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Contrasting effects of acute versus chronic intermittent hypoxia on leptin secretion in differentiated human adipocytes – Implications for sleep apnea

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ABSTRACT

Obstructive sleep apnea (OSA) is a common sleep disorder associated with repetitive episodes of nocturnal intermittent hypoxia (IH), obesity and elevated leptin. Newly diagnosed OSA patients have a history of significant recent weight gain. While IH is implicated in OSA pathophysiology, the factors contributing to weight gain in OSA are not completely understood. Leptin is an adipokine with a central role in energy homeostasis and appetite control. Increases in leptin suppress appetite, while decreases in leptin increase appetite and may consequently cause weight gain. Using an *in vitro* approach, we examined the role of acute and chronic IH exposure on leptin secretion in differentiated human white preadipocytes. We show that acute 24-h exposure to IH and sustained hypoxia both increased leptin secretion, compared to normoxic controls ($p = 0.01$). In contrast, chronic repetitive IH exposure for 7 days decreased leptin secretion, compared to normoxic controls ($p = 0.02$). The decrease in leptin secretion during chronic IH exposure suggests a mechanism which may contribute to increased appetite and thereby predispose patients with untreated OSA to weight gain and obesity in early stages. As obesity progresses, leptin levels likely rise secondary to the increase in body fat. Elevated leptin levels in patients with longstanding OSA may be indicative of increased fat mass and not a consequence of IH-mediated effects on adipocytes.

1. Introduction

Obstructive sleep apnea (OSA) is characterized by a repetitive cessation in breathing during sleep due to inspiratory upper airway obstruction, resulting in intermittent hypoxia during sleep [1]. Among the factors contributing to the OSA related pathophysiology, obesity and nocturnal intermittent exposure to hypoxia are well recognized [1]. Standard clinical management of OSA includes use of positive airway pressure devices to maintain an open airway during sleep to mitigate intermittent hypoxia exposure along with recommendations to lose weight, if needed. Importantly, patients with OSA also have a higher risk of developing obesity, evident in both males and females in the year prior to the diagnosis of OSA [2]. Patients with OSA are also at increased risk for developing related cardiovascular disease [1]. However, the relationship between obesity and OSA is bidirectional in that increases in obesity result in increased OSA severity and loss of weight mitigates OSA [3].

Among obesity related factors that contribute to increased cardiovascular risk, the role of altered adipokines such as leptin are well established. Leptin is elevated in obesity and hyperleptinemia is known to contribute to obesity associated metabolic dysfunction and high cardiovascular risk [4]. Centrally, leptin plays an important role in appetite control and energy expenditure [4–6]. In the absence of leptin or in the context of low levels of leptin, food intake is increased while energy expenditure is reduced resulting in weight gain and obesity, so that leptin deficient individuals are at high risk for severe obesity. Accordingly, leptin treatment in leptin deficient individuals results in a reduction of appetite and also contributes to improvement in metabolism, resulting in significant weight loss [6]. However, only a very small minority of human obesity is due primarily to underlying leptin deficiency, and most individuals with obesity have high circulating levels of leptin due to leptin production by the high fat mass. However,

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the sustained high leptin levels in chronic obesity do not suppress appetite because of development of resistance to appetite suppressing central effects of leptin [6]. In addition to its central effects, circulating levels of leptin are also considered a biomarker for energy reserve as determined by body fat content. Weight loss reduces leptin levels due to reduced available fat mass expressing leptin. However, studies suggest that the low leptin levels after weight loss help promote subsequent weight regain.

In patients with established OSA, leptin is elevated [2] and high leptin levels have been implicated as a potential mechanism for generation of reactive oxygen species, inflammation and consequent cardiovascular disease [4]. However, the trajectory of changes in leptin during the early stages of development of OSA is not well understood. Notably, newly diagnosed OSA patients have a history of significant recent weight gain [2]. However, in contrast to the history of weight gain observed in OSA, animal models of hypoxia [6] are associated with increases in leptin and weight loss. However, the adipose tissue leptin response may be mediated in part by the duration of hypoxic exposure [4]. While 12-h of IH and 12-h of chronic hypoxia resulted in increases in leptin in mice [7], both lean and obese Zucker rats exposed to 14 days of IH showed no increases in leptin levels [8].

We postulated that the duration and intermittency of hypoxia may be two of the key factors defining the effects on leptin and weight gain. We therefore sought to experimentally simulate OSA using chronic administration of intermittent hypoxia, and to examine the interactions between intermittent hypoxia and leptin secretion, comparing acute versus chronic exposure to intermittent hypoxia, and also examining the effects of continuous hypoxia. We tested the hypothesis that although acute intermittent hypoxia and continuous hypoxia increase leptin secretion, repeated chronic exposure to IH will decrease leptin secretion, and thereby may increase appetite and predispose non obese or mildly obese patients with early OSA to weight gain.

2. Methods

We used an *in vitro* approach using commercially available primary human white preadipocytes obtained from healthy individuals to ensure relevance to humans and limit confounding from other factors such as comorbidities and species differences. Furthermore, the *in vitro* approach is key to evaluate the direct effects of intermittent hypoxia on leptin secretion. Adipocytes are the main source of circulating leptin in humans – therefore human white preadipocytes were differentiated prior to examining the effects of intermittent hypoxia.

Cell culture: All experiments were performed using commercially available human white preadipocytes (HWP, ZenBio Inc, Durham, North Carolina) isolated from subcutaneous abdominal adipose tissue of healthy subjects (See Table 1). Cells from 3 to 5 passages were grown in cell culture flasks using complete medium (PM-1, ZenBio Inc, Durham, North Carolina) until confluence at 37 °C. Human white preadipocytes were differentiated for 14 days prior to exposure to intermittent hypoxia. For differentiation, preadipocytes were grown in adipocyte differentiating medium (DM-2, ZenBio Inc, Durham, North Carolina) for 7 days followed additional growth for 7 days in adipocyte maintenance medium (AM-1, ZenBio Inc, Durham, North Carolina). Each experiment was conducted using at least 3 different human preadipocyte lots in duplicate.

Intermittent hypoxia model: Differentiated human white preadipocytes were treated with hypoxia intermittently using a previously established model [9]. Cells were maintained in basal adipocyte nutrition media (BM-1) lacking supplements or serum during the acute intermittent hypoxia treatment and in complete media (AM-1) for chronic intermittent hypoxia treatment. The growth of cells in complete media during chronic 7-day treatment is needed to make sure that the cells remain viable during the treatment duration. Briefly, intermittent hypoxia was achieved by cycles of 30 min 0.1 % O_2 followed by 30 min exposure to 21 % O_2. Acute effects of intermittent hypoxia were examined after 24 cycles. We also examined the effects of chronic intermittent hypoxia by exposing cells to 9 cycles of intermittent hypoxia (9 h) each day for 7 days. We have shown that using our intermittent hypoxia protocol, namely intermittent exposure of the cells to 0.1 % oxygen in presence of complete media, leads to a decrease in oxygen in the media by approximately 20 % [9]. The chronic intermittent hypoxia treatment has been previously shown to mimic the molecular signature observed in adipose tissue of patients with OSA [9]. Cells grown in sustained normoxic conditions (continuous 21 % O_2) and continuous hypoxia (0.1 % O_2) served as comparators for acute experiments. For 7-day chronic exposure, cells grown in sustained normoxic conditions served as controls. Each experiment was conducted on 3 independent occasions.

Measurement of secreted leptin: Conditioned media was collected after appropriate treatment duration, centrifuged to remove particulates and batched for analysis at −80 °C. Leptin levels in the conditioned media were quantified using quantikine ELISA kit for human leptin (R&D Systems) as per manufacturer's instructions.

Statistics: The intermittent hypoxia effects/treatments on leptin secretion were estimated by calculating the relative changes and expressed as % change compared to appropriate control conditions. The observations between any treatment and the control group were treated as paired observations as samples were derived from cells of the same lot. Statistical significance and pairwise analysis were determined using Wilcoxon rank sum test. A two-tailed p value < 0.05 was considered significant. Data are presented as mean ± SD. Data were analyzed using JMP 9.0.1 (SAS Institute Inc, Cary, North Carolina).

3. Results

Compared to normoxic conditions, both acute 24-h exposure to intermittent hypoxia and exposure to continuous hypoxia increased leptin secretion ($p = 0.01$) (Fig. 1). In contrast, exposure of differentiated human white preadipocytes to chronic 7-day intermittent hypoxia caused decreases in leptin secretion ($p = 0.02$) (Fig. 2).

4. Discussion

The main finding of this study is that acute and chronic intermittent hypoxia treatment affect leptin secretion differently in differentiated human preadipocytes. Patients with OSA are exposed to chronic nocturnal episodes of intermittent hypoxia. Acute and chronic exposures to intermittent hypoxia have been implicated in oxidative stress [4], inflammation, metabolic dysfunction [10] and cardiovascular disease in OSA. Furthermore, OSA and obesity are known to be interrelated, with

Table 1
Adipocyte donor information.

Cells	Lot	Gender	Age	BMI	Smoker	Ethnicity	Location	Medication
spf1	08201B	Female	42	21.1	No	Caucasian	Abdomen	None
spf1	100610B	Female	40	23.3	No	Caucasian	Abdomen	None
spf1	101101	Female	43	24.0	N/A	Caucasian	Abdomen	N/A
spf2	10605A	Male	36	28.8	No	Unknown	Abdomen	None
spf3	21606	Female	46	32.1	No	Unknown	Abdomen	Unknown

(N/A = not available).

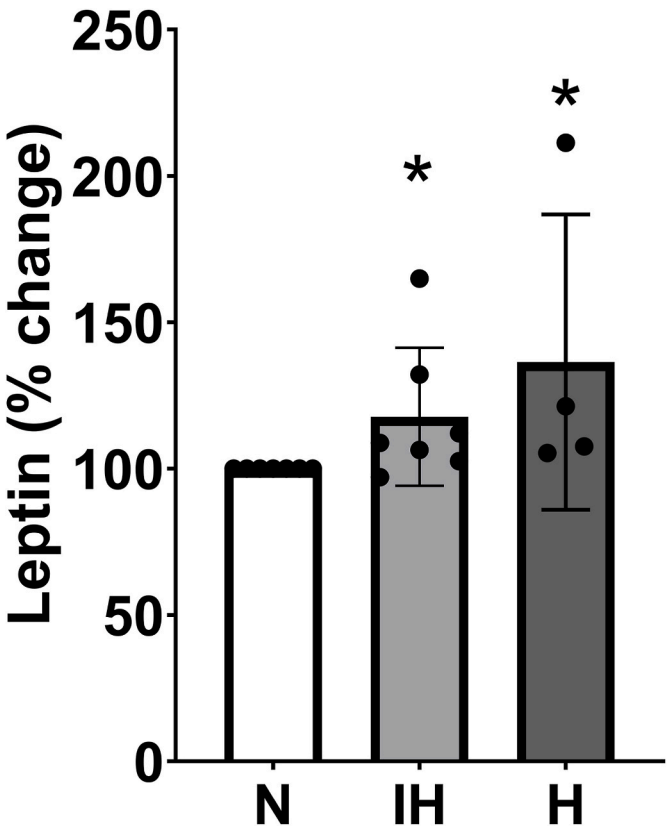

Fig. 1. Acute 24-h exposure to intermittent hypoxia leptin secretion in differentiated human white preadipocytes. Leptin secretion in response to intermittent hypoxia (IH, light grey middle bar) and continuous hypoxia (H, dark grey bar on right) increased in comparison to normoxic controls (N, white bar on left) (p,0.05) but were not different from each other (p = 0.64). Data presented as Mean ± SD. (* = p < 0.05 determined by Wilcoxon Rank Sum Test).

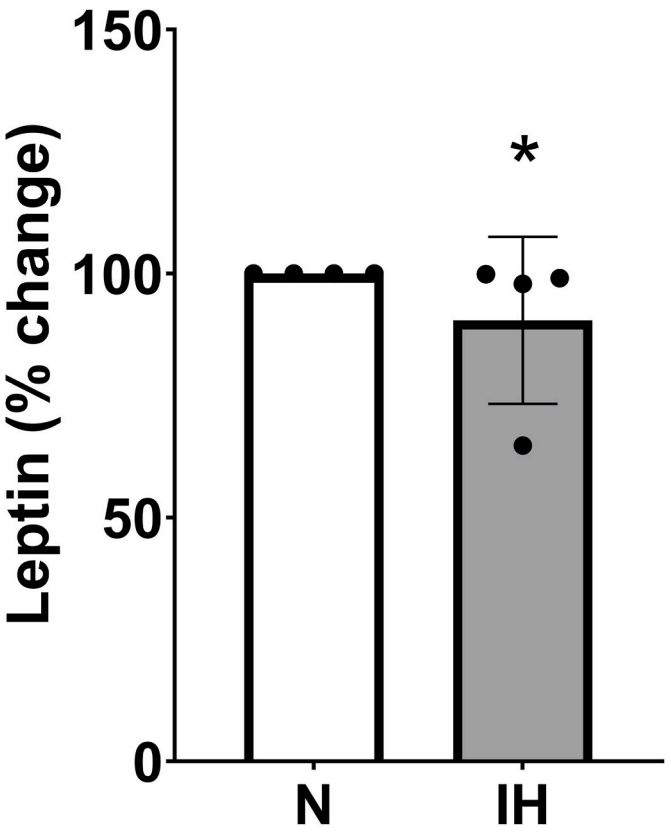

Fig. 2. Chronic 7-day exposure to intermittent hypoxia (IH, grey bar on right) decreases leptin secretion in differentiated human white preadipocytes compared to leptin secretion during control normoxia exposure (N, white bar on left). Data presented as Mean ± SD. (* = p < 0.05 determined by Wilcoxon Rank Sum Test).

obesity contributing to development of OSA but OSA potentially predisposing to obesity as well [2]. Newly diagnosed OSA patients have an increased likelihood of recent weight gain [2], the reasons for which remain unclear. Our data suggest that reduced leptin expression as a consequence of exposure to chronic intermittent hypoxia in early onset of OSA may be implicated in weight gain associated with OSA.

Leptin has previously been proposed as a potential link between OSA and obesity [6]. Leptin reduces appetite and food intake – hence decreases in leptin may predispose to weight gain. Since adipocytes are the primary source of circulating leptin, we sought to examine the leptin response of differentiated human white preadipocytes exposed to 1 or 7 days of intermittent hypoxia. Our data suggest that responses to chronic repetitive nocturnal intermittent hypoxia early in the course of OSA may reduce leptin and hence predispose to weight gain and consequent worsening of OSA.

Under conditions of acute intermittent hypoxia (24 h) and continuous hypoxia, an increase in leptin secretion was observed in differentiated human white preadipocytes. By contrast, under conditions of chronic intermittent hypoxia, there was a decrease in leptin secretion, suggesting a potential mechanism for development of obesity in early stages of OSA. We speculate that decreased leptin levels due to exposure to chronic intermittent hypoxia may result in increased appetite and subsequent weight gain, resulting in increased overall adipose tissue mass, with consequent increases in leptin and subsequent leptin resistance [6,10].

Our findings also align with studies of intermittent hypoxia in animal models [6]. For example, 12-h of IH and 12-h of chronic hypoxia both resulted in increases in leptin in mice, consistent with our findings of increased leptin with 24-h of IH and 24-h of chronic hypoxia exposure. By contrast, and directionally consistent with our *in vitro* adipocyte data, both lean and obese Zucker rats exposed to 14 days of IH showed no increase in leptin levels. Taken together these findings in animal studies are consistent with our data showing differences in the leptin response in human preadipocytes during 24-h of IH versus 7 days of IH.

Leptin levels typically correlate with adipose tissue mass. We therefore propose that as obesity progresses due to the intermittent hypoxia mediated inhibition of leptin expression, leptin levels nevertheless start to rise secondary to the increase in body fat. In patients with longstanding OSA, elevated leptin levels may thus be primarily indicative of increased fat mass and less a consequence of intermittent hypoxia mediated effects on adipocytes.

The strong obesity-OSA relationship is well established. Indeed, recent clinical trials using long acting glucose dependent insulinotropic polypeptide receptor and glucagon-like peptide-1 receptor agonists such as tirzepatide showed that treatment with these pharmaceuticals was able to reduce the severity of the apnea-hypopnea index (a metric of OSA severity) along with body weight loss in patients with moderate-to-severe OSA [11]. Similarly, weight loss induced by bariatric surgery has been shown to reduce severity and resulted in remission of OSA in approximately 65 % of the cases [12]. While the effect of weight loss on OSA is clear, the effect of OSA treatment on body weight remains inconsistent, although a randomized controlled trial of continuous positive airway pressure suggested that treatment of OSA reduced both visceral and subcutaneous fat [13]. Nevertheless, the role of untreated OSA in weight regain after lifestyle or surgery-based weight loss is acknowledged.

The primary driver of intermittent hypoxia due to OSA is impaired breathing control. Interestingly, leptin has also been implicated in respiratory control and impairment in leptin action has been linked to

development of obesity hypoventilation syndrome [14]. It is therefore conceivable that our findings regarding reduced leptin levels in response to chronic intermittent hypoxia may also be relevant to further disruption of ventilatory control in the early stages of OSA. Thus, in patients with early onset OSA, inhibition of leptin secretion due to intermittent hypoxia may not only contribute to increased obesity risk but may also conceivably result in further impairment of respiratory control mechanisms and thus worsen OSA severity. Indeed, leptin is considered to be a respiratory stimulant [15], and it has been proposed that OSA may in fact "represent a state of leptin deficiency" [15]. Leptin suppression in early onset OSA and leptin resistance in later stage established OSA may in fact be consistent with the construct of OSA as a state of leptin deficiency.

The strength of our study is in the *in vitro* approach which allows clear delineation of acute and chronic effects of IH in primary human cells. However, our model may not fully reflect adipose tissue hypoxia in an *in vivo* setting. Thus our *in vitro* cellular model is not able to integrate any influences on leptin secretion induced by the effects of intermittent hypoxic apneas causing repetitive sleep disruption [5,16] We did not investigate underlying mechanisms, such as hypoxia-inducible factors [17,18], which may regulate increases and decreases in leptin expression in response to acute intermittent hypoxia versus chronic intermittent hypoxia respectively. In this regard, He et al. showed, in studies of murine 3T3-L1 differentiated adipocytes, that 8 days of IH did in fact result in increases in hypoxia-inducible factor-1α, with accompanying increases in leptin [19]. Reasons for the discrepancy between our studies and those of He et al. include their use of different IH cycles (2-min cycles of IH versus the 1-h cycles used in the current study). Species differences may also be implicated. Indeed, Lempesis et al. have reviewed potential reasons underlying species' differences in the adipose tissue responses to hypoxia [20]. A further limitation of our study is that we did not measure other adipokines. In mitigation, adipocyte production of CCL2, TNF- α, Resistin and adiponectin have already been reported to increase in response to IH by Uchiyama et al. [21] We did not focus on these since they do not contribute substantially to weight changes. In addition, it needs to be considered that hypoxia during exposure to sustained hypoxia is far more severe than that during chronic IH. Furthermore we did not evaluate for any differences in preadipocyte differentiation in normoxia versus IH, which would be an interesting question for future studies. Finally, our studies were limited to adipocytes. It is important to recognize that studies of intermittent moderate hypoxia in intact lean and obese mice models show increases in plasma leptin, increased liver leptin receptor expression, and reduced body weight [22].

In conclusion, *in vitro* studies of differentiated human white preadipocytes show that both acute intermittent hypoxia and chronic hypoxia elicit increases in leptin secretion. However, chronic repetitive intermittent hypoxia results in decreases in leptin secretion. We suggest that these data help explain the increases in leptin and loss of weight noted with exposure to altitude induced continuous hypoxia, and further suggest a mechanism for development of obesity and potentially impairment of ventilation and ventilatory control mechanisms in early-stage OSA, due to OSA associated intermittent hypoxia resulting in reduced leptin levels. Future studies are needed to confirm these findings and explore the effects of chronic IH on leptin, weight regulation and breathing control in humans.

CRediT authorship contribution statement

Kiran R. Somers: Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Christiane Becari:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis. **Katarzyna Polonis:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis. **Prachi Singh:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Prachi Singh:** Writing - review &editing, Resources, Project adminisration, Methodolygy, Conceptualization.

5. Disclosures

None of the authors have any disclosures relevant to this manuscript.

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Declaration of competing interest

None of the authors have any conflicts of interest to disclose.

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None.

Data availability

Data will be made available on request.

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