endogenous leptin levels, respiratory control is effectively matched to the demands of adiposity and respiratory depression, particularly during sleep can be prevented (19).

## Role of leptin on human respiratory control

In humans, the role of leptin in the regulation of ventilation is far more complicated and poorly understood. As observed in the diet induced obese wild type mice, leptin levels are raised in obese human which show strong positive correlation with BMI. The ob RNA content of adipocytes is also twice as high in the obese subjects as in the normal subjects (3). These findings suggest that obese subjects are insensitive to endogenous leptin production. This could be due to failure of feed back loop leading to central leptin resistance.

When the leptin levels in serum were simultaneously compared with that present in the cereberospinal fluid

(CSF) in individuals with a wide range of body weight, it was found that the leptin CSF/serum ratio was four fold higher in lean individuals than that of obese individuals. This data suggests that leptin enters the brains by a saturable transport system. The capacity of leptin transport is lower in obese individuals and may provide a mechanism of leptin resistance (22).

In the context of respiratory and sleep physiology, the leptin has an important role because of its effect on ventilation and weight homeostasis. Obesity has become an important epidemiological phenomena throughout the world (23). As obesity progresses an increase in the resting $PaCO_2$ may develop in some individuals (24,25) leading to obesity hypoventilation (OHS), respiratory failure and premature deaths (26, 27). To date there is no satisfactory explanation why only a minority of severely obese people develop hypoventilation and others breath normally. When fasting serum leptin levels were measured and compared in obese and non obese patients with and without daytime hypercapnia, it was found that there was a close correlation between serum leptin levels and the percentage of body fat, and more importantly serum leptin levels were found to be better predictor of hypercapnia than the body mass index (BMI). In other words those obese individuals who were hypoventilating had a much higher leptin levels than that of eucapnic obese individuals (28). These findings are indicative of a much higher level of leptin resistance in obese hypercapnic individuals.

Obesity is an important risk factor for obstructive sleep apnea syndrome (OSAS), obesity hypoventilation syndrome (OHS) and acute hypercapnic respiratory failure (29). Approximately 10% of patients with OSAS have daytime hyper capnia (30). The high prevalence of OSA in obese patients and the established role of leptin as a respiratory stimulant and appetite suppressant in the mouse raises the possibility that OSAS could be a leptin resistance/deficient state (31). This was observed in a study, which showed much higher serum leptin levels in OSA patients than the non OSA subjects who were matched for age, BMI, sex and menopause (32).

In an another study when serum leptin levels of a group of eucapnic OSAS patients were compared with a group of hypercapnic OSAS patients with similar BMI, age and severity of OSAS, it was found that hyper capnic OSAS patients had a significantly higher leptin levels and the logistic regression analysis of data clearly showed that leptin level was the only variable predictive of hypoventilation (33). The results of these two studies suggest that independent of the known relationship between obesity and increased circulating leptin levels, OSA & OHS could represent leptin resistant state.

It has been found by two groups of investigators that when OSAS patients were treated with nasal CPAP for a period of six months, there was a significant decrease in serum leptin levels almost equal to obese individuals with similar BMI but without OSA (32, 34). Similarly in an another recent study when OHS patient with hypercapnia were treated with non invasive ventilation for a period of 1.5 to 3 years, there was a significant reduction in the serum leptin levels in patients with regular NIV use without a significant change in BMI (35).

The results of these studies suggest that increased levels of serum leptin in patients with OSAS and OHS are a consequence of rather than a cause of sleep disordered breathing. The mechanism underlying this is poorly understood. Unfortunately much needs to be learned. Some have speculated that impaired transport across the blood-brain barrier may be one mechanism of peripheral / central leptin imbalance (36,37), other explanation is impaired central leptin signaling. This latter mechanism could include down-regulation of central leptin receptors, defects in a second messenger or influence from other molecules such as neuropeptide Y, which is an antagonist to leptin in its physiological effect (38).

It has been reported previously that OSAS may lead to depressed ventilatory response and hypoventilation (39,40). Chronic exposure to hypoxia and sleep fragmentation attenuates central respiratory drive. Even healthy subjects with chronic exposure to hypoxic of high altitude have a reduction in both hypoxic and hypercapnic respiratory drive (41). In patients with OSAS, chronic recurrent hypoxia with sleep fragmentation may, in susceptible individuals lead to diminished ventilatory drive and resultant hypoventilation (40,41,42).

A minority of obese patients with hypercapnia do not have OSAS and instead have sustained periods of hypoventilation, particularly during REM sleep and this has been termed sleep hypoventilation syndrome (43). The cause of hypoventilation in these patients could be abnormal ventilatory control i.e. impairment of both hypercapnic and hypoxic ventilatory responses which has

been described previously by many investigators (44,45,46).

There is a possibility of a complex interaction amongst the degree of obesity leading to impared respiratory mechanics and increase work of breathing, severity of OSAS and OHS, and suppression of central respiratory drive which in turn leads to down regulation of leptin receptors with possibly a rise in leptin levels.

## Summary

In summary a complex and intriguing relationship exists between leptin, obesity and sleep disordered breathing. Obesity is associated with high serum leptin levels and the increase is directly proportional to the BMI. The leptin CSF/serum ratio is four fold higher in lean than that of obese individuals. This suggests that obesity is a leptin resist state. When it is complicated with sleep disordered breathing and hypoventilation, leptin resistance becomes more intense with further rise in serum leptin levels. The treatment of sleep disordered breathing with nasal CPAP or NIV results in reduction of leptin levels to that seen in individuals with similar degree of obesity but without OSAS or OHS. However, the mechanism by which OSAS or sleep hypoventilation results in increased leptin level is poorly understood. Further research is required to understand these complex issues.

**Authors' affiliations**

**Dr. J. C. Suri,** Head of the Department, Department of Pulmonary, Critical Care & Sleep Medicine, Vardhaman Mahavir Medical College & Safdarjang Hospital, New Delhi

## 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. **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
4. **Tartaglia L**. The leptin receptor. *J Biol Chem* 1997;**272**:6093–6
5. **Flier JS**, Maratos-Flier E. Obesity and the hypothalamus: novel peptides for new pathways. *Cell* 1998;**92**:437–40
6. **Mantzoros CS**. Leptin and the hypothalamus: neuroendocrine control of food intake. *Mol Psychiatry* 1999;**4**:8–12
7. **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
8. **Dumbar J. C.** Hu Y, Lu H, 1997. Intracerebroventricular leptin increases lumbar and renal sympathetic nerve activity and blood pressure in normal rats. Diabetes 46, 2040-2043
9. **Haynes W.G,** Morgan D.A., Walsh S. A., Sivitz W. I, Mark A. L. 1998. Cardiovascular consequences of obesity: role of leptin. *Clin Exp. Pharmacol. Physiol.* 25, 65-69
10. **Tritos N**, Mantzoros CS. Leptin: its role in obesity and beyond. *Diabetologia* 1997;**40**:1371–9
11. **Welt, C,** Chan, J, Bullen, J, et al Recombinant human leptin in women with hypothalamic amenorrhea. *N Engl J Med* **2004;351**,987-997
12. **Fried SK**, Ricci MR, Russell CD, *et al*. Regulation of leptin production in humans. *J Nutr* 2000;**130**:3127–31S
13. **Mantzoros CS**. The role of leptin in human obesity and disease: a review of current evidence. *Ann Intern Med* 1999;**130**:671–80
14. **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.
15. **Ingalls A.M.,** Dickie M.M., Snell G.D., 1950. Obese, a new mutation in the house mouse. J. *heredity* 41, 317.
16. **Tankersley C,** kleeberger S., Russ B., Schwartz A. R., Smith, P. L. 1996. Modified control of breathing in genetically obese (ob/ob) mice. J appl, Physiol. 81, 716-723
17. O'Donnell C.P., schaub C.D., Haines A. S. et al, 1999. Leptin prevents respiratory depression in obesity. Am J. Resp. Crit. Care Med. 159, 1477-1484.
18. **Tankersley CG**, O'Donnell C, Daood MJ. Leptin attenuates respiratory complications associated with the obese phenotype. *J Appl Physiol* 1998;**85**:2261–9
19. **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
20. **Mercer J. G,** Moar K. M., Hoggarad N., et al. 1998. Localization of leptin receptor (Ob-R) messenger ribonucleic acid in the rodent hindbrain. *Endocrinology* 139, 29-34.
21. **Shioda S,** Funahashi H, nakajo S, Yada T, Maruta O, Nakai Y; 1998. Immunohistochemical localization of leptin receptor in the rat brain. *Neurosci. Lett.* 243, 41-44.
22. **Caro, J,** Kolaczynski, J, Nyce, M, et al Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. *Lancet* **1997;348**,159-161.
23. **Molarius A,** Seidell JC, Sans S, et al. Educational level, relative body weight, and changes in their association over 10 years : an international perspective from the WHO MONICA Project. *Am J Public health* 2000; 90:1260-1268

24. **Burwell,** C. S., E. D. Robin, R. D. Whaley, and A. G. Bicklemann. 1956. Extreme obesity associated with alveolar hypoventilation a Pickwickian syndrome. *Am. J. Med.* 21: 811-818.

25. **Zwillich, C. W.,** F. D. Sutton, D. J. Pierson, E. M. Creagh, and J. V. Weil. 1975. Decreased hypoxic ventilatory drive in obesity hypoventilation syndrome. *Am. J. Med.* 59: 343-348

26. **MacGregor, M. I.**, A. J. Block, and W. C. Ball Jr.. 1970. Serious complications and sudden death in the Pickwickian syndrome. *Johns Hopkins Med. J.* 126: 279-295

27. **Bray, G. A.** 1985. Complications of obesity. *Ann. of Intern. Med.* 103(6, Pt. 2):1052-1062

28. **Phipps, P,** Starritt, E, Caterson, I, et al Association of serum leptin with **hypoventilation** in human obesity. *Thorax* **2002;57**,75-76

29. **Janssens JP,** Derivaz S, Breitenstein E, et al. Changing patterns in long-term noninvasive ventilation ; a 7- year prospective study in the Geneva Lake area. Chest 2003;123:67-79.

30. **Kessler R,** Chaouat A, Schinkewitch P, et al. The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. *Chest* 2001;120:369-376.

31. **M. Fitzpatrick.** Leptin and the obesity hypoventilation syndrome: a leap of faith?. *Throax* 2002:57, 1-2

32. **Phillips BG,** Kato M, Narkiewicz K, et al. Increases in leptin levels, sympathetic drive and weight gain in obstructive sleep apnea. *Am J Physiol heart Circ Physi*ol 2000;279:H234-7.

33. **Shimura, R,** Tatsumi, K, Nakamura, A, et al Fat accumulation, leptin, and hypercapnia in obstructive **sleep** apnea-hypopnea syndrome. *Chest* **2005;127**,543-549

34. **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.

35. **Yee BJ,** Cheung U. Phipps P, Banerjee D, Piper AJ, Grunstein RR. Treatment of Obesity Hypoventilation Syndrome and Serum leptin. *Respiration* 2005 Sep 20;[Epub ahead of print]

36. **Polotsky V,** Wilson J. Smaldone M, et al. Femal gender exacerbates respiratory depression in leptin-deficient obesity. *Am J Respir Crit Care Med* 2001;164:1470-1475.

37. **Nowbar, S,** Burkart, KM, Gonzales, R, et al Obesity-associated **hypoventilation** in hospitalized patients: prevalence, effects, and outcome. *Am J Med* **2004;116**,1-7

38. **Schwartz MW,** Seeley R. Neuroendocrine responses to starvation and weight loss. *N Engl J Med* 1997;336:1802-1811.

39. **Piper A.J.,** Sullivan C.E., Effects of short-term NIPPV in the **treatment** of patients with severe obstructive sleep apnea and hypercapnia. *Chest* (1994) **105** : pp 434-440

40. **Koenig S.M.,** Pulmonary complications of **obesity** . *Am J Med Sci* (2001) **321** : pp 249-279

41. **Weil J.V.,** Byrne-Quinn E., Sodal I.E., Acquired attenuation of chemoreceptor function in chronically hypoxic man at high altitude. *J Clin Invest* (1971) **50** : pp 186-195

42. **Cooper K.R.,** Phillips B.A., Effect of short-term sleep loss on breathing . *J Appl Physiol* (1982) **53** : pp 855-858.

43. The Report of an American Academy of Sleep Task Force. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* (1999)

44. **Zwillich C.W.,** Sutton F.D., Pierson D.J., Decreased hypoxemic ventilatory drive in the **obesity hypoventilation** syndrome. *Am J Med* (1975) **59** : pp 343-348.

45. **Emigril C.,** Sobol B.J., The effects of weight reduction on pulmonary function and the sensitivity of the respiratory center in **obesity** . *Am Rev Respir Dis* (1973) **108** : pp 831-842

46. **Garay Sm,** Rapoport D., Sorkin B., Regulation of ventilation in the obstructive sleep apnea syndrome. *Am Rev Respir Dis* (1981) **124** : pp 451-457.