



## Research report

# Diurnal secretion of ghrelin, growth hormone, insulin binding proteins, and prolactin in normal weight and overweight subjects with and without the night eating syndrome <sup>☆</sup>

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## ABSTRACT

The regulatory peptide ghrelin has been proposed to help mediate both hunger and sleep. The neuroendocrine circadian patterns in the night eating syndrome (NES) have been distinguished by an attenuated nocturnal rise in the plasma concentrations of melatonin and leptin and a greater increase in the concentrations of cortisol. In this study we wanted to test the hypothesis that night eaters have disturbances in the circadian levels of ghrelin, growth hormone (GH) and associated regulatory peptides. In 12 female night eaters (6 normal weight and 6 overweight), and 25 healthy controls (12 normal weight and 13 overweight), blood was sampled over a 24-hour period. Four meals were served from 8 AM to 8 PM, and blood samples were drawn every second hour for determination of plasma ghrelin concentrations and GH by radioimmunoassay (RIA). Analysis of serum GH, IGF-1, IGFBP-3 and prolactin were performed by ELISA. In healthy normal weight subjects there was a slight but non significant nocturnal increase of ghrelin, whereas a more or less flat curve was observed for healthy overweight, NES normal weight and NES overweight patients. The RMANOVA analysis showed a significant independent lowering effect of overweight on the grand mean of ghrelin. No direct effects on NES normal weight and overweight subjects were found, but a near-significant interaction was found between healthy overweight and overweight NES subjects. There were independent significant lowering effects of overweight and NES on the serum GH levels. During the time course no changes in the serum levels of IGF-1 or IGFB-3 were observed. Independent significant lowering effects of overweight and NES on the levels of IGF-1 were detected, whereas a near significant reduction in the global levels of IGFBP-3 was observed in both NES groups. Finally, significant nocturnal changes were observed for serum levels of prolactin in all four subgroups. Grand mean levels tended to be higher in NES subjects whereas the opposite was observed in healthy overweight (ns). We conclude that in both NES groups and in healthy overweight subjects more or less attenuated ghrelin and GH secretions were observed, whereas divergent secretions were observed for prolactin.

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## Introduction

Night eating syndrome (NES), characterized by morning anorexia, evening hyperphagia, and insomnia was first described in obese individuals in 1955 by Stunkard, Grace, and Wolf (1955). NES often

develops during periods of stress and is associated with unsuccessful attempts at weight reduction. In 1999 Birketvedt et al. reported that night time awakenings were far more common among night eaters than among controls, and more than half of these awakenings were associated with food intake (Birketvedt et al., 1999). It is estimated that NES occurs in more than 1.5% of the general population (Rand, Macgregor, & Stunkard, 1997). Moreover, NES has been found in 8.9% in an obesity clinic (Stunkard et al., 1996), in 12% of the obese patients in a nutrition clinic (Stunkard, 1959) and in 27% and 26%, respectively in two samples of severely obese persons (Rand et al., 1997; Rand & Kuldau, 1993). However, NES is also found in normal weight individuals and in postoperative obesity surgery patients (Rand & Kuldau, 1993).

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The pathophysiological mechanisms underlying NES are largely unknown. Previously, we have described some atypical neuroendocrine patterns with an attenuation of nocturnal rises in melatonin and leptin, increased diurnal levels of cortisol, and normal diurnal insulin levels when comparing NES patients with controls with fixed meals during the day-time (Birketvedt et al., 1999). Some of these nocturnal changes appeared to be normalized when NES patients were allowed to eat during the night (Allison et al., 2005). Additionally, disturbances in the hypothalamic-pituitary-adrenal (HPA) axis in NES with an attenuated ACTH and cortisol response to CRH were also confirmed (Birketvedt, Sundsfjord, & Florholmen, 2002), whereas (Goel et al., 2009) demonstrated significant changes in the timing and amplitude of various behavioural and physiological circadian markers.

Ghrelin, a relatively recently discovered regulatory peptide, is the endogenous ligand of the GH secretagogue receptor (Jarkovska, Krsek, Rosicka, & Marek, 2004) and is proposed to play a role in the regulation of body weight and metabolism (Castaneda, Tong, Datta, Culler, & Tschöp, 2010; Horvath, Diano, Sotonyi, Heman, & Tschöp, 2001). Ghrelin, an orexigenic peptide released primarily by the stomach, is elevated prior to meals and declines during and after meals (Ariyasu et al., 2001; Cummings et al., 2001; Tschöp et al., 2001a,b). There is a nocturnal increase in ghrelin secretion in parallel to that observed for other regulatory peptides, such as leptin (Sinha et al., 1996) and prolactin (Freeman, Kanyicska, Lerant, & Nagy, 2000). Ghrelin promotes sleep (Weikel et al., 2003) although gender and age differences exist (Kluge et al., 2010; Steiger, Dresler, Schüssler, & Kluge, 2011). Leptin also promotes sleep (Mullington et al., 2003). However, these two regulatory peptides have opposite effects on eating behavior (Cummings et al., 2001; Sinha et al., 1996). It is well established that ghrelin secretion is lower in overweight individuals compared to normal weight subjects, and according to one report, the nocturnal increase in ghrelin is absent in overweight subjects (Lindeman et al., 2002). Moreover, it has been proposed that the hyposomatotropism of obesity is associated with reduced plasma ghrelin levels (Lindeman et al., 2002; Tschöp et al., 2001a; Tschöp et al., 2001b), but the causality is unsettled (Castaneda et al., 2010).

Furthermore, ghrelin stimulates growth hormone (GH) release, appetite, and weight gain (Weikel et al., 2003). GH is a hypothalamic neuropeptide that regulates feeding, sleep, energy metabolism and reproduction (Yujin, Tamotsu, Asuka, Hideki, et al., 2002). GH modulates arousal and appetite by stimulating wake-and appetite-promoting neurons (Schüssler et al., 2006). GH is lower in patients with narcolepsy (Higuchi et al., 2002), and may also explain lower energy metabolism also in patients with NES. In blood, a diurnal variation of GH is observed (Lindeman et al., 2002), and it has been proposed that growth hormone releasing hormone stimulates GH and slow-wave-sleep simultaneously. Finally, in a study of both ghrelin and GH, subjects with high visceral fat mass had reduced levels of both hormones during a 24 hour period, and the diurnal variation was greatly attenuated (Lindeman et al., 2002).

The secretions of ghrelin, GH, and prolactin in NES are poorly described in the literature. Elevated plasma levels of ghrelin have been reported in a case report of NES and was normalized after treatment of the disease. (Rosenhagen, Uhr, Schüssler, & Steiger, 2005). In another study the ghrelin levels were the same as in the controls, but phase advanced circadian rhythm were observed compared to the controls (Goel et al., 2009). Finally, in the same study, no phase differences were observed in the prolactin rhythms compared to controls (Goel et al., 2009).

Therefore, the aim of this study was to study the diurnal variation of serum ghrelin, GH and its co-stimulator and principal circulating and tissue mediator, insulin growth factor (IGF)-1, its binding protein IGF-binding protein (IGFBP) and prolactin, in patients with NES and the relationship to body weight.

## Methods

In this study conducted in the Clinical Research Department and the Laboratory of Gastroenterology of the University Hospital, Tromsø, Norway, we investigated the circadian pattern of ghrelin and GH in subjects with NES and healthy controls. This study was conducted with the approval of the Ethical Committee of Region V, Norway and performed according to the Declaration of Helsinki.

## Subjects

The criteria for the diagnosis of the night eating syndrome were: consumption of more than 50% of the daily food intake after 6 PM and 1–3 awakenings per night at least three times a week. Twelve female night eaters (age 42–67) and 25 healthy female controls (age 28–70) were recruited from the previously reported study (Birketvedt et al., 2002). In the night eating group, 6 subjects were overweight with a BMI > 25 kg/m<sup>2</sup> (34.4 ± 3.5 [SD] kg/m<sup>2</sup>), and 6 were normal weight (22.6 ± 3.5 kg/m<sup>2</sup>). In the control group, 12 subjects were overweight (29.5 ± 2.2 kg/m<sup>2</sup>) and 13 subjects were of normal weight (22.8 ± 1.4 kg/m<sup>2</sup>). The incidence of night eating episodes during the 7 day observation period was 3.2 ± 0.5 among the night eaters (equal between normal weight and overweight) and none among the healthy controls.

During the 24 h study, four meals of 1255 kJ each were served at 8 AM, 12 PM, 4 PM, and 8 PM, and blood samples were drawn every second hour (13 in total) for analysis of serum ghrelin (biological active) concentrations by a radioimmunoassay method (Linco Research, St. Charles, MI, USA), and analysis of serum GH, IGF-1, IGFBP-3 by Immulite 2000 (Siemens, Oslo, Norway) and serum prolactin by Roche Modular E 170 (Roche Diagnostics, Indianapolis, IN, USA).

## Statistical analysis

The datasets were analyzed by repeated measures ANOVA (RMANOVA) with the 13 consecutive blood sample results as dependent variables, and overweight and NES as independent variables using a full factorial model. A few (<4%) values in each dataset were interpolated to avoid censoring of the record because of missing values. In most cases, the assumption of sphericity was not met, hence the data were re-centered and a logarithmic transformation performed of all the raw data. Adjustment of degrees of freedom was made with Greenhouse–Geisser or Huynh–Feldt methods as appropriate. Analyses were performed in SPSS (16.0).  $P < 0.05$  was considered statistically significant.

## Results

### Serum ghrelin

Fasting ghrelin concentrations were negatively correlated to BMI and weight ( $r = 0.45$ ;  $P = 0.005$ ; Pearson). In healthy normal weight subjects there was a slight, but non significant increase of ghrelin at time points 24 AM and 2 PM when compared to time point 8 AM, whereas a more and less flat curve was observed for healthy overweight, NES normal and overweight patients. In the group of healthy normal weight subjects, there was a significantly higher mean level of ghrelin when compared to healthy overweight subjects and to overweight NES patients (Fig. 1). The RMANOVA analysis showed a significant independent lowering effect of overweight on the global values of ghrelin ( $P = 0.004$ ). No direct effects of NES was found, but a near-significant interaction between overweight and NES ( $P = 0.07$ ) showed that the lowering effect of overweight may be less pronounced for NES patients.

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