Somatotropic axis in hypocretin-deficient narcoleptic humans: altered circadian distribution of GH-secretory events

SEBASTIAAN OVEREEM, SIMON W. KOK, GERT JAN LAMMERS, ALLA A. VEIN, MARIJKE FRÖLICH, AREND E. MEINDERS, FERDINAND ROELFSEMA, AND HANNO PIJL

Department of Neurology and Clinical Neurophysiology, Department of General Internal Medicine, and Department of Endocrinology, Leiden University Medical Center, 2300 RC Leiden, The Netherlands

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Overeem, Sebastiaan, Simon W. Kok, Gert Jan Lammers, Alla A. Vein, Marijke Frölich, Arend E. Meinders, Ferdinand Roelfsema, and Hanno Pijl. Somatotropic axis in hypocretin-deficient narcoleptic humans: altered circadian distribution of GH-secretory events. Am J Physiol Endocrinol Metab 284: E641–E647, 2003. First published November 26, 2002; 10.1152/ajpendo.00421.2002.—Narcolepsy is a sleep disorder caused by impaired hypocretin (orexin) neurotransmission. Growth hormone (GH) secretion may be altered in narcolepsy for various reasons. Slow-wave sleep episodes, which are closely associated with GH-secretory events, are more randomly dispersed over 24 h in narcoleptics. Furthermore, hypocretins may inhibit pituitary GH release. We assessed the function of the somatotropic axis in narcolepsy by deconvolving 24-h plasma GH concentration profiles in seven hypocretin-deficient narcoleptic patients and in seven healthy controls matched for age, sex, and body weight. Both basal and pulsatile GH secretion rate and secretagogue-induced GH release were similar in patients and controls. However, narcoleptics secreted ~50% of their total production during the daytime, whereas controls secreted only 25% during the day. Also, the GH output pattern of narcolepsy was significantly less regular. We propose that hypocretin deficiency disrupts the circadian distribution of hypothalamic GH-releasing hormone release in narcoleptic patients to simultaneously cause daytime GH release and promote their propensity to fall asleep during the day.

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NARCOLEPSY PRIMARILY AFFECTS the organization and regulation of sleep and wakefulness. Its main symptoms are excessive daytime sleepiness, cataplexy, and fragmented nocturnal sleep (20). Narcolepsy is caused by disruption of hypocretin (orexin)-mediated neurotransmission (7, 16, 21). The vast majority of human patients lack hypocretin in their cerebrospinal fluid (CSF) (17, 18, 28). An autoimmune-mediated destruction of hypocretin neurons is currently presumed to be the principal cause of narcolepsy in humans (21, 30).

Sleep and the activity of the somatotropic axis are intimately related (33). In particular, slow-wave sleep (SWS) is associated with pituitary growth hormone (GH) release. In healthy individuals, a major GH-secretory event occurs often shortly after sleep onset, in close temporal association with the first period of SWS. Conversely, sleep deprivation is consistently associated with a reduction of circulating GH levels, and the age-related decline of SWS is accompanied by a marked decrease of GH secretion (32).

Because SWS episodes are more randomly distributed over 24 h in narcoleptic patients than in healthy subjects (5, 6), the circadian distribution of GH-secretory events may be altered in hypocretin-deficient narcoleptic humans. Moreover, because intracerebroventricular injection of hypocretin-1 causes a dose-dependent reduction of plasma GH in rats (13), hypocretin deficiency may exert a direct excitatory effect on GH release in narcoleptics.

Only a limited number of studies have assessed the status of the somatotropic axis in narcoleptic humans. In general, these studies have suggested that the rise of plasma GH concentrations around sleep onset is markedly damped or even absent in narcolepsy (2, 8, 15). It was hypothesized that an intrinsic disturbance of SWS and/or the frequent occurrence of sleep-onset rapid eye movement (REM) periods underlies these alterations in GH secretion in narcoleptic humans (33). However, the interpretation of data obtained in these early studies was hampered by methodological imperfections, particularly with respect to the selection of control subjects [e.g., not matched for age and/or body mass index (BMI)]. Moreover, in the course of time, novel analytical techniques [deconvolution and approximate entropy (ApEn)] have been developed, which allow estimation of the pituitary GH secretion rate and quantification of the orderliness of the release process on the basis of frequently sampled plasma GH concentration time series (24, 34, 38).
To further evaluate the impact of a disturbance of circadian (slow-wave) sleep distribution and/or hypocretin deficiency on various features of pulsatile GH secretion in humans, we deconvolved 24-h plasma GH concentration profiles in narcoleptic patients and in healthy controls matched for age, sex, and BMI. We specifically hypothesized that the circadian distribution of peaks and troughs of plasma GH concentrations would be disrupted and that the total daily GH production would be increased in narcoleptic patients.

METHODS

Subjects. We included seven male patients from the outpatient clinic of the Department of Neurology. A physician experienced with narcolepsy (G. J. Lammers) made the clinical diagnosis of narcolepsy with cataplexy. The diagnosis was confirmed by Multiple Sleep Latency Testing, which showed results typical for narcolepsy (1). All patients were HLA-DQB1*0602 positive. We confirmed that all patients were hypocretin deficient; hypocretin-1 was undetectable in the CSF with direct radioimmunoassay (RIA) as previously described (28). The subjects, except three (two using psycho-stimulants, and one using clomipramine), who discontinued their medication for ≥2 wk before the study, were free of medication.

Weight and height of all subjects were measured, as well as waist and hip circumference (waist halfway between the lowest rib and crista iliaca, and hip as the maximum circumference in standing position). The waist-to-hip ratio (WHR) was used as a relative measure of abdominal fat mass. Total body fat mass was determined by dual-energy X-ray absorptiometry (Hologic QDR4500, Waltham, MA) (3).

We recruited seven male control subjects through advertisements in local newspapers. Controls were matched for age, BMI, total fat mass, and WHR. Controls did not take any medication and had no history of sleep disorders.

Subjects were eligible for the study after exclusion of hypertension (defined as a repeated blood pressure measurement showing systolic pressure of >140 mmHg or diastolic pressure of >90 mmHg), any known (history of) endocrine disease, recent weight change (>3 kg weight gain or loss within the last 3 mo), and a fasting blood glucose of >7.0 mmol/l.

The study protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center. All subjects gave written, informed consent to participate.

Experimental protocol. All investigations were performed in the Clinical Research Center (CRC) of the Department of General Internal Medicine. Subjects were admitted to the CRC and prepared for sleep registration. During the 24-h study occasion, three standardized meals were served, at 0900, 1300, and 1800 (Nutridrink 1.5 kcal/ml, 1500–1800 kcal/day; macronutrient composition per 100 ml: 5 g protein, 6.5 g fat, 17.9 g carbohydrate; Nutricia, Zoetermeer, Netherlands). Subjects remained sedentary throughout the study except for bathroom visits. Lights were switched off at 2300.

An intravenous cannula was inserted in an antecubital vein 1 h before the start of blood sampling. Blood samples were taken from a three-way stopcock attached to an extended line to prevent sleep disturbances by manipulations of the investigators. The catheter was kept patent by a 0.9% NaCl and heparin (1 U/ml) drip (500 ml/24 h). Blood was collected in S-monovertex tubes (Sarstedt, Etten-Leur, Netherlands) at 10-min intervals for 24 h, allowed to clot, centrifuged at 4°C for 20 min within an hour of collection, and serum frozen at −20°C until assays were performed. Serum IGF-I and IGF-binding protein-3 (IGFBP-3) concentrations were measured only once in an early morning sample.

After the 24-h sampling procedure, at 0900 the next morning, 50 μg of GH-releasing hormone (GHRH) were given as an intravenous bolus, and serum GH concentrations were measured in blood samples taken every 10 min for 90 min after bolus injection (31).

Assays. Serum GH concentrations were measured using a sensitive time-resolved immunofluorometric assay (Wallac, Turku, Finland). The assay is specific for the 22-kDa GH isoform. Human biosynthetic GH (Pharmacia, Uppsala, Sweden) diluted in bovine calf serum was used as a standard, which was calibrated against the World Health Organization First International Reference Preparation 80–505 (1 μg = 2.6 mU). The detection limit of the assay (defined as the value 2 SD above the mean value of the zero standard) was 0.03 mU/l. The interassay coefficients of variation varied from 2.7 to 8.2% over a GH concentration range of 0.1–100 mU/l. All samples from one subject were measured in the same assay. Total serum IGF-I and IGFBP-3 concentrations were measured by RIA as previously described (23).

Sleep recording and analysis. During the 24-h sampling procedure, sleep was recorded graphically using a Porti-5 ambulant electroencephalogram recording system (Twente Medical Systems International, Enschede, Netherlands) and scored on EEG-2100 review software (Nihon Kohden, Tokyo, Japan). An experienced technician, blinded for the subject under study, visually scored the sleep recordings at 30-s epochs by means of standardized criteria (27). Nocturnal sleep onset was identified as the first epoch of stages II, III, IV, or REM sleep after lights off, provided that the subsequent interval was not scored as awake. The sleep period was defined as the time between sleep onset and final awakening in the morning. Sleep efficiency was calculated as the percentage of the sleep period actually spent asleep.

Data analysis. For the GH time series, we used multiple-parameter deconvolution analysis to estimate various specific measures of pulsatile secretion and half-life on the basis of simultaneous consideration of all serum hormone concentrations and their dose-dependent intrasample variances (35, 37). Results are expressed as milliunits per liter of distribution volume (mU/l). The following parameters were estimated by the GH series: number of secretory bursts, secretory burst half-duration (duration at half-maximal amplitude), burst amplitude, mean mass secreted per burst, hormone half-life, pulsatile secretion rate, basal secretion rate, and total secretion per 24 h. Furthermore, we quantified the amount of GH secreted from 0900 to 2300 and from 2300 to 0900 during the 3 h before and after sleep onset and during the first secretory burst after sleep onset.

We quantified the minute-to-minute regularity (“serial orderliness”) of GH secretion by use of the ApEn statistic, a scale- and model-independent metric (24). ApEn estimates the regularity of subordinate (nonpulsatile) patterns in the data and as such yields information complementary to deconvolution techniques (25, 39). Greater regularity yields smaller ApEn values, whereas greater independence among sequential values of a time series yields larger ApEn values. We applied normalized ApEn parameters of m = 1 and r = 20% of the intraseries SD, as previously validated for GH series of this length (26). The ApEn ratio delineates the orderliness of a concentration time series compared with the ApEn score associated with maximal randomness in the same time series as estimated by computer simulation. Thus an ApEn ratio equal to 1 reflects maximal randomness in the
time series under study, and smaller ApEn ratios denote greater regularity.

GH release in response to GHRH injection was determined using deconvolution analysis (see above).

Unless otherwise stated, all results are expressed as means ± SE. Median values are shown between parentheses. Comparisons were made using the unpaired two-tailed Student’s t-test after log-transformation of the GH concentration/secretion data. Differences between groups were considered significant for \( P < 0.05 \). Statistical calculations were performed using SPSS for Windows (release 9.0) and Systat (release 10; SPSS, Chicago, IL).

RESULTS

Subject characteristics. The clinical characteristics of the subjects under study are shown in Table 1. Note that the mean BMI of the subjects was in the overweight range (i.e., between 25 and 30 kg/m²), which was expected for narcoleptic patients (8). All participants were well matched for anthropometric variables potentially influencing GH secretion, including BMI and body composition.

Sleep analysis. The duration of the sleep period did not differ between patients (405 ± 30 min) and controls (383 ± 41 min, \( P = 0.67 \)). Both groups had a relatively low sleep efficiency (narcolepsy: 64 ± 6.4%; controls: 72 ± 4.9%, \( P = 0.41 \)), resulting in 263 ± 32 min of nocturnal sleep in the patients and 274 ± 36 min in the controls (\( P = 0.82 \)). However, the relative amount of nocturnal stage I sleep was 50% higher in narcoleptics (21.8 ± 2.5 vs. 14.5 ± 1.7%, \( P = 0.04 \)), which suggests that they had more fragmented nocturnal sleep. The amount of SWS during the night did not differ between patients and controls (25.1 ± 9.3 vs. 22.4 ± 6.9 min, \( P = 0.82 \)). None of the control subjects slept during the daytime. In contrast, all narcoleptics took at least two daytime naps (average 3.3 naps). An average of 14.8 ± 6.1 min of these daytime sleep episodes were spent in SWS, and 40.4 ± 4.1 min were spent in REM sleep.

GH secretion. Figure 1 illustrates the 24-h sleep pattern of a patient and his individual control, together with the concomitant serum GH concentration profiles and the deconvolution-based estimates of GH secretion rates. The 24-h mean serum concentration of GH was not significantly different in narcoleptic patients and controls (1.35 ± 0.42 mU/l vs. 0.86 ± 0.21 mU/l, respectively, \( P = 0.31 \)). Likewise, serum IGF-I and IGFBP-3 concentrations did not differ between groups (data not shown).

<table>
<thead>
<tr>
<th>Table 1. Clinical characteristics of the study subjects</th>
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<tr>
<td>Patients (n = 7)</td>
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<td>Age, yr</td>
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<tr>
<td>BMI, kg/m²</td>
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<tr>
<td>Waist, cm</td>
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<tr>
<td>WHR</td>
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<tr>
<td>Lean body mass, kg</td>
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<td>Body fat, %</td>
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<td>Controls (n = 7)</td>
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<tr>
<td>46.1 ± 15.9(26–71)</td>
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<td>64.9 ± 16.1(26–72)</td>
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<td>29.3 ± 2.6(23.3–31.0)</td>
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<td>28.4 ± 2.1(24.5–30.7)</td>
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<td>102 ± 10.8(80–112)</td>
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<td>105 ± 10.8(85–117)</td>
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<td>0.96 ± 0.08(0.81–1.05)</td>
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<td>0.97 ± 0.05(0.87–1.04)</td>
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<td>73.7 ± 5.0(67.1–83.7)</td>
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<td>71.4 ± 3.2(68.2–77.8)</td>
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<td>23.4 ± 5.3(12.9–30.4)</td>
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<tr>
<td>25.5 ± 3.4(18.8–29.1)</td>
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Values are means ± SD; ranges are in parentheses. BMI, body mass index; WHR, waist-to-hip ratio.

The deconvolution-derived 24-h GH secretion parameters are summarized in Table 2. Patients with narcolepsy did not differ from controls with respect to basal secretion rate, total number of GH peaks, peak amplitude, or area. Consequently, the total production of GH was not different in the two groups (Fig. 2). However, the distribution of GH-secretory events over 24 h differed considerably between groups. Narcoleptics secreted almost one-half of their total pulsatile production during the day, whereas controls produced only one-quarter during the day (pulsatile release during daytime as a fraction of total pulsatile release: 0.48 ± 0.05 vs. 0.26 ± 0.05, respectively, \( P = 0.01 \)).

Sleep onset GH secretion was assessed by determination of GH production during the first 3 h of sleep and by quantifying the first GH pulse after sleep onset. Both narcoleptics and controls secreted approximately one-third of their total 24-h GH production in the first 3 h of sleep (29.1 ± 4.8% vs. 26.0 ± 8.1%, \( P = 0.34 \)). The amount secreted in the first secretory event after sleep onset was also similar in both groups (10.0 ± 3.9 vs. 10.3 ± 6.9 mU/lD, \( P = 0.48 \)).

The total amount of GH released per day was strongly correlated with the total (24 h) amount of SWS in controls (\( r^2 = 0.69, P = 0.02 \); Fig. 3). This relationship remained intact in narcoleptics (\( r^2 = 0.74, P = 0.01 \); Fig. 3). In contrast, GH release was not correlated with the total amount of REM sleep in either group (\( r^2 = 0.44, P = 0.2 \) and \( r^2 = 0.36, P = 0.1 \), in narcoleptics and controls, respectively).

The GH secretion pattern was less orderly in the narcoleptic patients (which may reflect disruption of GHRH feedforward inputs; see DISCUSSION). Both the ApEn(1,20%) values (0.59 ± 0.08 vs. 0.36 ± 0.03, \( P = 0.02 \)) and the ApEn ratio (0.47 ± 0.04 vs. 0.37 ± 0.01, \( P = 0.03 \)) were increased in the patient group, reflecting a decrease in the serial orderliness of GH secretion.

The narcoleptic patients responded to GHRH injection by secreting amounts of GH similar to those of the control subjects. With the use of multiparameter deconvolution, GH secretion after GHRH injection was calculated to be 56.5 ± 23.4 [median 34.5] and 50.2 ± 11.4 [median 48.9] mU/lD in patients and controls, respectively (\( P = 0.72 \)).

DISCUSSION

We assessed 24-h sleep patterns and GH secretion profiles conjointly in a well-defined group of narcoleptic patients and controls who were matched for various confounding variables. The patients had several daytime naps, including SWS episodes, whereas sleep was confined to nighttime in controls. Total daily GH production was strongly correlated with the total time of SWS in narcoleptic patients and controls alike (Fig. 3). As a result, the dispersion of GH-secretory events and (slow-wave) sleep epochs over 24 h was altered concomitantly in narcoleptics such that they secreted a larger fraction of their total GH production during the day (48 vs. 26% in controls). The GH output pattern was significantly less regular in the narcoleptic patients.
Against expectations, both basal and pulsatile GH production and secretagogue-induced GH release were similar in patients and controls (Fig. 2).

Only a few previous studies have examined plasma GH concentrations in patients with narcolepsy. The results of these studies generally suggested that GH release (both spontaneous 24-h and secretagogue-induced) is blunted in narcoleptics (2, 8, 15). However, interpretation of the data obtained in these studies is hampered by potential imperfections regarding the selection of control subjects. For example, in two of the studies (2, 15), body weight of the participants was not reported, and a third study (8) did not include healthy control subjects at all. We now know that narcoleptic patients tend to be obese (9) and that GH production is profoundly reduced in (abdominally) obese humans.

Table 2. Secretory parameters of 24-h serum GH in narcolepsy patients and controls

<table>
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<tr>
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<th>Patients</th>
<th>Controls</th>
<th>P Value*</th>
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<tbody>
<tr>
<td>Pulse frequency, no. 24 h</td>
<td>15.9 ± 2.4 [14.0]</td>
<td>12.3 ± 1.6 [13.0]</td>
<td>0.24</td>
</tr>
<tr>
<td>Peak half-duration, min</td>
<td>21.6 ± 0.6 [21.3]</td>
<td>23.0 ± 3.1 [23.6]</td>
<td>0.67</td>
</tr>
<tr>
<td>Peak amplitude, mU/l₀</td>
<td>0.34 ± 0.14 [0.15]</td>
<td>0.23 ± 0.06 [0.20]</td>
<td>0.50</td>
</tr>
<tr>
<td>Peak area, mU/l₀</td>
<td>7.5 ± 3.0 [5.7]</td>
<td>4.9 ± 1.2 [4.7]</td>
<td>0.50</td>
</tr>
<tr>
<td>Half-life, min</td>
<td>14.1 ± 0.41 [14.3]</td>
<td>13.8 ± 0.81 [13.7]</td>
<td>0.74</td>
</tr>
<tr>
<td>Basal secretion, mU/l₀⁻¹·24 h⁻¹</td>
<td>5.30 ± 1.50 [5.00]</td>
<td>4.80 ± 1.20 [5.4]</td>
<td>0.82</td>
</tr>
<tr>
<td>Pulsatile secretion, mU/l₀⁻¹·24 h⁻¹</td>
<td>90.7 ± 29.3 [67.7]</td>
<td>61.0 ± 17.9 [28.1]</td>
<td>0.51</td>
</tr>
<tr>
<td>Total secretion, mU/l₀⁻¹·24 h⁻¹</td>
<td>96.0 ± 30.3 [72.7]</td>
<td>65.8 ± 18.9 [29.3]</td>
<td>0.52</td>
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</table>

Values are means ± SE; medians are in brackets. l₀, liter distribution volume. *Unpaired t-test after logarithmic transformation.
to explain their impact on energy balance and several neuroendocrine ensembles (for reviews, see Refs. 20 and 41). Intracerebroventricular administration of hypocretin-1 causes a dose-dependent decrease of plasma GH in rats (13). Furthermore, it was recently reported that somatotropic cells in the human pituitary express the hypocretin receptor-1 (4). These data suggest that hypocretins directly blunt GH secretion. We therefore hypothesized that hypocretin deficiency would enhance total daily GH production in narcoleptic humans. Our results do not support this contention, as narcoleptic patients produced normal total amounts of GH (Fig. 2). However, we do believe that our data support the thesis that hypocretin deficiency disrupts the circadian dispersion of hypothalamic GHRH release, which normally confines sleep and GH secretion to the night.

Sleep and the activity of the somatotropic axis are intimately related (33). The most reproducible GH-secretory event in humans occurs around nocturnal sleep onset, in close temporal association with the first epoch of SWS (see Ref. 33). The secretion of GH is controlled mainly by two hypothalamic peptides, GHRH and somatostatin (12, 14). A large body of evidence suggests that GHRH simultaneously promotes sleep and GH release, which can explain the consistent association between sleep and GH secretion (see Ref. 19 and references therein). The present study shows that this dual regulatory effect of GHRH is probably intact in narcoleptics, as SWS and GH release remain closely associated in these patients (Fig. 3). This inference may imply that the circadian distribution of hypothalamic GHRH release is disrupted in narcolepsy to simultaneously cause diurnal GH secretion and enhance daytime sleepiness. Specifically, the hypocretin system, which is particularly active during the day (11), may normally inhibit hypothalamic GHRH secretion to promote arousal and reduce pituitary GH output. Conversely, diminution of hypocretin tonus at night (11) may relax inhibitory restraint of

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(23, 36). Also, age was reported in only two studies (2, 15). In one of these (15), the narcoleptic patients were ~10 yr older than the controls (32 vs. 24 yr), which may also have biased the results (32). In the present study, the control subjects were carefully matched with respect to age, sex, BMI, and body fat distribution to preclude analogous bias. Therefore, we believe that the data presented in the present paper are more conclusive than any previous study as to whether narcolepsy per se impacts GH secretion. Moreover, the narcoleptic patients in the present study were confirmed to be hypocretin deficient, which was not possible to determine in any of the previous studies (as hypocretin peptides were unknown at that time). Thus the present data pertain specifically to hypocretin-deficient narcoleptic humans. Our results clearly argue against a reduction of spontaneous or secretagogue-induced GH secretion in human narcolepsy.

What can we learn about the regulation of GH secretion and sleep from the results of this study? First, the onset of nocturnal sleep remains an important correlate of GH release, even when numerous naps have interrupted daytime wakefulness. Both in narcoleptics and in controls, ~30% of total daily GH secretion occurred in the 3 h after nocturnal sleep onset. Second, the relationship between SWS and GH release remains robust, even if sleep is fragmented and more randomly dispersed over 24 h. A strong, positive, and highly significant correlation between both variables was observed in narcoleptics and in controls. Third, the dispersion of GH-secretory events and sleep epochs over 24 h appears to be altered analogously in narcoleptic patients: they had more (slow-wave) sleep time and more GH secretion during the day. Finally, endogenous hypocretins do not significantly impact the amount of GH that is produced daily in humans.

The hypocretin peptides (hypocretin-1 and -2, also known as orexin A and B) are produced exclusively by a small number of neurons located in the perifornical area of the hypothalamus (10, 29). Hypocretin neurons connect with other nuclei within the hypothalamus (including the arcuate nucleus) and the pituitary (22)
GHRH release to dampen arousal and increase GH output. In this scenario, hypocretin deficiency particularly enhances GHRH release during the day (when the system normally has its peak activity) to concurrently promote daytime GH secretion and compromise daytime wakefulness in narcoleptic patients.

The irregular GH output pattern we found in narcoleptics also supports the notion that hypothalamic GHRH release may be enhanced in this disorder. The serial orderliness of pulsatile GH release, as determined by the ApEn statistic, reflects the balance of feedforward and feedback inputs into the somatotropic neuroendocrine ensemble (40). In the present study, GH output was more irregular in narcoleptic patients than in their healthy controls, which suggests that negative feedback restraint of somatotropic activity is muted and/or that positive feedforward inputs are enhanced in narcolepsy (40).

In conclusion, this study documents irregular release of normal amounts of GH in hypocretin-deficient narcoleptic humans. In addition, the circadian dispersion of GH-secretory events is altered in narcoleptics, so that a relatively large fraction of total production occurs during the daytime. We propose that an altered circadian distribution of GHRH release, brought about by hypocretin deficiency, simultaneously causes increased daytime GH secretion and enhanced daytime sleepiness in narcolepsy.

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