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Effects of ghrelin on psychopathology, sleep and secretion of cortisol and growth hormone in patients with major depression

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ABSTRACT

Ghrelin showed antidepressant-like effects in mice. Furthermore, ghrelin influences sleep and the activity of hypothalamic-pituitary-adrenal (HPA) and somatotropic axis in healthy humans as indicated by increased cortisol and growth hormone (GH) plasma levels. Both sleep and the activity of these endocrine axes are disturbed in depression. We therefore studied the impact of ghrelin on psychopathology, sleep and secretion of cortisol and GH in patients with major depression. Depressive symptoms as assessed by a validated self rating scale ('Befindlichkeits-Skala', [mental state scale]), secretion profiles of cortisol and GH and sleep-EEGs were determined in 14 unmedicated patients with major depression (7 women) twice, receiving 50 μg ghrelin or placebo at 22:00, 23:00, 00:00, and 01:00 hours. Overall, depressive symptoms did not change significantly after ghrelin administration (placebo: 37 ± 8; ghrelin: 33 ± 10, $p = 0.178$). However, there was an improvement at trend level in men (placebo: 36 ± 9 to ghrelin: 30 ± 9, $p = 0.093$) but not in women. In men, ghrelin was associated with less time awake (placebo: 149.0 ± 11.1; ghrelin: 88.0 ± 12.2 min, $p = 0.029$) and more non-REM sleep (placebo: 263.2 ± 24.1; ghrelin: 304.9 ± 14.1 min, $p = 0.027$), in women with less REM sleep (placebo: 108.6 ± 15.7; ghrelin: 74.1 ± 13.8 min, $p = 0.031$) and longer REM latency (placebo: 49.9 ± 6.5; ghrelin: 85.6 ± 14.1 min, $p = 0.019$). In both sexes, ghrelin caused strong transient increases of GH and cortisol. In conclusion, our study may provide some initial indication that ghrelin can exert antidepressant effects in patients with major depression. Ghrelin strongly affected sleep and secretion of GH and cortisol in a partly different way as previously reported in healthy subjects.

1. Introduction

Several findings suggest that the orexigenic hormone ghrelin, the intrinsic ligand of the growth hormone (GH) secretagogue receptor (GHSR), is involved in mood regulation and pathogenesis of depression: three out of nine healthy subjects reported elevated mood as an unsolicited adverse event after a single dose of ghrelin in a previous study from our group (Schmid et al., 2005). A ghrelin gene polymorphism was associated with major depressive disorder (Nakashima et al., 2008). Strong evidence for an antidepressant effect provides a study in mice: antidepressant-like effects were produced by a single dose of ghrelin within 45 min as assessed in the forced swim test (Lutter et al., 2008). In addition, depressive-like symptoms induced by the depression model 'chronic social defeat stress' were associated with an increase of ghrelin. The finding that these depressive-like symptoms were significantly stronger in GHSR knockout mice than in the wild-type corroborates an antidepressant effect of ghrelin (Lutter et al., 2008). Likewise, ghrelin's inhibiting action on the release of proinflammatory cytokines which are known to impair mood may suggest an antidepressant effect (Dixit et al., 2004; Himmerich and Sheldrick, 2010). Also, the repeated (Date et al., 2006; Kawakami et al., 2008; Emanuel and Ritter, 2010) but not consistent (Brunetti et al., 2002) finding that ghrelin increases noradrenergic transmission in the hypothalamus, being not only a link between nervous and endocrine system but also part of a circuitry relevant in depression (Krishnan and Nestler, 2008) and crucially involved in sleep regulation (Saper et al., 2005), supports an antidepressant action; decreased central monoaminergic function is an established hypothesis for the etiopathogenesis of depression (Krishnan and

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Nestler, 2008). In contrast, ghrelin's suppressive effect on central release of another monoamine, namely serotonin (Brunetti et al., 2002), may rather suggest a depressogenic effect such as its stimulatory action on the hypothalamic-pituitary-adrenal (HPA) axis (Takaya et al., 2000; Mozid et al., 2003; Kluge et al., 2007d); hyperactivity of the HPA axis is another model for development of depression (de Kloet et al., 2005). Also, an antidepressant-like effect of *antisense* DNA for ghrelin in rats may rather suggest a depressogenic effect (Kanehisa et al., 2006). This view receives some further support from studies showing that psychopathological improvement of depressed patients after electroconvulsive therapy (Kurt et al., 2007) and psychopharmacological treatment (Schmid et al., 2006; Barim et al., 2009) was associated with a decrease of ghrelin plasma levels. Yet, one study reported an increase during antidepressant medication (Pinar et al., 2008). Reports on ghrelin plasma levels in untreated depressed patients being similar (Kluge et al., 2009a), increased (Gecici et al., 2005) or decreased (Barim et al., 2009) as compared to healthy controls were conflicting.

Thus, while there is reason to believe that ghrelin is involved in mood regulation, current evidence does not allow to predict how ghrelin will affect overall depressive symptomatology in depressed patients. We therefore investigated effects of ghrelin on depressive symptomatology in patients with major depression allowing us to detect as well a potential antidepressant as a potential depressogenic effect. In addition, we determined factors being both commonly disturbed in depression and strongly influenced by ghrelin, namely secretion patterns of cortisol and growth hormone (GH), and sleep.

2. Subjects and methods

2.1. Subjects

Fourteen unmedicated inpatients with major depressive disorder (7 women, 7 men), as defined by the 'Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision' (DSM-IV-TR) were included in this study (American Psychiatric Association, 2000). Diagnosis was established independently by two senior psychiatrists. Inclusion criteria comprised a total score on the Hamilton Depression Rating Scale, 21 items version ($HDRS_{21}$) of $\geq$15 (Hamilton, 1960). Patients with a concomitant axis I or axis II disorder or non-psychiatric disorders were excluded. Patients had to be drug-free for at least two weeks (fluoxetine: 6 weeks) prior to study entry. Study eligibility was assessed by taking the past and current psychiatric and medical history, and performing a physical examination and screening tests (electroencephalogram [EEG]; electrocardiogram [ECG]; routine laboratory parameters; drug screening). Men and women did not significantly differ in terms of age (men: 41 ± 7 years, women 37 ± 5 years), body mass index (men: 25 ± 3, women 22 ± 3), severity of depressive symptoms ($HDRS_{21}$ total score men: 22.9 ± 5.4, women: 27.1 ± 5.8) and number of depressive episodes (men: 4.1 ± 2.2, women 3.4 ± 2.4). 3 men and 2 women were smokers. Patients had a controlled food intake including breakfast (08:30 h), lunch (12:00 h) and dinner (18:00 h). The study followed the guidelines in The Declaration of Helsinki. Written informed consent was obtained and ethical review board approval given.

2.2. Study design

This was a single-blind, placebo-controlled study comprising one block of three consecutive nights. Inpatients were included within three days after admission to the ward. The first night served for adaptation to the sleep laboratory setting. During the second night placebo, during the third night 50 μg acylated ghrelin (Clinalfa, Läufelfingen, Switzerland) was administered at 22:00, 23:00, 00:00, and 01:00 h. For minimizing the burden of patients and allowing starting medication as soon as possible after study end, the study consisted of one block only. Since effects of ghrelin on both sleep (Kluge et al., 2008) and secretion of various hormones (Kluge et al., 2007b, 2009b, 2010b) can be delayed for several hours and then last for several hours we refrained from randomizing ghrelin and placebo to the second or third night in order to avoid hang-over effects. However, patients were not aware in which of these nights they received either substance. During the second and third night, 4 ml of blood was drawn every 30 min (20:00–22:00 h) and 20 min (22:00–07:00 h) respectively from the adjacent room, using an iv cannula and a tubic extension. Furthermore, sleep-EEGs were conducted between 23:00 and 07:00 h. Severity of depressive symptoms at baseline was assessed with the $HDRS_{21}$. Severity of depressive symptoms in the morning before and in the morning after the third night (ghrelin) was assessed using an extensively validated self rating scale ('Befindlichkeits-Skala' [mental state scale]) consisting of 28 opposite word pairs (e.g. happy–unhappy) each with three answer options (word 1; word 2; neither nor) (Von Zerssen et al., 1970, 1974; Schwarz and Strian, 1972). In contrast to most other depression scales such as the HDRS or 'Beck Depression Inventory' it does not refer to the whole previous week but to the moment of rating and is therefore particularly able to repeatedly assess depressive symptoms (Schwarz and Strian, 1972). Substances (e.g. coffee, alcohol) or activities (e.g. naps during the day, excessive exercises) potentially influencing vigilance were restricted or prohibited.

2.3. Hormone analysis

Blood samples were centrifuged immediately and plasma was frozen at −25 °C. Concentrations of cortisol and GH were determined using a solid phase, two-site, sequential chemiluminescent immunometric assay in an automated analyzer (Immulite 2005, Siemens Medical Solutions, Erlangen, Germany). All samples of an individual were measured in the same assay run. Detection limits were 2 ng/ml for cortisol and 0.01 ng/ml for GH. Within-run coefficients of variation were below 9%. Between-run coefficients of variation were below 11%.

2.4. Polysomnography

Polysomnography consisted of two EEGs, vertical and horizontal electrooculograms, and ECG (Comlab 32 Digital Sleep Lab, Schwarzer GmbH, Munich, Germany). Sleep stages were scored visually per 30-s epoch according to conventional criteria (Rechtschaffen and Kales, 1968) by experienced raters, who were unaware of the study aim. The sleep-EEG was additionally analyzed quantitatively as previously reported (Weikel et al., 2003). The Fast Fourier Transform routine using a rectangular window for consecutive, non-overlapping 2-second miniepochs was applied. EEG frequency bands were defined as follows: delta, 0.5–4 Hertz (Hz); theta, 4.5–8.0 Hz; alpha, 8.5–12.0 Hz; sigma, 12.5–16.0 Hz; beta, 16.0–20.0 Hz.

2.5. Statistical methods

Effects of treatment on conventional and quantitative sleep parameters (variables) were identified using multivariate analyses of variance (MANOVAs) with repeated measures design. Sleep variables were determined both for the whole night (23:00–07:00 h) and the two halves of the night. When significant treatment effects were found, univariate *F*-tests were performed to identify those variables significantly contributing to treatment effects. Severity of depression was tested for significant differences between the two treatments by