Ghrelin promotes slow-wave sleep in humans

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Ghrelin, a peptide hormone, was recently isolated from stomach, hypothalamus, and other tissues from humans and rats (25). It was identified as an endogenous ligand of the growth hormone (GH) secretagogue (GHS) receptor. This receptor was cloned before the detection of ghrelin (22) and is known to be the target of synthetic GHSs. Ghrelin shares the capacity of these compounds to stimulate the release of GH from the pituitary in humans (36, 46) and rats (25, 54). Ghrelin is thought to be, besides GH-releasing hormone (GHRH) and somatostatin, a third endogenous factor in the regulation of GH release. Furthermore, in the daytime, ghrelin (5) stimulates the secretion of the hormones of the hypothalamo-pituitary-adrenocortical (HPA) system, adrenocorticotropic hormone (ACTH) and cortisol, and of prolactin. Finally, ghrelin is hypothesized to play a key role in energy balance (for review see Ref. 21). In rodents, ghrelin stimulates food intake and weight gain (31, 50, 53). In young, normal human subjects, appetite was enhanced after ghrelin administration (43, 52). Preclinical data suggest an inverse interaction of the orexigenic ghrelin and the anorexigenic leptin (21, 38).

Besides its influence on food intake and body weight, ghrelin may also participate in sleep regulation. This appears likely, since synthetic GHSs modulated sleep in young men. After pulsatile administration of GHRP-2, sleep electroencephalogram (EEG) power density increased during the second half of the night. Rapid-eye-movement (REM) sleep was reduced during the second third of the night, whereas all other sleep EEG variables remained unchanged. Furthermore, GH and prolactin plasma levels were enhanced throughout the night, and cortisol levels increased during the first part of the night (2200–0300). The response of GH to ghrelin was most distinct after the first injection and lowest after the fourth injection. In contrast, cortisol showed an inverse pattern of response. Leptin levels did not differ between groups. Our data show a distinct action of exogenous ghrelin on sleep EEG and nocturnal hormone secretion. We suggest that ghrelin is an endogenous sleep-promoting factor. This role appears to be complementary to the already described effects of the peptide in the regulation of energy balance. Furthermore, ghrelin appears to be a common stimulus of the somatotropic and hypothalamo-pituitary-adrenocortical systems. It appears that ghrelin is a sleep-promoting factor in humans.

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GHRH, in contrast to the effects of GHRP-6 and hexarelin, cortisol secretion is blunted in young men (41). On the other hand, SWS is elevated when GHRH is enhanced (reviewed in Ref. 33). In contrast to GHRH, CRH administration decreases SWS in young men (20), rats (12), and rabbits (34). On the other hand, wakefulness was reduced after decrease of CRH by CRH antagonists (9), and SWS increased in transgenic animals with reduced CRH activity (35). It is thought that changes in the ratio between GHRH and CRH contribute to impaired sleep during depression and in normal aging (11, 42). Similarly to CRH, the antagonists of GHRH in the release of GH, somatostatin and its analog octreotide, impaired sleep in humans (15, 45) and rats (7).

Two recent studies report conflicting data on sleep in rodents after ghrelin administration. In one study, a decrease of REM sleep was found after administration of ghrelin to rats (48). The authors concluded that a direct action of the hormone per se or the indirect effects of feeding, which increased after administration of the peptide, cannot be differentiated. In another study, ghrelin was given to two different strains of mice, intact animals and those with nonfunctional GHRH receptors. Only in mice with intact GHRH receptors did NREM sleep increase after administration of the peptide (32). The influence of ghrelin on human sleep is unknown. We chose a protocol according to various previous studies on the sleep-endocrine effects of peptides, including GHRH (41), GHRP-6 (14), hexarelin (40), and vasoactive intestinal peptide (VIP) (30). Here, we investigated the effects of the pulsatile administration of ghrelin on sleep EEG and of GH, ACTH, cortisol, and leptin in healthy male subjects.

METHODS

Subjects. The subjects were healthy male volunteers (mean ± SE: age 25.3 ± 1.6 yr; height 180 ± 0 cm; weight 75.9 ± 1.6 kg; body mass index 22.5 ± 0.5; n = 7). The study was approved by the Ethics Committee for Human Experiments of the University of Munich.

After the purpose of the study had been explained to the subjects,written consent was obtained. They underwent extensive psychiatric, physical, and laboratory (hematology, virology, clinical chemistry, endocrinology, EEG, and electrocardiography) examinations. Individuals with a personal or family history of psychiatric disorders or a recent stressful life event were excluded, as were shift workers and persons who had recently made a transmeridian life event were excluded, as were shift workers and persons. Consumption of alcohol was not allowed during the previous 3 mo was also ruled out. A total of nine smokers (2 cigarettes per day), other except alcohol and caffeine was restricted to 200 ml of coffee in the morning. Any history of medical treatment during the previous 3 mo was also ruled out. A total of nine subjects entered the screening procedure, and two of them were not admitted to the study because they met the exclusion criteria.

Experimental procedure. The sleep-endocrine studies consisted of two sessions, separated by ≥1 wk, in which placebo (saline) or ghrelin (Clnalfa, Läufelfingen, Switzerland) was administered according to a double-blind, randomized sched-ule (3 subjects received placebo, and 4 subjects received ghrelin in the first session). The experimental sessions consisted of two successive nights in our sleep laboratory. The first night served for adaptation to the laboratory setting. On the second night, a dose of 4 × 50 µg of ghrelin or placebo was administered as a bolus injection through an indwelling intravenous catheter, which was inserted at 1930 and connected to plastic tubing that ran through a soundproof lock into the adjacent room. This allowed us to test drug administration and repeated blood collection in the adjacent laboratory without disturbing the subject. According to our experience from various similar studies (42) and the literature (24), cannulation does not affect sleep EEG distinctly. All subjects were supine from 2000. Injections of ghrelin or placebo were given hourly between 2200 and 0100. Blood samples were collected every 30 min between 2000 and 2200 and every 20 min between 2200 and 0700. Specimens collected before 2200 served to control for stress effects after cannulation, and only those collected between 2200 and 0700 were included in the time course analysis. The subjects were observed on a television screen in the adjacent room.

EEG recordings. Electroencephalographic recordings (Comlab 32 Digital Sleep Lab, Brainlab v. 3.3 software, Schwarzer, Munich, Germany) were fixed between 2100 and 2200. The subjects were not allowed to sleep until the lights were turned off at 2300. Polysomnographic recordings were obtained from 2300 to 0700 and consisted of two EEGs (C3-A2, C4-A1; time constant 0.3 s, low-pass filtering 70 Hz), vertical and horizontal electrooculograms, and electromyogram.

Conventional sleep EEG analysis. Sleep stages (wakefulness, stages I-IV sleep (stages III and IV sleep are SWS), and REM sleep) were scored visually in all subjects off-line according to conventional criteria (37) by a rater who was unaware of the treatment. Calculations of sleep parameters included time in bed (TIB), sleep onset latency (time between lights off and the first occurrence of stage II sleep), SWS latency (interval between sleep onset and the first 30-s epoch containing stage III sleep), REM latency (interval between sleep onset and the first 30-s epoch containing REM sleep), number of awakenings, and the time spent in the different sleep stages with reference to TIB. Sleep EEG parameters were analyzed for the TIB (480 min; equal to the total night), the two halves of the night (each 240 min), and the three thirds of the night (each 160 min).

Quantitative sleep EEG analysis. The quantitative EEG (qEEG) included all epochs of stable NREM sleep (stages II, III, and IV). Before qEEG, artifacts and arousals, defined according to criteria of the American Sleep Disorders Association (1), were rejected by visual inspection. The qEEG was performed by the Fast Fourier Transform routine by use of a rectangular window for consecutive, nonoverlapping 2-s miniepochs, which allowed a frequency resolution of 0.5 Hz. The spectral profiles were calculated as the mean values for the entire sleep and separately for each of the halves and each of the thirds of the night. Furthermore, the spectral power in the δ-frequency range was aggregated through all analyzed NREM sleep epochs. This approach enabled expression only of the sleep intensity but also of the accumulated SWA during TIB. The EEG frequency bands were defined as follows: δ (0.5–4 Hz), θ (4.5–8 Hz), α (8.5–12 Hz), β1 (12.5–15 Hz), β2 (15.5–25 Hz), γ1 (25.5–35 Hz), and γ2 (35.5–45 Hz).

Endocrine analysis. Plasma ACTH (RIA Kit J125; Nichols Institute, San Juan Capistrano, CA; intra- and interassay coefficients of variation <5%), cortisol (RIA Kit J125; ICN Biomedicals, Carson, CA; intra- and interassay coefficients of
GH surge was enhanced markedly, resulting in significant changes in the spectral power of other frequency bands were found.

**RESULTS**

Conventional sleep EEG analysis. On the night of ghrelin administration, the time spent in SWS and particularly its stage IV component, sleep increased significantly compared with the placebo night. Separate inspections of the three thirds of the night showed significant increases of SWS during the first and second thirds of the night but not during the last third. REM sleep showed a significant decrease only during the second third of the night. Intermittent wakefulness appeared descriptively to decrease, although it did not reach significance. All other sleep continuity and sleep architecture variables remained unchanged (see Table 1).

Quantitative sleep EEG analysis. In the qEEG of NREM sleep, an increase in power of 6-activity (especially <2 Hz) was found after ghrelin administration. It was restricted to the second half of the night (accumulated 6-activity (µV²) placebo 117,671 ± 26,270 vs. ghrelin 144,060 ± 30,525; P < 0.05; Fig. 1). No significant changes in the spectral power of other frequency bands were found.

Endocrine variables. Under ghrelin, the nocturnal GH surge was enhanced markedly, resulting in significant increases of GH concentration throughout the night and particularly during the first part of the night (2200–0300). During the same interval, but not during the second part of the night (0300–0700), cortisol concentration was elevated. Cortisol concentrations collected before 2200 revealed no differences between the two conditions [cortisol concentration 2000–2200 (in ng/ml) 33.4 ± 4.4 after ghrelin vs. 33.8 ± 5.8 after placebo]. Inspection of the mean maximum following each of the four bolus injections showed that the highest GH values occurred after the first and second injections at 2200 and 2300, whereas the lowest GH value was found following the fourth injection at 0100 [GH maximum (in ng/ml) after ghrelin vs. placebo after each of the four injections: first, 41.5 ± 12.12 vs. 2.0 ± 1.2; second, 42.7 ± 12.2 vs. 6.5 ± 2.2; third, 35.4 ± 10.3 vs. 11.8 ± 2.8; fourth, 20.7 ± 7.0 vs. 9.0 ± 2.8; P < 0.05 at each injection]. In contrast, the lowest cortisol maximum was found after the first injection [cortisol concentration (in ng/ml) 40.5 ± 9.1 after ghrelin vs. 24.5 ± 4.9 after placebo, not significant (NS)], followed by stepwise-increasing values until the last bolus [second, 49.1 ± 14.5 vs. 18.9 ± 1.9 (NS); third, 57.3 ± 21.0 vs. 13.7 ± 2.0 (NS); fourth, 70.2 ± 11.4 vs. 11.4, P < 0.002]. The ACTH maximum was significantly higher after ghrelin than after placebo. ACTH levels showed a tendency to increase during the first part of the night, although the difference was not significant. Prolactin concentration increased throughout the night and particularly during the first part of the night. Leptin concentration did not differ between the two conditions (Fig. 2 and Table 2).

**DISCUSSION**

Our data show that ghrelin promotes SWS, GH, and cortisol secretion in young, healthy, normal men. Only a weak increase of ACTH was found, whereas leptin levels remained unchanged. The effect of ghrelin on sleep EEG resembles that of GHRH in our complementary, previous protocol (41). Similar to ghrelin in the present study, GHRH selectively promoted SWS and had no major significant effect on other sleep stages. GHRH promotes SWS to a similar extent to ghrelin: in a paired t-test, no differences in promoting SWS under GHRH or ghrelin were found. The major difference in sleep EEG analysis was a longer-lasting effect of GHRH than of ghrelin on SWS. After GHRH administration, SWS was higher up to the last third of the sleep period; after ghrelin administration, it was higher only up to the second third of the sleep period. Our finding is similar to the increase of NREM sleep after ghrelin administration in mice (32). Associated with the increase of SWS, SWA, as reflected by EEG 6-power, increased significantly but only in the second half of the night. Furthermore, after ghrelin administration, REM sleep decreased during the second third of the night, and intermittent wakefulness showed a nonsignificant tendency to decrease. This observation resembles the decrease of REM sleep after administration of ghrelin to the rat (48), whereby in that study NREM sleep remained unchanged.

The effect of ghrelin on sleep EEG differed from that of synthetic GHS. Pulsatile administration of GHRP-6 to young men increased stage II sleep, whereas SWS and SWA remained unchanged. Subchronic oral administration of the GHS MK-677 increased SWS in young men (10) on a level similar to that of ghrelin and GHRH (41). Repetitive intravenous hexarelin, however, decreased SWS and SWA (40).
Ghrelin not only influenced sleep but also affected hormone secretions similarly to its effects after administration to humans during the daytime (5, 36, 46) or to rats (25, 54). Furthermore, these changes are similar to the effects after the administration of synthetic GHSs GHRP-6 and hexarelin in our previous studies. However, the potency in stimulating GH and cortisol (Table 3) and the pattern of hormone secretion after ghrelin differ from the changes after these GHSs. Similarly to GHRH (41), GHRP-6 (14), and hexarelin (40), ghrelin augmented the physiological GH surge.

Comparison of our present study with our previous reports shows hexarelin to be the most potent stimulus of GH release during the total night, followed by...
GHRH, ghrelin, and GHRP-6 (Table 3). When the first part of the night is inspected separately, ghrelin is slightly less potent than hexarelin but superior to GHRH and GHRP-6. These findings differ from a comparative study in daytime. The same dosage (1 μg/kg) of ghrelin, hexarelin, and GHRH was given intravenously to normal young men in the morning. Ghrelin was more effective in stimulating GH than hexarelin or GHRH (5).

Ghrelin and the synthetic GHSs also modulated cortisol secretion. After the GHS GHRP-6 and hexarelin, cortisol increased during the first part of the night. This change was followed by a decrease of cortisol levels, probably due to feedback inhibition, during the second part of the night (40). A similar course of cortisol secretion was found after pulsatile intravenous administration of CRH in young males (20). Also, after ghrelin administration, cortisol increased during the first part of the night, whereas no blunting of cortisol occurred during the second part of the night. Unlike ghrelin, GHRP-6, and hexarelin, GHRH inhibited cortisol throughout the night in young males (41). As depicted in Table 3, in our hands, GHRP-6 was the most potent stimulus of cortisol secretion during the total night, followed by ghrelin. Ghrelin was even more potent than CRH, which was as effective as hexarelin. Separate inspection of the first and second parts of the night shows that, during the first part, CRH and hexarelin were more potent than ghrelin in stimulating cortisol. During the second part of the night, however, ghrelin was the most effective of all of the investigated peptides. Similarly, after intravenous administration in the morning, the response of cortisol was higher after ghrelin than after hexarelin (5). The mechanisms by which ghrelin influences cortisol may be via CRH. In mice, ghrelin increased hypothalamic CRH mRNA (6). This may explain the increase of cortisol after ghrelin administration. Alternatively, given the weak effect of ghrelin on ACTH, a direct adrenocortical action of exogenous ghrelin appears possible, since ghrelin and GHS receptors were found in the adrenal gland (18). Besides CRH, arginine vasoressinergic mechanisms (26) and GABAergic pathways (4) were also suggested to be mediating the HPA-stimulating effect of synthetic GHS.

A more detailed look at the response of GH and cortisol to ghrelin reveals variations in the effects of the repetitive injections. The first two injections of ghrelin prompted the most distinct increases of GH and had the weakest effect on cortisol. In contrast, the fourth injection was followed by the lowest response of GH and the highest of cortisol. This observation suggests a time-dependent, reciprocal variation in the potency of ghrelin in promoting either GH or cortisol. This pattern may reflect the circadian process of endocrine activity, with the predominance of the somatotropic system around sleep onset, which is followed by the increase of HPA system activity. Similarly in the rat model, the GHS GHRP-6 was more potent in stimulating GH during a spontaneous GH-secretory period than during a trough period (47). Alternatively, it appears possible that the potency of ghrelin in stimulating GH release preponderates as long as sufficient amounts of GH are stored in the pituitary. Declining pituitary GH stores may then be followed by the increasing stimulation of the HPA system.

Similar to the effect of hexarelin (40), prolactin was elevated after ghrelin administration, particularly during the first part of the night. Leptin levels remained unchanged in our study. Similarly, we did not observe a change of leptin after hexarelin administration (40). Also, in the rat, subchronic intravenous administration of ghrelin failed to prompt changes of leptin levels (49). Our finding does not exclude an inverse interaction of the orexigenic ghrelin and the anorexigenic leptin in energy balance, as suggested by preclinical findings (21, 38). In the present study, subjects did not report changes of appetite, whereas after a single bolus of 100 μg of ghrelin in the morning, appetite was elevated (43). Circadian differences in the effect of ghrelin on appetite appear unlikely, since we observed in a single case a distinct stimulation of appetite in a normal subject after 100 μg of ghrelin were given at 2200 (Held, Weikel, and Steiger, unpublished observations). Therefore, we suggest that the dosage of ghrelin given in the present study promotes sleep but has no effect on appetite. This observation differs from the recent observation that, in rats, feeding increases and REM sleep decreases after ghrelin administration (48). On the other hand, in mice with nonfunctional GHRH
receptors, ghrelin stimulated feeding, whereas sleep remained unchanged, in contrast to the promotion of NREM sleep after administration of the peptide in intact mice (32).

The increase of SWS after ghrelin administration may represent a direct, central effect of the peptide; however, various other peptides and neurotransmitters are thought to mediate the endocrine and behavioral influences of ghrelin and have to be considered as contributing to the changes of sleep EEG. Because this effect is similar to that of GHRH on sleep, the question arises whether ghrelin and GHRH are two redundant sleep-promoting factors or whether GHRH mediates the effects of ghrelin on sleep. The latter hypothesis...
It is unlikely that the blood-brain barrier prevents effects of peripherally administered peptides on the sleep EEG, as we have discussed in detail elsewhere (30). We (43) and others (53) found a rapid increase of appetite after administration of ghrelin via infusion or by a single intravenous bolus, respectively. Also, this change is probably a direct central effect of ghrelin. The unique Ser3 acylation is thought to facilitate the penetration of the blood-brain barrier by ghrelin (21). This hypothesis is supported by studies reporting increases of the number of neurons expressing Fos protein in the arcuate nucleus after systemic ghrelin administration in rats (19, 51). Therefore, it is most likely that the increase of SWS is due to a central action of ghrelin. This view is supported, since GH administration decreased SWS (28), cortisol markedly decreased REM sleep besides increasing SWS (17), and excessive levels of prolactin in prolactinoma patients were the prerequisite for inducing SWS (16). The similarity of the effects of pulsatile ghrelin in the present study, of ghrelin in mice (32), of pulsatile intravenous GHRH in humans (44), and of intravenous GHRH in rats (33) supports the view that a strong central effect of ghrelin, which may involve GHRH, overrides the potential influence of changes of peripheral hormone concentrations.

Taken together, our data show a distinct action of exogenous ghrelin on sleep EEG and nocturnal hormone secretion. We suggest that, besides its influence on GH secretion, food intake, and weight gain, ghrelin is an endogenous sleep-promoting factor. This role appears to be complementary to the already described effects of the peptide in the regulation of energy balance. Furthermore, ghrelin appears to be a common stimulus of the somatotropic and HPA systems. Given the reciprocal interaction of GHRH and CRH in sleep regulation (11, 42), it is of particular interest that ghrelin shares the sleep- and GH-promoting effects of GHRH and the stimulating effect of CRH on cortisol. Therefore, it may act as an interface between the two endocrine systems.

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### Table 2. Effects of ghrelin compared with placebo on GH, ACTH, cortisol, prolactin, and leptin secretion in 7 young men

<table>
<thead>
<tr>
<th>Time/Endocrine Variable</th>
<th>Placebo</th>
<th>Ghrelin</th>
<th>P Value</th>
<th>T Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2200-0300</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td>1.268 ± 270</td>
<td>6.90 ± 1,908</td>
<td>&lt;0.05</td>
<td>-3.3</td>
</tr>
<tr>
<td>ACTH</td>
<td>3.063 ± 431</td>
<td>4.754 ± 1,444</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>4.751 ± 575</td>
<td>13,739 ± 2,985</td>
<td>&lt;0.05</td>
<td>-2.8</td>
</tr>
<tr>
<td>Prolactin</td>
<td>3.464 ± 602</td>
<td>5.450 ± 788</td>
<td>&lt;0.05</td>
<td>-3.2</td>
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<tr>
<td>Leptin</td>
<td>984 ± 191</td>
<td>845 ± 186</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>0300-0700</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td>233 ± 88</td>
<td>139 ± 43</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>4.96 ± 804</td>
<td>4,114 ± 387</td>
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<td></td>
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<tr>
<td>Cortisol</td>
<td>11,966 ± 1,617</td>
<td>11,985 ± 1,993</td>
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<tr>
<td>Prolactin</td>
<td>4,087 ± 735</td>
<td>3,766 ± 713</td>
<td>NS</td>
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<tr>
<td>Leptin</td>
<td>655 ± 154</td>
<td>652 ± 162</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>2200-0700</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td>1,500 ± 287</td>
<td>7,129 ± 1,948</td>
<td>&lt;0.05</td>
<td>-3.3</td>
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<tr>
<td>ACTH</td>
<td>8,031 ± 1,15</td>
<td>8,865 ± 1,603</td>
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</tr>
<tr>
<td>Cortisol</td>
<td>16,717 ± 1,813</td>
<td>25,724 ± 4,133</td>
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<tr>
<td>Prolactin</td>
<td>4,087 ± 735</td>
<td>3,766 ± 713</td>
<td>NS</td>
<td></td>
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<tr>
<td>Leptin</td>
<td>1,639 ± 340</td>
<td>1,497 ± 345</td>
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</table>

Values are means ± SE as area under curve (pg · ml⁻¹ · min for ACTH and leptin, ng · ml⁻¹ · min for growth hormone (GH), cortisol, and prolactin). P and T values were determined by t-tests for paired samples.

### Table 3. Relative changes of GH and cortisol concentrations after administration of ghrelin compared with various other peptides

<table>
<thead>
<tr>
<th>Ref. No.</th>
<th>GH</th>
<th>Cortisol</th>
</tr>
</thead>
<tbody>
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<td>2200-0700</td>
<td>2200-0300</td>
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<tr>
<td>Ghrelin</td>
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<td>GHRP-6</td>
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</tr>
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<td>Hexarelin</td>
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<td>142.75</td>
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<tr>
<td>GHRH</td>
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<td>142.75</td>
</tr>
<tr>
<td>CRH</td>
<td>142.21</td>
<td>142.75</td>
</tr>
</tbody>
</table>

Responses are standardized according to the concentrations of the placebo condition (M = 100; SD = 10). GHRP-6, GH-releasing peptide-6; GHRH, GH-releasing hormone; CRH, corticotropin-releasing hormone. Values >100 indicate higher responses compared with placebo, values <100 indicate lower responses compared with placebo.
REFERENCES


