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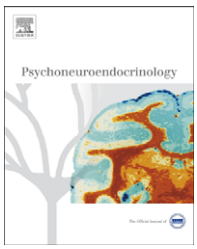

Ghrelin enhances the nocturnal secretion of cortisol and growth hormone in young females without influencing sleep

Michael Kluge*,[1], Petra Schüssler[1], Verena Zuber, Sara Kleyer, Alexander Yassouridis, Martin Dresler, Manfred Uhr, Axel Steiger

Max-Planck Institute of Psychiatry, Munich, Germany

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Summary
Ghrelin was shown to increase slow wave sleep (SWS) and the secretion of growth hormone (GH) and cortisol in young males. In terms of sleep, such information for females, however, is lacking. Therefore, polysomnographies were recorded (23:00–07:00 h) and nocturnal (20:00–07:00 h) secretion profiles of GH and cortisol were determined in 10 healthy females (24.9±2.4 years, body mass index: 21.2±1.1) twice, receiving four boluses of 50 μg ghrelin or placebo at 22:00, 23:00, 00:00, and 01:00 h, in this single-blind, randomized, cross-over study. No significant differences of conventionally or quantitatively analyzed sleep were observed between ghrelin and placebo condition. First administration of ghrelin caused a marked mean increase of GH by 53.3 to 64.4±14.2 ng/ml (placebo: 5.9±1.5 ng/ml) and cortisol by 54.2 to 96.4±15.3 ng/ml (placebo: 27.5±4.7 ng/ml). The following ghrelin injections were associated with smaller increases of GH and cortisol. In the ghrelin condition, GH plasma levels remained significantly ($P<0.05$) higher from 22:20 to 02:00 h and cortisol plasma levels from 22:20 to 02:20 h. In contrast to findings in young men, ghrelin did not affect sleep in young women, indicating a sexual dimorphism. In accordance with the findings in young men, ghrelin stimulated secretion of GH and cortisol.

1. Introduction

Ghrelin, the endogenous ligand of the growth hormone (GH) secretagogue receptor (GHS-R), has been named after its potent GH-releasing effect (Kojima et al., 1999). It is primarily produced in the stomach but have been also

*Corresponding author. Tel.: +49 89 30622 396; fax: +49 89 30622 7548.
E-mail address: kluge@mpipsykl.mpg.de (M. Kluge).
[1]Both authors contributed equally to this work.

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detected in several other organs, such as kidney, bowels, thyroid, lung, testes, placenta, hypothalamus, and pituitary (Korbonits et al., 2004; van der Lely et al., 2004). Accordingly, a variety of endocrine effects (releasing factor of GH, prolactin, ACTH and cortisol; inhibiting factor of luteinizing hormone, orexigenic hormone) and non-endocrine effects (e.g. modulator of cell proliferation and apoptosis) have been described (Korbonits et al., 2004; van der Lely et al., 2004; Kluge et al., 2007a). In addition, there is also evidence that ghrelin affects sleep. In rodents, both an enhancing (Obal et al., 2003) and impairing effect on non-rapid eye movement (NREM) sleep have been reported (Szentirmai et al., 2006, 2007). In humans, our group showed an increase of slow wave sleep (SWS) in young males (Weikel et al., 2003). A sleep promoting effect was also suggested by a simultaneous increase of SWS and ghrelin (trend) in the first half of the recovery night after sleep deprivation (Schüssler et al., 2006). Ghrelin is very akin to GH releasing hormone (GHRH). Both are potent hypothalamic GH releasing factors and affect the secretion of cortisol and the amount of NREM sleep. In GHRH, all of the actions described, particularly the two latter, showed a sexual dimorphism: GHRH increased amount of NREM sleep in male animals (Obal and Krueger, 2004; Van Cauter et al., 2004) and humans (Steiger et al., 1992; Kerkhofs et al., 1993) but decreased it in females (Antonijevic et al., 2000a). GHRH decreased cortisol in males (Steiger et al., 1992; Antonijevic et al., 2000b) but increased cortisol in females (Antonijevic et al., 2000b). In terms of GH release, differences between genders were more subtle, e.g., GHRH was reported to maintain basal GH secretion in women but not in men (Jessup et al., 2003).

Studies on the effect of ghrelin on sleep in females are lacking. In addition, we are aware of only one study investigating the GH and cortisol responses to ghrelin in healthy, normal weighted females (Broglio et al., 2003). In that study, GH and cortisol following a single dose of ghrelin increased similarly in females and males. Aim of this study was to investigate the effect of ghrelin on sleep and nocturnal plasma levels of GH and cortisol in young healthy women.

2. Subjects and methods

2.1. Subjects

A total of 10 healthy females, aged 20–30 years (mean $\pm$S.D.: 24.9 $\pm$ 2.4 years, body mass index (BMI): 21.2 $\pm$ 1.1, weight: 62.2 $\pm$ 6.3 kg) were included. Exclusion criteria included a lifetime or family history of psychiatric disorders, any current disease or drug-intake, smoking, more than moderate under- or overweight (permitted BMI between 18.5 and 27), and sleep disturbances or shift work within 3 months prior to study entry. Study eligibility was assessed by taking the past and current medical history and performing a physical examination and screening tests (electroencephalogram (EEG), electrocardiogram (ECG), routine laboratory parameters, drug screening). The study followed the guidelines of The Declaration of Helsinki. Written informed consent was obtained and approval of the Ethics Committee of the University of Munich was given.

2.2. Study design

This single-blind, placebo-controlled, randomized, cross-over study comprised two blocks of two consecutive nights. Each block took place during the follicular phase. Generally, both blocks occurred in two consecutive cycles, i.e. with an interval of about 4 weeks. The first night of each block served for adaptation to the sleep laboratory setting. In the second night, 4 ml blood were drawn every 30 min (20:00–22:00 h) and 20 min (22:00–07:00 h), respectively from the adjacent room, using an intravenous cannula and a tubic extension. Furthermore, polysomnographic recordings were conducted (23:00–07:00 h). In one of the second nights, four boluses of 50 μg acylated ghrelin (Clinalfa, Läufelfingen, Switzerland), in the other second night, four boluses of placebo were injected at 22:00, 23:00, 00:00, and 01:00 h. The order of administration was randomly distributed. The vast majority of subjects did not report any adverse event following ghrelin injection. One subject reported transient sweating. Substances (e.g. coffee, alcohol) or activities (e.g. naps during the day, excessive exercises) potentially influencing vigilance were restricted or prohibited. Food intake was not controlled prior to the study but all volunteers reported normal eating patterns including breakfast, lunch, and dinner. Study participants were advised to have dinner as usually during the study period in order not to affect the response to exogenous ghrelin.

2.3. Hormone analysis

Blood samples were centrifuged immediately and plasma was frozen at $-25\,^{\circ}$C. Hormone concentrations were analyzed using commercially available radioimmunoassays (cortisol: DRG Instruments GmbH, Marburg, Germany; GH: Advantage, Nichols Institute, San Juan Capistrano, USA). The detection limits were 0.2 ng/ml for GH and 1.7 ng/ml for cortisol. Intra- and interassay coefficients of variance were below 9% and 10%, respectively.

2.4. Polysomnography

The polysomnographic recordings consisted of two EEGs, vertical and horizontal electrooculograms, and ECG (Comlab 32 Digital Sleep Lab, Schwarzer GmbH, Munich, Germany). Sleep stages were visually scored per 30-s epoch according to conventional criteria (Rechtschaffen and Kales, 1968) by experienced raters, who were unaware of the study aim. The following sleep variables were calculated: sleep period time (SPT; time from first epoch containing stage 2 sleep until final awakening), time awake, sleep onset latency (time between lights off and first occurrence of stage 2 sleep), REM latency (interval between sleep onset and first epoch containing REM sleep), SWS latency (interval between sleep onset and first epoch containing stage 3 sleep), sleep efficiency index, and absolute time spent in each sleep stage. The sleep EEG was additionally quantitative analyzed. The fast Fourier transform routine using a rectangular window for consecutive, non-overlapping 2-s miniepochs was applied. EEG frequency bands were defined as follows: δ, 0.5–4 Hz; θ, 4.5–8.0 Hz; α, 8.5–12.0 Hz; σ, 12.5–16.0 Hz;