Sexually Dimorphic Effects of GHRH on Sleep-Endocrine Activity in Patients with Depression and Normal Controls-Part II: Hormone Secretion

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In depression and aging, an increase in nocturnal cortisol secretion and a blunted nocturnal growth hormone (GH) surge have been described. In normal young men, growth hormone-releasing hormone (GHRH) promotes GH release and reduces plasma cortisol. Here, we examined whether GHRH could help to restore sleep-endocrine regulation in patients with depression and aging. GHRH (4x50 µg, at 2200, 2300, 2400 and 0100 h) or saline (placebo) was injected intravenously into 42 patients with depression (19 females, 23 males) and matched controls (age range 19-76 years). Blood samples were withdrawn at 20 min intervals between 2200-0700 h and analyzed using Manova (D.F. 1, 72). Patients compared to controls had significantly higher levels of ACTH and cortisol, particularly during the first half of the night (F=9 and F=11.8, each p<0.05). GHRH reduced ACTH during the first half and cortisol secretion during the second half of the night in males, regardless of diagnosis, but enhanced it in females (F=5.1 and F=4.0, each p<0.05). ACTH and cortisol secretion were inversely related to NREM and stage 2 sleep in patients (r=-0.42, -0.42 and r=-0.36, -0.39, respectively, each p<0.05) but not in controls. Our data suggest that: 1) female gender, depression and aging add-on to enhance HPA activity; and 2) hyperactivity of the HPA system and the decrease in NREM and in particular stage 2 sleep in depression are interrelated. In men, GHRH can restore some of the sleep-endocrine alterations associated with depression and aging.

CURRENT CLAIM: Effects of GHRH on sleep-endocrine regulation are sexually dimorphic.

As described in the preceding paper, a major depressive episode is characterized by sleep-endocrine alterations, which reflect hyperactivity of the hypothalamos-pituitary-adrenocortical (HPA) system (Nemeroff et al., 1988; Holsboer and Barden, 1996). Thus, patients with depression, compared to controls, show an elevation of plasma cortisol (Linkowski, 1987; Rubin, 1987) and a reduction of the sleep-associated growth hormone (GH) surge (Jarrett et al., 1985; Steiger et al., 1989, 1994).

Normal aging is also characterized by a blunted sleep-associated GH surge (Kerkhofs et al., 1988; Van Coevorden et al., 1991), while an elevation of circulating cortisol remains controversial (Van Coevorden et al., 1991; Copinschi and Van Cauter, 1995; Van Cauter et al., 1996). The efficacy of growth hormone-releasing hormone (GHRH) to promote the sleep-associated GH surge in humans is reduced in the elderly (Guldner et al., 1997) and in patients with depression (Steiger et al., 1994). Since the GHRH/CRH ratio plays a critical role for sleep-endocrine regulation (Ehlers and Kupfer, 1987), reduced activity of the somatotropic system due to relatively enhanced somatostatin release in the elderly (Shibasaki et al., 1984; Ghigo et al., 1990; Van Coevorden et al., 1991), and hyperactivity of the HPA system in depression have been proposed to attenuate effects of GHRH (Steiger et al., 1994) on sleep-endocrine activity.

Recently, we have demonstrated a sexual dimorphism in nocturnal ACTH and cortisol secretion, as well as regarding effects of GHRH on sleep-endocrine regulation in young healthy humans (Antonijevic et al., 1998c). Also, gender has been shown to modulate age-related alterations of HPA activity (Born et al., 1995; Van Cauter et al., 1996) and GH secretion (Van Cauter et al., 1998).

Here, we further explored the role of gender and age for sleep-endocrine regulation in depression and examined possible therapeutic effects of pulsatile administration of GHRH. The sleep-EEG analysis is presented in the foregoing paper and will be discussed in the present study only in relation to hormone secretion.

METHODS

Subjects

The study has been approved by the Ethics Committee for Human Experiments of the Max Planck Institute of Psychiatry. Written informed consent was obtained from 42 patients with depression (19 females, 23 males) and 42 age- and sex-matched controls (21 females and 21 males). All patients scored above 16 points on the Hamilton Depression Scale (HAMD, 21-item version (American Psychiatric Association, 1987) in the morning of the first study night. All subjects were of normal height and weight and underwent a rigid medical examination including extensive psychiatric, physical and laboratory investigations (hematology, virology, clinical chemistry, endocrinology, EEG and electrocardiography).

Control Subjects

In all subjects, any personal or family history of psychiatric disorders, as well as any medical treatment during the past
three months, were ruled out in a lengthy interview by a senior psychiatrist. Also, subjects who reported sleep disturbances or showed signs of sleep apnea were excluded.

Patients
All patients have been hospitalized for evaluation and treatment of depression. At initial evaluation, all met criteria for major depression according to DSM-III-R (American Psychiatric Association, 1987) with an HAMD score \( \geq 16 \). The diagnosis was established and previous secondary and comorbid diagnoses were ruled out in an examination conducted by a senior psychiatrist. The patients have not been treated with depot neuroleptics, fluoxetine and irreversible monoamineoxidase-inhibitors for at least eight weeks prior to admission, and patients were drug-free for a minimum of one week prior to the study.

For both patients and controls, subjects who were shift workers and persons who had made a transmeridian flight within the last three months were excluded. Also, abuse of drugs, nicotine, alcohol and caffeine was ruled out.

Of female patients and controls, none were taking oral contraceptives. Nine of the 21 female controls and eight of 19 female patients were peri- or postmenopausal, but none of the women were on hormone replacement therapy. Premenopausal patients and controls were not matched with regard to the menstrual cycle, but most recordings were performed during the follicular phase and no recordings were performed during menstruation.

Study Design
Each subject spent three successive nights in the sleep laboratory: while the first night served as adaptation to the laboratory setting, during the second and third night (first and second recording night) the sleep EEG was recorded. During the recording nights, GHRH or placebo was administered at hourly intervals between 2200 and 0100 h (50 µg GHRH [Clinalfa, Läufelfingen, Switzerland] or 5 ml saline) through an indwelling intravenous catheter connected to plastic tubing that ran through a soundproof lock into the adjacent room. This allowed drug administration and repeated blood sampling in the adjacent laboratory without disturbing the subject’s sleep. The administration of GHRH or saline was randomized. Sleep was allowed between 2300-0700 h when lights were turned off. Most of the sleep-EEG analysis is presented in the preceding paper.

Blood samples were collected every 30 min between 2000 and 2200 h and every 20 min between 2200 and 0700 h. Specimens collected before 2200 h served to control for stress effects after cannulation (1930 h); specimens collected between 2200 and 0700 h were included in the time-course analysis. No food was permitted during the study until the subjects were awakened at 0700 h the next morning.

Hormone Analysis
Some of the hormone data were published separately (Antonijevic et al., 1999b). Plasma cortisol, ACTH and GH concentrations were measured by commercial radioimmunoassay. The intraassay variations were 5.6-6.9%, the interassay variations were 7.2-8.2%. Hormone data from one subject were analyzed in one assay. Data were analyzed by computing the mean value for the entire night (2200-0700 h), as well as for the first (2200-0300 h) and the second half (0300-0700 h) of the night.

Statistical Analysis
Statistical analysis was performed using MANOVA with repeated measures designed to examine effects of GHRH treatment (within-subject factor). Diagnosis (patients with depression vs. controls), gender and night of active treatment (first vs. second recording night) were included as between-subject factors. The night of active treatment was included to ensure detection of a possible carry-over effect of GHRH treatment. By significant main or interaction effects of the factors, univariate F-tests followed (D.F. 1, 72) in order to identify the parameters which contributed significantly to the effect. Furthermore, age was included as a covariate. Upon significant influence of age, correlation analysis with the SPSS for Windows system, using Pearson’s product-moment correlation two-tailed, was performed for patients and controls separately to estimate linear relationships between age and the respective variable. A value for \( p \leq 0.05 \) was considered significant; for \( p \leq 0.1 \) data were considered to reflect a trend for a significant difference. In order to keep the type I error less than 0.05, posteriori tests (F-tests) were carried out at a reduced level of significance (adjusted alpha according to the Bonferroni procedure). All data are expressed as means±SEM.

RESULTS

Demographic Data
Patients and controls did not differ in age (male controls: \( 37.2±2.9 \) years [range 22-63], female controls: \( 43.8±4.1 \) years [range 19-73], male patients: \( 41.8±3.2 \) years [range 19-72] and female patients: \( 45.8±4.2 \) years [range 19-72]). Male and female patients were very similar with regard to the HAMD Score (male patients: \( 25.5±1.2 \) [range 17-40], female patients: \( 25.5±1.4 \) [range 18-41]). In 13 of 23 male and 10 of 19 female patients the current depressive episode was the first episode; the number of previous episodes in the other patients ranged between one and four. Two male patients were diagnosed with bipolar disorder, while all other patients were classified as unipolar depressed patients.

Effect of Diagnosis
For the entire night, ACTH showed a trend to be elevated \( (F=4.1, p<0.1, \) Table 1) and cortisol was significantly elevated in patients compared to controls \( (F=8.0, p<0.01) \). During the first half of the night, patients with depression compared to controls had significantly higher plasma ACTH and cortisol secretion \( (F=9.0 \text{ and } F=11.8, \) respectively, each \( p<0.01, \) Table 2). No such effect was observed during the second half of the night. No significant effect of diagnosis on GH secretion was noted.
Table 1
**Nocturnal Hormone Secretion-Total Night**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>female controls</th>
<th>male controls</th>
<th>female patients</th>
<th>male patients</th>
<th>effect of (F value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>placebo</td>
<td>GHRH</td>
<td>placebo</td>
<td>GHRH</td>
<td>gender</td>
</tr>
<tr>
<td>ACTH</td>
<td>20.6 ± 2.0</td>
<td>22.3 ± 5.5</td>
<td>29.9 ± 11.7</td>
<td>28.1 ± 2.0</td>
<td>29.3 ± 2.4</td>
</tr>
<tr>
<td>Cortisol</td>
<td>81.7 ± 7.2</td>
<td>84.5 ± 9.3</td>
<td>71.8 ± 3.8</td>
<td>6.89 ± 2.8</td>
<td>102.2 ± 9.0</td>
</tr>
<tr>
<td>ratio A/C</td>
<td>0.30 ± 0.05</td>
<td>0.31 ± 0.04</td>
<td>0.48 ± 0.09</td>
<td>0.41 ± 0.02</td>
<td>0.31 ± 0.03</td>
</tr>
<tr>
<td>GH</td>
<td>2.3 ± 0.4</td>
<td>6.9 ± 1.2</td>
<td>2.3 ± 0.5</td>
<td>5.7 ± 0.9</td>
<td>1.6 ± 0.2</td>
</tr>
</tbody>
</table>

Values are means±SEM. Statistical analysis see text.

The time of the ACTH and cortisol minimum was not significantly different between groups (between 2340 and 0040 h for ACTH and 0040 and 0120 h for cortisol; see also Figures 1 & 2) and was not significantly affected by GHRH treatment. Neither the mean cortisol through nor the maximal cortisol concentration were significantly different between patients and controls (see Figures 1 & 2).

**Effect of Gender**

For the entire night there was only a trend for lower ACTH in females than males, regardless of diagnosis (F=5.1, p<0.1, Table 1), while during the second half of the night ACTH secretion was significantly lower in females (F=6.8, p<0.05, Table 2). Since no significant effect of gender on plasma cortisol was noted, the ACTH/cortisol ratio for the entire night was significantly smaller in females than males (F=4.9, p<0.05, Table 1).

The cortisol nadir was significantly higher in females than males, particularly in controls (minimal nocturnal cortisol concentration during baseline in female and male controls [25.5±4.5 vs. 13.5±1.5 ng/ml] and female and male patients [26.7±4.5 vs. 20.2±4.5 ng/ml]). Statistical analysis revealed a significant effect of gender (F=6.4, p<0.05), but no significant effect of diagnosis and no interaction (Figure 2). Also, no effect of GHRH treatment on the level of the cortisol nadir was noted (Figure 2).

GH secretion during the second half of the night showed a trend to be higher in females than males (F=4.9, p<0.1).

**Effect of Treatment**

Pulsatile administration of GHRH per se had no significant effect on hormone secretion during the entire night. However, during the first half of the night GHRH reduced plasma ACTH in males, but increased ACTH in females, regardless of diagnosis (F=5.1, p<0.05, Figure 1). Furthermore, during the second half of the night GHRH showed a trend to decrease plasma cortisol in males but increase cortisol in females (F=4.0, p<0.1, Figure 1).

Treatment with GHRH significantly elevated GH secretion during the entire night (F=73.2, p<0.001, Table 1) as well as the first half of the night (F=71.4, p<0.001) in all subjects. No significant effect of diagnosis or gender was noted on the percent increase in GH secretion following GHRH (compared to baseline, Table 2).

**Effect of Night of Active Treatment**

There was a significant interaction between diagnosis and the night of active treatment with regard to ACTH secretion during the entire night (Table 3). Thus, controls had lower levels of ACTH when GHRH was given in the second night compared to the condition when GHRH was injected during the first night. The reverse finding was noted in patients.

Table 2
**Nocturnal Hormone Secretion- 1st and 2nd half of the Night**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>female controls</th>
<th>male controls</th>
<th>female patients</th>
<th>male patients</th>
<th>effect of gender</th>
<th>(F value)</th>
<th>diagnosis</th>
<th>effect of age</th>
<th>t value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st half</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>15.6 ± 1.8</td>
<td>19.9 ± 1.4</td>
<td>22.6 ± 2.3</td>
<td>25.3 ± 2.2</td>
<td>n.s.</td>
<td>F=9.0</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>45.1 ± 5.3</td>
<td>30.1 ± 2.1</td>
<td>68.5 ± 11.2</td>
<td>66.2 ± 11.5</td>
<td>n.s.</td>
<td>F=11.8</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td>2.9 ± 0.5</td>
<td>3.4 ± 0.7</td>
<td>2.0 ± 0.3</td>
<td>2.5 ± 0.4</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>t= -5.1</td>
<td></td>
</tr>
<tr>
<td>ΔGH(%)</td>
<td>378.4 ± 66.4</td>
<td>269.9 ± 50.1</td>
<td>345.6 ± 94.9</td>
<td>332.7 ± 60.1</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd half</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>26.9 ± 2.5</td>
<td>42.3 ± 4.2</td>
<td>38.0 ± 3.5</td>
<td>40.2 ± 3.0</td>
<td>F=6.8</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>125.3 ± 11.4</td>
<td>121.9 ± 7.1</td>
<td>144.5 ± 8.6</td>
<td>146.5 ± 10.7</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td>1.5 ± 0.3</td>
<td>0.9 ± 0.3</td>
<td>1.0 ± 0.2</td>
<td>0.8 ± 0.1</td>
<td>F=4.9</td>
<td>n.s.</td>
<td>n.s.</td>
<td>t= -3.7</td>
<td></td>
</tr>
</tbody>
</table>

Values are means±SEM. Statistical analysis see text.
Figure 1. Nocturnal secretion of ACTH during placebo and GHRH treatment. Plasma ACTH during the entire night showed a trend to be higher in patients with depression than controls ($F=4.1$, $p<0.1$). Furthermore, in females, ACTH secretion during the second half of the night was significantly lower than in males, regardless of diagnosis ($F=6.8$, $p<0.05$). Following GHRH treatment, ACTH during the first half of the night was reduced in men, regardless of diagnosis, but increased in women, resulting in a significant gender x treatment interaction ($F=5.1$, $p<0.05$). No effect of diagnosis was noted for the timing of the ACTH nadir. Thick black line=Placebo; thin black line=GHRH.

Figure 2. Nocturnal secretion of cortisol during placebo and GHRH treatment. Plasma cortisol was significantly elevated in patients with depression compared with controls ($F=8.0$, $p<0.05$). Following GHRH, cortisol secretion during the second half of the night was reduced in men, while in women, regardless of diagnosis, cortisol was increased, showing a marginally significant gender x treatment interaction ($F=4.0$, $p<0.08$). No effect of diagnosis was noted for the timing of the cortisol nadir. The cortisol concentrations at the nadir, however, was significantly higher in women than men, regardless of diagnosis ($F=6.4$, $p<0.05$). Thick black line=Placebo; thin black line=GHRH.

Figure 3. Nocturnal secretion of GH during placebo and GHRH treatment. Plasma GH was not significantly affected by diagnosis or gender. Following GHRH treatment, GH secretion was significantly increased during the entire and first half of the night ($F=73.2$ and 71.4, each $p<0.01$). No significant effect of diagnosis or gender was noted. Thick black line=Placebo; thin black line=GHRH.

Figure 4. Correlation Between Cortisol and Age. Cortisol secretion during the entire night was significantly correlated with age in patients with depression (filled circles, $r=0.42$, $p<0.01$), but not in controls (open squares, $r=-0.19$).

Figure 5. Correlation for ACTH and Cortisol with NREM Sleep. ACTH secretion (top) during the entire night was inversely correlated with NREM sleep in patients, but not in controls (top: $r=-0.43$, $p<0.05$ and $r=-0.005$, respectively). Similarly, cortisol secretion (bottom) was inversely correlated with NREM sleep in patients only ($r=-0.42$, $p<0.05$ and $r=-0.09$, respectively); filled circles=patients, open squares=controls.
EFFECTS OF GHRH ON HORMONE SECRETION IN DEPRESSION

Table 3

<table>
<thead>
<tr>
<th>ACTH-total night</th>
<th>controls (µg/L)</th>
<th>patients (µg/L)</th>
<th>Interaction diagnosis x night of active treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st night placebo</td>
<td>24.8 ± 2.8</td>
<td>33.2 ± 2.3</td>
<td></td>
</tr>
<tr>
<td>2nd night GHRH</td>
<td>21.6 ± 1.7</td>
<td>31.4 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>1st night GHRH</td>
<td>29.1 ± 3.7</td>
<td>25.7 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>2nd night placebo</td>
<td>25.8 ± 2.2</td>
<td>27.2 ± 2.4</td>
<td></td>
</tr>
</tbody>
</table>

Values are means±SEM. Statistical Analysis see text.

Effect of Aging

No effect of age on plasma ACTH and cortisol secretion for the entire night was noted in the group of all subjects (r = -0.39 and r = -0.003, respectively). However, in the group of patients, age was significantly correlated with plasma cortisol (r = 0.42, p < 0.01, Figure 4), but not with ACTH (r = -0.09). Further analysis showed that only in female patients cortisol secretion showed a significant linear correlation with age (female patients: r = 0.52, p < 0.05, male patients: r = 0.35).

No correlation between age and ACTH and cortisol was observed in controls (r = -0.19 and r = -0.25, respectively). Age was significantly inversely related to GH secretion during the entire night for the group of all subjects (r = -5.6) as well as for patients and controls examined separately (r = -0.43 and r = -0.50, respectively, Table 2).

Correlation between hormones and sleep variables (see also sleep-EEG analysis of part I, in the preceding paper)

ACTH and cortisol secretion during the entire night of the placebo condition were highly inversely correlated with stage 2 sleep during the night in the group of all subjects (r = -0.28 and r = -0.33, respectively, each p < 0.02). Similarly, NREM sleep (stage 2, 3 and 4 combined) was inversely correlated with both ACTH and cortisol secretion (r = -0.33 and r = -0.37, p < 0.05). Further analysis showed that these inverse correlations were restricted to patients with depression (r = -0.36 and r = -0.39 for ACTH and cortisol with stage 2 sleep, and r = -0.43 and r = -0.42 for ACTH and cortisol with NREM sleep, respectively, each p < 0.05) and were not observed in controls (r = 0.07 and r = 0.14 for ACTH and cortisol with stage 2 sleep, and r = 0.01 and r = 0.09 for ACTH and cortisol with NREM sleep, respectively, each p > 0.05, Figure 5).

GH secretion during the first half of the night of the placebo condition was positively correlated with the duration of SWS during the first half of the night in the group of all subjects (r = -0.29, p < 0.05), while no correlation between GH secretion and SWS during the first sleep cycle (r = 0.20) or delta EEG activity (r = 0.11) was noted. Further analysis showed a positive correlation for GH secretion and SWS during the first half of the night in controls (r = 0.35, p < 0.05), but not in patients (r = 0.07). No correlation was noted between ACTH and cortisol secretion and REM duration, REM density and REM latency.

DISCUSSION

The main findings of the present study include: 1) significantly elevated trough levels of ACTH and cortisol in patients with depression; 2) a sexually dimorphic effect of GHRH on nocturnal ACTH and cortisol secretion, regardless of diagnosis; and 3) a significant inverse correlation between nocturnal ACTH and cortisol secretion and NREM, and in particular stage 2 sleep, in patients with depression, but not in controls.

We have reported before that in young normal women cortisol secretion during the first half of the night is greater than in men (Antonijevic et al., 1998c). In the present study we corroborated our previous data, demonstrating gender differences across a broad age-range as well as in depression. We observed higher cortisol trough levels in women compared to men among controls as well as patients. We have also shown, in patients with depression, a marked elevation of both ACTH and cortisol secretion during the first half of the night, and hence at the time of normally low HPA activity. These data are in agreement with previous studies (Linkowski et al., 1987; Rubin et al., 1987; Steiger et al., 1994) and support a reduced negative feedback and enhanced HPA activation in patients with depression (Holboer and Barden, 1996). In addition, we observed an age-associated increase in nocturnal cortisol secretion in female, but not male, patients with depression, in line with previous reports (Asnis et al., 1981; Akil et al., 1993), while in controls no such correlation was noted.

Gender differences have been demonstrated in rats with reduced negative cortisol feedback via both glucocorticoid and mineralocorticoid receptors in females (Burgess and Handa, 1992; Turner, 1997). Also, aging itself is associated with a decreased negative feedback by cortisol at hippocampal glucocorticoid and mineralocorticoid receptors (Sapolsky et al., 1986; De Kloet and Reul, 1987). Since in elderly women a more pronounced HPA reactivity and reduced resiliency compared with men has been reported (Heuser et al., 1994; Seeman et al., 1995; Born et al., 1995), our data are compatible with the hypothesis that female gender, aging and depression add-on to promote HPA activity, possibly by impairing the negative feedback, and hence contributing to the sexually dimorphic effects of GHRH.

In addition, sleep restrains HPA activation via mineralocorticoid receptors (Born et al., 1997; Antonijevic et al., 1998a), and the disrupted sleep continuity in patients with depression could further contribute to elevations of nocturnal ACTH and cortisol secretion. Elevated nocturnal cortisol, together with the repeated arousal due to disrupted sleep continuity could in turn further stimulate CRH release via brainstem noradrenergic neurons (Szafarczyk et al., 1985, 1995), initiating a vicious circle.

With increasing age an elevation of plasma cortisol in humans has been described in some studies (Heuser et al., 1994; Copinschi and Van Cauter, 1995; Van Cauter et al., 1996) but not in others (Van Coevorden et al., 1991). There is evidence that elderly subjects who exhibit elevations in plasma cortisol also show some cognitive impairment (Lupien et al., 1997; Van Londen et al., 1998). As the examination of control
subjects included a thorough interview to exclude those with a family or personal history of psychiatric disorders, the observed lack of an increase in cortisol with age might reflect the absence of any cognitive impairment in these subjects.

Interestingly, we observed in patients but not in controls a significant inverse correlation between nocturnal ACTH and cortisol secretion and NREM, and in particular stage 2 sleep. Disruptions of stage 2 sleep and sleep continuity (Salzarulo et al., 1997; Schulz and Salzarulo, 1997; Spiegel et al., 1999) as well as elevations in HPA activity (Seeman et al., 1995) have been associated with impaired memory functions. In addition, we and others describe a marked reduction in stage 2 sleep in patients with depression (see preceding paper), supporting the hypothesis that reductions in stage 2 sleep and HPA activity are related to each other. In contrast, no correlation between ACTH, cortisol and REM sleep parameters was observed, suggesting that these parameters are not tightly correlated.

Since GHRH was effective at reducing ACTH and cortisol secretion as well as promoting stage 2, NREM sleep and sleep continuity, at least in men, our data open up the possibility that GHRH can improve cognitive functioning in men, both patients with depression and healthy elderly controls.

In summary, we have shown that the effects of GHRH on sleep-endocrine regulation are sexually dimorphic, including a reduction of ACTH and cortisol secretion and an increase in NREM sleep, including stage 2 sleep, and sleep continuity in men, but opposite effects in women, regardless of diagnosis. Since female gender, aging and depression are associated with a reduced cortisol feedback, we propose that these factors are additive and contribute to the sexually dimorphic effects of GHRH. In addition, we have shown that elevated nocturnal secretion of ACTH and cortisol in depression is inversely correlated with NREM and, in particular, stage 2 sleep. This observation opens up the possibility that both phenomena are related and contribute to cognitive impairment in depression. The promotion of NREM and stage 2 sleep and the reduction in ACTH and cortisol secretion by GHRH, at least in men, could point to a therapeutic role to improve depression and cognitive impairment.

REFERENCES

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