Association of serum leptin with hypoventilation in human obesity

P R Phipps, E Starritt, I Caterson, R R Grunstein

INTRODUCTION
Obesity is rapidly increasing in prevalence with a major impact on ill health and health costs. Sleep disordered breathing, usually manifest by obstructive sleep apnoea (OSA), is common in obesity. However, some patients with obesity and OSA develop daytime hypercapnia (obesity hypoventilation syndrome, OHS).

Leptin is a protein hormone produced by mammalian adipocytes. It acts within the hypothalamus via a specific receptor to reduce appetite and increase energy expenditure. Serum leptin levels correlate closely with total body fat mass operating via a central feedback mechanism. In human obesity serum leptin levels are up to four times higher than in lean subjects, indicating a failure of the feedback loop and central leptin resistance. In leptin deficient obese mice (ob/ob mice) leptin infusion reverses hypoventilation. It was hypothesised that a relative deficiency in CNS leptin, indicated by high circulating leptin levels, may be implicated in the pathogenesis of obesity hypoventilation syndrome (OHS).

Methods: Fasting morning leptin levels were measured in obese and non-obese patients with and without daytime hypercapnia (n=56). Sleep studies, anthropometric data, spirometric parameters, and awake arterial blood gas tensions were measured in each patient.

Results: In the whole group serum leptin levels correlated closely with % body fat (r=0.77). Obese hypercapnic patients (mean [SD] % body fat 43.8 [6.0]%) had higher fasting serum leptin levels than eucapnic patients (mean % body fat 40.8 [6.2]%), with mean [SD] leptin levels of 39.1 [17.9] and 21.4 [11.4] ng/ml, respectively (p<0.005). Serum leptin (odds ratio [OR] 1.12, 95% CI 1.03 to 1.22) was a better predictor than % body fat (OR 0.92, 95% CI 0.76 to 1.1) for the presence of hypercapnia.

Conclusions: Hyperleptinaemia is associated with hypercapnic respiratory failure in obesity. Treatment with leptin or its analogues may have a role in OHS provided central leptin resistance can be overcome.

RESULTS
Results are expressed as mean (SD). A total of 56 patients were studied (16 women) with a mean age of 46 years (range 22–80). Forty four patients were eucapnic (PaCO₂ 5.5 (0.4) kPa) and 12 were hypercapnic (PaCO₂ 6.5 (1.1) kPa). Twenty patients were obese and hypoxic (PaO₂ 8.8 (1.6) kPa). As expected, fasting serum leptin levels were closely related to % body fat in the entire patient group (r=0.77). In the obese group (n=39) hypercapnic patients had significantly higher fasting serum leptin levels than eucapnic patients, with leptin levels of 39.1 (17.9) and 21.4 (11.4) ng/ml, respectively (p<0.005, fig 1). There was no difference in degree of body fat absence of metabolic and acute respiratory alkalosis) and hypoxaemia as arterial oxygen tension (PaO₂) of <10.7 kPa in patients aged <60 years and <10.0 kPa in those aged >60 years. Obesity was defined as a body mass index (BMI) of >28 kg/m².

Patients were excluded from the study if they were <20 or >80 years of age, had airways disease or FEV1/FVC ratio of <75%, neuromuscular disease, severe left ventricular failure, untreated thyroid disease, or were currently on a strict weight reducing diet. Patients were also excluded if arterial blood gas tensions could not be measured (patient declined, poor sample volume, venous sample, difficulty in collecting sample). The percentage body fat was calculated using Garrow’s formula which corrects for sex differences in BMI and was used for the comparison with fasting leptin.

Logistic regression analysis was performed with PaCO₂ as the dependent variable and leptin and % body fat as explanatory variables (SPSS for Windows 10.0, SPSS Inc, USA). Odds ratios with 95% confidence intervals were calculated for both variables. Statistical significance was taken at the 5% level.
in patients with obesity.

examining both serum leptin levels and the presence of OHS development of OHS. We are not aware of previous work disordered breathing, a higher leptin level predisposes to the OHS. This suggests that, in patients with obesity and sleep % body fat for the presence of hypercapnia in patients with

DISCUSSION

between the hypercapnic (% body fat 43.8 (6.0)%) and eucapnic (% body fat 40.8 (6.2)%) patients (p>0.4). Serum leptin (b=0.113, SE(b)=0.044, p=0.01, OR 1.12 (95% CI 1.03 to1.22)) but not % body fat (b=-0.087, SE(b)=0.094, p=0.4, OR 0.92 (95% CI 0.76 to 1.1)) was a predictor for the presence of hypercapnia. The results were similar in the obese hypoxic group of patients (fig 2). There was no difference in the apnoea-hypopnoea index (AHI) between the two groups (mean 47/hour for eucapnic patients and 57/hour for hypercapnic patients, p>0.2).

FIGURE 1 Fasting serum leptin levels versus % body fat in obese hypercapnic (diamonds) and eucapnic (squares) patients. Hypercapnic patients had significantly higher leptin levels (p<0.005).

FIGURE 2 Fasting serum leptin levels versus % body fat in obese hypoxic patients. Hypercapnic patients (OHS, diamonds) had significantly higher leptin levels than eucapnic patients (squares, p<0.005).

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