Hypothalamic-pituitary-adrenal axis in the night eating syndrome

GRETHE S. BIRKETVEDT,1 JOHAN SUNDSFJORD,2 AND JON R. FLORHOLMEN1

1Institute of Clinical Medicine and 2Department of Clinical Chemistry, University of Tromsø, 9037 Tromsø, Norway

Received 22 June 2001; accepted in final form 2 October 2001

Birketvedt, Grethe S., Johan Sundsfjord, and Jon R. Florholmen. Hypothalamic-pituitary-adrenal axis in the night-eating syndrome. Am J Physiol Endocrinol Metab 282: E366–E369, 2002; 10.1152/ajpendo.00251.2001.—The typical neuroendocrine characteristics of the night eating syndrome have previously been described as changes in the circadian rhythm by an attenuation in the nocturnal rise of the plasma concentrations of melatonin and leptin and an increased circadian secretion of cortisol. The aim of this study was to test the hypothesis that night eaters have an overexpressed hypothalamic-pituitary-adrenal axis with an attenuated response to stress. Five female subjects with the night-eating syndrome and five sex-, age-, and weight-matched controls performed a 120-min corticotropin-releasing hormone (CRH) test (100 μg iv). Blood samples were drawn intravenously for measurements of the plasma concentrations of ACTH and cortisol. The results showed that, in night eaters compared with controls, the CRH-induced ACTH and cortisol response was significantly decreased to 47 and 71%, respectively. In conclusion, disturbances in the hypothalamic-pituitary-adrenal axis with an attenuated ACTH and cortisol response to CRH were found in subjects with night-eating syndrome.

NIGHT-EATING SYNDROME, characterized by morning anorexia, evening hyperphagia, and insomnia was first described in obese subjects in 1955 by Stunkard et al. (24). It occurred during periods of stress and was associated with a poor outcome of efforts at weight reduction. In 1999 Birketvedt et al. (3) reported that nighttime awakenings were far more common among night eaters than among controls, and more than one-half of these awakenings were associated with food intake. The typical neuroendocrine characteristics were an attenuation of nocturnal rises in secretions of melatonin and leptin and increased diurnal secretion of cortisol. Cortisol, melatonin, and leptin are regulatory hormones with typical circadian rhythms that regulate various physiological and metabolic functions (2, 23). Another main regulator is the hypothalamic-pituitary-adrenal (HPA) axis, which orchestrates several biological functions. The circadian rhythms represent the biological endocrine clock, whereas the HPA represents the stress-induced biological response. However, the interplay between these two main regulators of biological functions is not well understood. Therefore, our observations of dysregulations of circadian neuroendocrine secretions inclusive of cortisol are of special interest, as the night-eating syndrome most likely represents changes in the HPA axis.

Several disorders, such as obesity (21), fatigue syndrome (17), anorexia nervosa (25), bulimia nervosa (10), insomnia (8), and depression (14), have been linked to disturbances in the HPA axis and to changes in the circadian rhythms. Therefore, the objective of this study was to test the hypothesis that night eaters have an attenuated response to stress.

MATERIALS AND METHODS

This study, conducted in the Clinical Research Department and the Laboratory of Gastroenterology of the University Hospital, Tromso, Norway, in August 2000, investigated the neuroendocrine patterns of subjects with night-eating syndrome. This study was conducted with the approval of the Ethical Committee of Region V, Norway.

Subjects. Five female night eaters and corresponding age- and weight-matched healthy controls were recruited from the previously reported study (3). The same criteria for the diagnosis of the night-eating syndrome were used with the consumption of >50% of the daily food intake after 8:00 PM and with one or more nighttime awakenings associated with food intake (3).

Materials. Registrations of night eating episodes were recorded for seven consecutive days. Subjects were then admitted to the Clinical Research Center at 8:00 AM after an overnight fast. Shortly after admission, blood samples were drawn from an indwelling catheter at time points indicated during the next 150 min. After an observation period of 30 min of rest in bed, 100 μg corticotropin-releasing hormone (CRH; corticorelin human trifluoroacetat; Ferring, Kiel, Germany) were injected intravenously, and the response parameters of ACTH and cortisol levels in plasma were measured. The subjects stayed in bed during the observation period. Blood was collected in precooled glass tubes containing 20 mmol EDTA and 1,000 KIU aprotinin (Trasylool; Bayer, Leverkusen, Germany) per milliliter blood and were kept on ice until centrifugation at 4°C and storage at −27°C. Cortisol

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
and ACTH were measured using commercial immunoassay kits (Immulite chemiluminescent immunoassay; DPC, Los Angeles, CA).

**Statistical analysis.** The significance of differences between the two groups in the plasma concentrations at time point 0 was evaluated by a Wilcoxon's rank sum test. The significance of differences between the two groups in the changes in plasma concentrations (after subtracting the levels at baseline, 0 min) during the CRH test was evaluated by repeated-measures multivariate analysis of variance. *P < 0.05* was considered statistically significant.

**RESULTS**

The incidence of night eating episodes during the 7-day observation period was 3.2 ± 0.5 among the night eaters, whereas among the healthy controls no night eating episodes took place.

**Plasma ACTH.** The nonrested (−30 min) concentrations of ACTH were 15.4 ± 5.5 and 13.6 ± 3.2 (SD) nmol/l in the night-eating and control groups, respectively (not significant [NS]). After 30 min of rest (−30 to 0 min) in bed, stable levels of plasma concentrations of ACTH were obtained in both groups (Fig. 1). At time 0 min, a slightly elevated plasma concentration of ACTH was observed among the night eaters (12.3 ± 3.9 pg/ml) compared with the controls (10.6 ± 1.3 pg/ml; NS). Among the night eaters, CRH induced a gradual increase of the plasma concentration of ACTH with a maximum of 22.8 ± 13.3 pg/ml at 30 min followed by a gradual decrease to 12.4 ± 3.1 pg/ml at 120 min. In the control group, the plasma concentrations of ACTH increased significantly, with a maximum of 33.7 ± 11.1 pg/ml at 40 min followed by a gradual decrease to 12.2 ± 1.8 pg/ml at 120 min. Significant differences between the two groups were observed between 10 and 60 min (*P = 0.04; Fig. 1). The greatest difference between the incremental values from the start (0 min) was at 50 min, where the range was 0–11 pg/ml in the night-eating syndrome group and 12 to 28 pg/ml in the control group. As shown in Fig. 1, the maximal CRH-induced ACTH secretion in the night eaters was reduced to 47% of that observed in the control group.

**Plasma cortisol.** The nonrested (−30 min, 9:00 AM) concentrations of cortisol were 328 ± 171 (SD) nmol/l in the night-eating group and 283 ± 62 nmol/l in the control group (NS). After 30 min of rest in bed (−30 to 0 min), stable levels of plasma concentrations of cortisol were obtained in both groups. At time 0 min, the plasma concentrations of cortisol were 231 ± 11 nmol/l in the night eaters and 262 ± 81 nmol/l in the controls (NS). In the night eaters, CRH induced a gradual increase in the plasma concentration of cortisol with a maximum of 302 ± 165 nmol/l (*P < 0.05* vs. 0 min) after 40 min, followed by a gradual decrease to 133 ± 91 nmol/l at 120 min (NS). Similarly, in the control group, a significant increase in the plasma concentrations of cortisol occurred with a maximum of 479 ± 79 nmol/l at 50 min, followed by a gradual decrease to 351 ± 109 nmol/l at 120 min. Significant differences between the two groups were observed between 20 and 120 min (*P = 0.001; Fig. 2). The greatest difference between the incremental values from the start was at 60 min, where the range was −9 to 65 nmol/l in the night-eating syndrome group vs. 89 to 286 nmol/l in the control group. As shown in Fig. 2, the increase in cortisol secretion was less than in the control group, and the maximum secretion was reduced to 71% of that observed in the control group.

**DISCUSSION**

In night eaters, there are complex neuroendocrine characteristic changes, with attenuation in nocturnal
secrections of melatonin and leptin and increased circadian secretion of cortisol (3). In this study, we have described an attenuated response of ACTH and cortisol in plasma after injection of CRH. Although the response to CRH was the same in all night-eating syndrome patients, the number of observations is small, and the data should therefore be interpreted with some caution. Nevertheless, the data presented may indicate that the night-eating syndrome is associated with an impaired pituitary-adrenal response to CRH.

The attenuated response to CRH in night eaters was observed in plasma concentrations of both ACTH and cortisol, with reduction in the secretory capacity of 47% and 71%, respectively. This might imply that the pituitary and adrenal secretory capacity is attenuated because of stress stimuli, indicating that night eaters are more or less constantly exposed to stress. In the previous paper, the nonresting cortisol levels in the night eating group were observed with the maximal values occurring at 8:00 AM (3). This may indicate an overexpressed HPA axis. The present study was not designed to confirm the hypercortisolemia in the early morning. At 9:00 AM, the ACTH and cortisol concentrations of the hormones were only slightly increased compared with the controls. This is most likely because of the timing (9:00 AM) and the low number of observations. Therefore, the attenuated CRH response in the night eaters is an additional indication but not the final proof of an overexpressed HPA axis.

A healthy response to acute stress is of great importance in our daily physical and psychological challenges. This response is mediated from the hypothalamus to the pituitary gland, which in turn mediates various neuroendocrine signals. When the stressor is gone, the neuroendocrine responses are normally terminated. Failure to terminate this response is observed in various conditions of an overexpressed HPA axis (4, 11, 17, 21, 25) with a subsequent attenuation of the pituitary neuroendocrine response.

It is well known that the night eaters experience wide variability in frequency of symptoms; they can have periods when they experience many awakenings and eating episodes, but also periods when these events are minimal. In this study, the patients were observed during a period of frequent night eating and awakenings. Whether the endocrine diurnal variation and the pituitary-adrenal response to CRH also vary according to the symptoms is of great importance for a more comprehensible characterization of the disease. This awaits further studies. Moreover, whether this attenuated CRH response among night eaters is the result of the fasting state only is another interesting question. To test this hypothesis was also beyond the scope of this study.

Melatonin plays a pivotal role in regulating biological rhythms, especially sleep behavior. Melatonin induces sleep (28), and hypomelatoninemia has been associated with sleeping disorders (27) and depression (15). The interactions between the pineal melatonin secretion and the hypothalamic secretion of CRH are so far not fully understood. Most likely, melatonin down-regulates the binding sites of CRH (7). As reported by Konakchieva et al. (15), exogenous melatonin administration in rats attenuated the adrenocortical response to both acute and chronic stress and prevented the decline in ACTH release resulting from chronic stress exposure. In this way, melatonin treatment may protect against disruptions caused by stress and thereby may reestablish homeostasis (16). Moreover, as reported earlier, CRH may also inhibit secretion of melatonin in humans (13). Therefore, the disturbances observed in the melatonin secretion in the night eaters may reflect an apparent overexpressed HPA axis. Whether the primary neuroendocrine deficit in the night eating syndrome is located either in the pituitary gland and/or in the HPA axis is unresolved. We might be able to prevent the decline in ACTH release resulting from chronic stress exposure by giving melatonin, but this awaits further studies.

It is generally accepted that leptin plays a role in the afferent signaling to the hypothalamus, regulating the appetite and energy expenditure (6) by inhibition of neuropeptide Y. This activates CRH by effects on the transcription of the two regulatory peptides (21, 26). Most likely, leptin, at least partially, enhances the anorectic effect of CRH by increased secretion and/or increased expression of the CRH receptor of the ventromedial hypothalamus (18).

The mechanism behind the nocturnal rise in leptin is unknown, but several causal mechanisms have been proposed. Among others, increased daily insulin secretion has been proposed to increase the transcription of leptin mRNA, with a lag of time effect toward night (1). In this context, it is of interest to discuss if the apparent increased CRH activity in night eaters may cause the attenuation of the diurnal increase of plasma leptin and thus increase the transcription of leptin mRNA, which results in an increased appetite. Normally, there is an inverse relationship between the diurnal secretions of leptin and cortisol. Whether there is a causal relationship between these two secretions remains unclear. In two reports, stress did not influence the diurnal secretion of leptin (9, 19), whereas in two other reports, stress indeed inhibited the leptin secretion and abolished the diurnal secretion (5, 12).

The night eating syndrome appears to represent a new eating disorder, different from the established disorders of anorexia nervosa, bulimia nervosa, and binge eating disorders. It differs from the latter two disorders in the frequency and size of ingestions at night, as described by Birketvedt et al. (3) in 1999. The elevated plasma levels of cortisol reflected increased activity of CRH, as expressed by an attenuated ACTH and cortisol response that may well explain the disrupted sleep and appetite pattern observed in night eaters. Several other disorders, such as obesity (21), fatigue syndrome (17), anorexia nervosa (25), bulimia nervosa (10), insomnia (8), and depression (14), have been linked to disturbances in the HPA axis. All of these disorders share some phenotypes with the night eaters, such as mood disruptions, eating disorders, and sleeping disorders. Whether these clinical features are
the result of common pathophysiological mechanisms in the HPA axis remains to be clarified and awaits further studies.

In conclusion, subjects suffering from night-eating episodes have signs of disturbances in the HPA axis with an attenuated ACTH and cortisol response to CRH. The mechanisms behind the increased CRH stimulation may involve alterations in the neurotransmitter systems, causing increased nocturnal appetite and disruption in the sleep pattern. This may, to some extent, explain the disturbances in the circadian secretions of melatonin and leptin and the behavioral characteristics of the night eating syndrome.

We thank Ingrid Christiansen and Line Wilsgaard at the Laboratory of Gastroenterology of the University of Tromsø. We are greatly indebted to Inger Myrland and Astrid Lindvall, Clinical Department and the Clinical Research Department of The University of Tromsø, for technical assistance.

This study was supported in part by the Norske Kvinner S计划生育 fonds.

REFERENCES


