The effect of sodium oxybate on growth hormone secretion
in narcolepsy patients and healthy controls

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Hypocretin deficiency causes narcolepsy and may affect neuroendocrine systems and body composition. Additionally, growth hormone (GH) alterations may influence weight in narcolepsy. Symptoms can be treated effectively with sodium oxybate (SXB, gamma-hydroxybutyrate) in many patients. This study compared growth hormone secretion in patients and matched controls and established the effect of SXB administration on GH and sleep in both groups. Eight male hypocretin deficient narcolepsy with cataplexy and eight controls matched for sex, age, BMI, waist-to-hip ratio, and fat percentage were enrolled. Blood was sampled before and on the 5th day of SXB administration. SXB was taken 2 times 3g per night for 5 consecutive nights. Both groups underwent 24-h blood sampling at 10-min intervals for measurement of GH concentrations. The GH concentration time series were analyzed with AutoDecon, and approximate entropy (ApEn). Basal and pulsatile GH secretion, pulse regularity and frequency, as well as ApEn values were similar in patients and controls. Administration of SXB caused a significant increase in total 24 hour GH secretion rate in narcolepsy patients, but not in controls. After SXB, slow wave sleep (SWS) and, importantly, the cross-correlation between GH levels and SWS more than doubled in both groups. In conclusion, SXB leads to a consistent increase in nocturnal GH secretion and strengthens the temporal relation between GH secretion and SWS. These data suggest that SXB may alter somatotropic tone in addition to its consolidating effect on nighttime sleep in narcolepsy. This could explain the suggested non-sleep effects of SXB, including body weight reduction.
INTRODUCTION

Classically, narcolepsy is defined as a sleep disorder with excessive daytime sleepiness and cataplexy as the main symptoms (31). However, in recent years, there is increasing attention to other core features of the syndrome. For example, fragmented nighttime sleep is a prominent symptom in many narcoleptic patients, and often warrants treatment (9). In addition, patients are frequently overweight, storing excess fat in abdominal depots (21). The increasing interest for the broad symptomatology of narcolepsy was further fuelled by new insights in the pathophysiology of the disease. In the last decade, it has been shown that deficiencies in hypothalamic hypocretin (orexin) neurotransmission are the primary cause of narcolepsy both in humans and in several animal models of the disease (3; 23; 34). The hypocretin system is involved in a broad range of functions, including autonomic and hormonal regulation. Recent research therefore focused on consequences of the hypocretin deficiency in narcolepsy beyond disordered sleep regulation, such as metabolic and endocrine changes (33).

Given the relation between sleep and the somatotropic axis, changes in growth hormone (GH) dynamics have received particular attention in narcolepsy (2; 13; 29; 30). In healthy subjects, there is a clear association between GH secretion and sleep. This is especially clear in young males, in which the majority of 24-hour GH is secreted during the first period of slow wave sleep (SWS) at night (14; 45). In a previous study, we showed that GH secretion was less strictly confined to the night in hypocretin-deficient narcolepsy (30). As the relation between SWS and GH secretion was preserved, it was suggested that a shift of SWS episodes to the day was paralleled by a daytime shift of GH secretion.

Sodium oxybate has evolved into a first-line treatment for narcolepsy (39-42; 50). SXB is a short-acting hypnotic which is dosed twice at night, at bedtime and 2.5-4 hours later. It significantly consolidates nighttime sleep, ameliorates cataplexy and in higher doses it may decrease excessive daytime sleepiness. In contrast to other hypnotics, SXB is one of the few compounds that increases rather than decreases SWS. This led to the hypothesis that it may also act as a GH-secretagogue.
Indeed, it has been shown that single-dose SXB administration leads to an increase in GH secretion in healthy young men, paralleled by an increase in SWS (46).

In the present study, we assessed the effect of repeated, twice-a-night administration of SXB on 24-hour GH secretion patterns in both patients with hypocretin-deficient narcolepsy, and matched healthy controls. GH secretion was assessed during a 24-hour sample occasion with concomitant sleep registrations at baseline, and after 5 nights of SXB. We hypothesized that SXB administration would lead to a persistent increase in nocturnal GH secretion in both patients and controls, paralleled by an increase in SWS.

MATERIALS AND METHODS

Subjects

We included 8 male narcolepsy patients who fulfilled the diagnostic criteria for narcolepsy with cataplexy according to the 2nd edition of the International Classification for Sleep Disorders (17). All patients were hypocretin-1 deficient, using a standardized cerebrospinal fluid assay (34). All patients were free of medication for at least 2 weeks before study. Eight male control subjects were individually matched for age, body mass index (BMI), waist-to-hip ratio (WHR) and body fat percentage. Medical exclusion criteria were hypertension, any known (history of) pituitary, psychiatric or neurological disease, and any other chronic conditions except narcolepsy as assessed by clinical examination. Routine laboratory tests were performed to rule out diabetes (fasting plasma glucose >6.9 mmol/L), anaemia, as well as hepatic and renal failure. Furthermore, we excluded recent weight change (>3 kg weight gain or loss within the last 3 months), a sleep disorder history assessed through clinical interview (controls), endurance sports and alcohol or drug abuse. The study was approved by the ethics committee of the Leiden University Medical Center. All subjects provided written informed consent to participate.
Study design
All subjects underwent two 24-hour blood sampling studies, with a 5-day interval. After the baseline sampling study, subjects received SXB for 5 consecutive nights (see below). The second sampling occasion took place on the 5th day of SXB use.

Medication protocol
The first night of SXB administration took place in the hospital to provide instruction for proper usage and to monitor for possible side effects. Subjects received 3 grams of SXB in the evening (23:00 h) and during the night (3:00). Subjects were fasted at least 2.5 hours before drug intake, as food reduces the bioavailability of SXB. When no significant adverse effects occurred, subjects were allowed to continue the study protocol and take SXB at home during the next three nights. The 5th night on SXB took place at the Clinical Research Center during the next sampling occasion.

Clinical protocol
Subjects were admitted to the Clinical Research Center for 24-hour blood sampling. A cannula was inserted into an antecubital vein 45 minutes before the start of blood sampling at 12:00 h. Blood samples were collected with S-monovetten (Sarstedt, Etten-Leur, The Netherlands) from a three-way stopcock attached to a 0.9% NaCl and heparin (1 U/ml) infusion (500 ml/24 h) to keep the cannula from clotting. Sampling was performed through a long line to prevent sleep disruption by investigative manipulations. Samples for IGF-1 and IGFBP-3 were both taken just before breakfast at 8:30 on each day of study. For GH measurements, blood was collected at 10-minute intervals. After clotting, the blood was centrifuged within 30 minutes of sampling (20 minutes, 1250 g, 4 °C). Serum was then stored at -80 °C until hormonal assays. Bioelectrical impedance analysis (Bodystat, Douglas, Isle of Man, UK) was used to assess lean body mass and fat percentage at 8:25 (just before breakfast). Subjects remained sedentary except for bathroom visits. Lights were switched off at 23:00 and switched on at 07:30 the next morning. Three standardized meals were served at 08:30, 13:00, and 18:00 (Nutridrink, Nutricia, Zoetermeer, The Netherlands; 1.5 kcal/ml, 2100 kcal/d; macronutrient composition per 100 ml protein, 6 g; fat, 5.8 g; carbohydrate, 18.4 g). Subjects were asked to complete
each meal provided. Water and caffeine free redbush tea were the only drinks available during the study.

**Sleep analysis**

Sleep was polygraphically recorded throughout both sampling occasions, using an Emblettia X100 recorder (Embla, Broomfield, CO, USA). The recordings were scored visually at 30-second intervals according to the AASM criteria (16) by an experienced sleep technician. To allow assessment of the associations between changes in serum GH levels (measured every 10 minutes) and sleep stages (scored every 30 seconds), sleep profiles were divided into the 10 minute segments separating consecutive GH measurements, as described previously (44). Every segment was condensed from the 30-second sleep epochs into percentage of time spent in wake, stage I/II non-REM sleep, stage II/IV slow wave sleep (SWS) and REM sleep.

**Assays**

Serum GH was measured by a time-resolved fluoroimmunoassay (DELFIA® hGH, PerkinElmer Life and Analytical Sciences, Turku, Finland). The detection limit of the assay was 0.03 mU/L, and the interassay variation ranged from 1.6 to 8.4%. Samples from each patient and matched control were handled in the same run. Total serum insulin-like growth factor IGF-1 and insulin-like growth factor binding protein IGFBP-3 concentrations were measured by radioimmunoassay (Serono, Biomedica, Milan, Italy; and Nichols, San Juan Capristano, CA, respectively). Glycosylated hemoglobin (HbA1c) levels were measured with a high performance liquid chromatography (HPLC) system (Variant, Biomed, Hercules, CA, USA). Urinary epinephrine, norepinephrine and dopamine concentrations were assessed by HPLC with electron capture detection (ESTA-Coulochem, Chelmsford, MA, USA).

**Deconvolution analysis**

A recently developed, fully automatic, multi-parameter deconvolution procedure, AutoDecon, was used to estimate various specific measures of secretion and serum disappearance rate of GH, considering all serum hormone concentrations and their dose-dependent intra-sample variance.
simultaneously (18; 19). The AutoDecon process is a statistically based algorithm to test the significance of hormone secretion events, obviating the subjective nature of previously used deconvolution methods. Apart from the initial concentration and the basal secretion rate, which both were initialized to zero, the AutoDecon algorithm requires only two approximations of the parameter values that are to be estimated: 1) The standard deviation of the Gaussian-shaped secretion events (SecretionSD) which is generally initialized as half of the data-sampling interval, and 2) a starting value for the elimination parameter, or hormone half-life. Thus, for 10-minute sampled data, the SecretionSD was initialized to 5-minutes together with a starting value for the GH half-life of 16-minutes. To account for intrinsic errors in the estimates of hormone secretion and clearance rates, the AutoDecon algorithm was then used to find the best fits for both parameters. The following parameters of the serum GH concentration time series were estimated: number of secretory bursts, secretory burst half-duration (duration at half-maximal amplitude), mean mass secreted per burst, hormone half-life, basal secretion rate, pulsatile secretion rate, and total secretion rate. Finally the first GH peak after SXB administration was defined as the first peak after medication intake detected by AutoDecon as described earlier (19).

Approximate entropy (ApEn)

ApEn is a model-independent statistic used to quantify the regularity of a time series, which estimates, within a predefined tolerance r given a pattern of window length m, the likelihood of a similar pattern in the next incremental window (32). Greater regularity yields smaller ApEn values, whereas greater independence among sequential values of a time series yields larger ApEn values. ApEn parameters of m = 1 and r = 20% of the intra-series standard deviation were used, the statistical suitability of which has been established previously (32).

Statistical analyses

Results are expressed as mean ± standard error (SE), unless otherwise specified. Unpaired t tests were used to assess differences in means between the two groups. In order to account for
the two repeated measurements within each individual, mixed-effects models were used to assess the effects of SXB treatment and potential interaction effects. Cross-correlation analysis was applied to assess the association between serum GH concentrations and the percentage of time spent in slow wave sleep in the preceding 10 min sampling interval, taking into account all of the sampling intervals during sleep. Because of the individual matching of patients and controls and small number of subjects in each group, paired parametric (paired sample t-test) and non-parametric tests were also performed (Wilcoxon signed rank test). All tests were two-tailed and significance level was set at $p < 0.05$. Statistical calculations were performed using Systat software (version 11, Systat Software, Inc, San Jose, CA) and SPSS (release 17.0, SPSS, Inc., Chicago, IL). When p-values according to the unpaired parametric tests approached the significance level, we also report the p-values for the corresponding paired parametric and non-parametric tests.

RESULTS

Patients and controls were well-matched for age, BMI, waist-to-hip ratio and body fat content (Table 1). Serum HbA1c and glucose concentrations were similar in narcolepsy patients and controls ($5.3 \pm 0.08$ vs. $5.3 \pm 0.03$, $p = 0.80$, and $4.9 \pm 0.21$ vs. $5.1 \pm 0.12$, mmol/L $p = 0.47$ respectively) SXB was well tolerated by all participants. Apart from mild drowsiness, no other side-effects were reported during the study. After 5 days of SXB, mean concentrations of IGF-1 remained similar in both patients ($16.1 \pm 1.4$ vs. $16.5 \pm 0.9$ nmol/L) and controls ($20.7 \pm 2.5$ vs. $21.7 \pm 3.1$ nmol/L), $p = 0.14$ and $p = 0.30$ for group and treatment effect, respectively. However, after SXB treatment IGFBP-3 levels significantly decreased in both patients ($4.05 \pm 0.46$ vs. $3.9 \pm 0.3$ mg/L), and controls ($4.06 \pm 0.31$ vs. $3.84 \pm 0.28$ mg/L), $p = 0.62$ and $p = 0.035$ for group and treatment effect, respectively. (Wilcoxon signed rank test: $p$
for intergroup difference = 0.58, p for treatment effect in patients = 0.48 ; p for treatment
effect in controls = 0.024).

**Sleep analysis**

On average, compared to controls, narcolepsy patients spent significantly less time awake
both during basal conditions and after SXB (Table 2); paired t-tests and Wilcoxon signed-
rank tests yielded similar results (all p ≤ 0.039) During the day (defined as the lights-on
period between 07:30 h-23:00 h), narcolepsy patients also spent significantly less time awake,
while the time spent in non-REM sleep was significantly higher regardless of treatment;
paired t-tests and Wilcoxon signed-rank tests yielded similar results (all p ≤ 0.047). SXB
administration resulted in a significant decrease in stages I/II non-REM and REM sleep over
24 hours in both groups (p = 0.011 and p = 0.009, respectively), while the time spent in SWS
significantly increased (p = 0.001). During the day, SXB treatment also reduced the time
spent in stages I/II non-REM and REM sleep (p=0.038 and p = 0.041, respectively), while
there was a trend for a longer period of wakefulness as well (p = 0.098). The percentage of
SWS during the night more than doubled in both groups after SXB treatment (narcolepsy: 6.5
± 1.9 % vs.16.5 ± 3.0 %, controls: 7.1 ± 1.9 % vs. 18.5 ± 2.4 %; p = 0.001 for treatment
effect), whereas there were trends for a decline in the percentages of stages I/II non-REM and
REM sleep. During the night, SXB treatment also significantly reduced the number of
awakenings (p = 0.002), while sleep efficiency was not affected (p = 0.082) (Table 2).

**Deconvolution analysis of GH time series**

The deconvolution-derived GH secretory kinetics in patients and controls at baseline and after
SXB are shown in table 3. At baseline and after treatment, there were no significant
differences between the groups. However, SXB resulted in a significant increase in total 24 hour GH secretion rate in narcolepsy patients (73 ± 21 vs. 112 ± 36 mU/L) vs. controls (120 ± 19 vs. 102 ± 12 mU/L), \( p = 0.047 \) for treatment × group interaction.

### Regularity of serum GH concentration time series

The ApEn values of the GH time series were not significantly different between narcolepsy patients and controls, either during basal conditions (0.31 ± 0.06 vs. 0.45 ± 0.07, \( p = 0.17 \)) or following SXB (0.23 ± 0.03 vs. 0.27 ± 0.05, \( p = 0.47 \)). SXB administration, however, increased the regularity of GH secretion as indicated by lower ApEn values during the second study occasion in both patients and controls (\( p = 0.002 \) for treatment effect).

### GH release and sleep association

After SXB, the ratio between GH released at night to total GH secretion significantly increased in both narcolepsy patients (0.72 ± 0.06 vs. 0.84 ± 0.03) and controls (0.55 ± 0.06 vs. 0.79 ± 0.05); \( p < 0.001 \) and \( p = 0.456 \) for treatment and group effect, respectively (Figure 1).

We also compared the first GH secretory burst right after SXB administration (at 23:00 and 3:00 hours). Compared to the baseline condition, the first dose of SXB at 23:00 h led to a significant GH secretory burst in both patients and controls (\( p=0.005 \) for treatment effect; Table 3). However, the effect of SXB treatment on the first GH secretory burst was not different between patients and controls (\( p=0.063 \)) (paired t-test: \( p=0.071 \); Wilcoxon signed-rank test: \( p = 0.093 \)). After the second dose the increase in GH secretion was less pronounced (Table 3).
During basal conditions, the mean cross-correlation between GH levels and the percentage of
time spent in SWS in the previous 10 min equaled 0.24 ± 0.10 in narcolepsy patients and 0.28 ± 0.09 in controls ($p = 0.76$ for the difference in the means). SXB more than doubled the cross-correlation between GH levels and SWS in both groups (narcolepsy: 0.49 ± 0.10, controls: 0.63 ± 0.07; $p = 0.002$ for treatment effect, Figure 2).
DISCUSSION

We have shown that twice-a-night administration of SXB for 5 consecutive days consistently increases nocturnal GH secretion in both healthy controls and hypocretin-deficient narcolepsy patients. This was paralleled by a concomitant increase in SWS. Both the increase in GH and SWS were most prominent after the first dose of SXB at sleep onset. SXB reinforced the relation between GH and SWS, as evidenced by an almost doubled cross-correlation between the two.

GH secretion in narcolepsy has been the topic of a number of studies. Several groups found diminished or even unmeasurable GH concentrations around sleep onset (2; 4; 13). In contrast, we did not find lowered total 24-hour concentrations of GH in a previous study, but rather a more dispersed pattern with a shift towards daytime secretion (30). However, in both scenarios, SXB may partly restore the nocturnal GH ‘deficit’, by increasing nighttime GH secretion. The potency of SXB as a GH-secretagogue was previously shown in two daytime studies without sleep recordings (11; 38), and more recently in a controlled single-dose study using repeated sampling together with sleep registrations in healthy young males (46). Even at the lowest dose (2.5 grams) a twofold increase in sleep-related GH secretion was observed. We confirmed and extended these observations, showing that a second nighttime dose may further enhance GH secretion, albeit to a lesser extent than the first dose. Furthermore, stimulation of GH secretion persists after repeated use, at least after 5 consecutive days.

However, in controls we did not find a difference in 24 h GH secretion before and during SXB administration. Van Cauter, Gerra, and Takahara did find an increase in GH secretion after administration of a single dose of SXB in healthy controls as well as in narcoleptic patients (46). As a putative explanation of our findings, we believe that subchronic
administration of SXB may elevate GH levels to induce feed back inhibition in controls, but not in narcoleptic patients, suggesting that narcolepsy does indeed disrupt normal control of GH release. Obviously, a single dose of SXB will not evoke such feed back inhibition, which explains the fact that other authors did not report a reduction of GH release in healthy humans. As SXB was well tolerated by subjects, this indeed suggests a potential for SXB as a strategy to counteract the relative growth hormone deficiency and sleep disturbances in the elderly, as was previously suggested (45; 46).

The close relation between sleep and the activity of the somatotropic axis has been known for a long time (27; 47). There is a wealth of data supporting the hypothesis that this relation is brought about by the simultaneous promotion of sleep and GH release by GHRH (24; 28; 45). The mechanism through which SXB promotes GH secretion is unknown (46). Some researchers claim that SXB may exert its central nervous system effects through dedicated GHB-receptors in the brain, but the existence of these receptors has been disputed (25; 49). There is clear evidence that SXB does modulate GABAergic tone through agonism of GABAB receptors, also in sleep-promoting regions of the hypothalamus (25; 45). Our data showed that SXB further strengthened the relation between SWS and GH secretion, so its effect may be mediated by an increase in GHRH activity. SXB increased the regularity of GH secretion as well. This may imply that sodium oxibate simultaneously promotes endogenous somatostatin release, as negative feedback has been shown to increase secretory regularity (48). Although animal studies showed that hypocretin administration induced a dose-dependent reduction of GH concentrations in rats, (12) the effects of SXB on GH secretion are unlikely to be mediated by altering hypocretin tone, as results were not different between controls and hypocretin-deficient patients.
Influencing somatotropic activity in narcolepsy may have clinical relevance regarding body composition. Narcolepsy is associated with an increase in body weight. The BMI in the majority of patients is in the overweight range, as has been shown in several population based studies (6; 21; 37). In fact, there often is a clear increase in body weight around the first onset of symptoms of narcolepsy, especially excessive daytime sleepiness. Obesity in narcolepsy is not due to decreases in motor activity throughout the day (26; 33). Furthermore, the total amount of calories consumed is not increased in narcolepsy (22). Basal metabolic rate has been studied by several groups, but inconsistent results have been reported (8; 10). The same holds true for well-known endocrine factors regulating bodyweight, such as leptin (1; 7; 20; 36). Obesity in narcolepsy is notoriously difficult to treat. This lends particular interest to a recent case series suggesting that SXB may decrease body weight in patients with narcolepsy (15). In 54 treated patients, the average reduction in body weight amounted to 3.4 kg. In the patients with cataplexy, the mean weight reduction was even larger: 5.1 kg. GH has a potent lipolytic activity, while GH deficiency leads to decreases in lean body mass and an increased fat mass (5; 35). It is therefore tempting to speculate that the putative weight reducing effect of SXB is mediated by its stimulatory effect on the somatotropic axis.

We report a relatively low sleep efficiency in controls. It is conceivable that the laboratory setting disrupts sleep more than a natural environment. However the percentages of SWS and awakenings are comparable with earlier studies (43; 46). Proper assessment of the secretion pattern of hormones that fluctuate during the day, requires repeated blood sampling over longer periods of time. Obviously, this complicates study design, and limits the number of subjects that can be included. Furthermore, five nights of SXB administration may not correctly reflect the long-term effects of SXB. Our results therefore need confirmation in future long-term studies. Nevertheless, our results suggest that...
future prospective long-term studies should especially focus on the effects of SXB on body
weight, as this would provide a major improvement in the treatment of narcolepsy.

In conclusion, repeated administration of SXB leads to a consistent increase in nocturnal GH
secretion in both healthy controls and hypocretin-deficient narcoleptic patients. SXB also
strengthens the temporal relation between GH secretion and slow wave sleep. These data
suggest that SXB may alter somatotropic tone in addition to its consolidating effect on
nighttime sleep in hypocretin-deficient narcolepsy. This could explain the suggested non-
sleep effects of SXB, including body weight reduction.

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DISCLOSURES

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None of the other authors have financial conflicts of interest.


Figure 1. Mean serum GH concentrations and slow wave sleep in narcolepsy and matched control subjects. Blood sampling started at 12:00 and was continued at 10-min intervals for 24 hours, while sleep EEG was continuously recorded. SXB administration induced an immediate rise in GH levels in both narcolepsy patients (A) and controls (B). Similarly, after five consecutive days of SXB treatment (including the second sampling occasion), the percentage of slow wave sleep had significantly increased in both narcolepsy patients (C) and controls (D). The black bar on the abscissa indicates the dark period (23:00-7:30). The grey arrows indicate the timings of the lunch, dinner and breakfast at 13:00, 18:00 and 08:30, respectively. The black arrows indicate the timings of SXB administration during the second occasion at 23:00 and 03:00. Error bars show means ± standard errors of the mean (SEM).

Figure 2. Cross-correlation coefficient between GH levels and slow wave sleep (SWS). SXB treatment resulted in a substantial increase in the coupling between GH release and SWS as evidenced by a significant increase in the cross-correlation (p = 0.002 for treatment effect). However, the effect did not differ between narcolepsy patients and controls (p = 0.282 for group effect).
Table 1. Demographics, body composition, baseline parameters.

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<th>CONTROLS</th>
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<td>Body fat (%)</td>
<td>23.6 ± 2.1</td>
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Data are shown as mean ± SEM.
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<th>Narcolepsy vs. controls (SXB)</th>
<th>Treatment effect</th>
<th>Interaction (group × treatment)</th>
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<td>SXB</td>
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<td>SXB</td>
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<td>60.8 ± 2.2</td>
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<td>0.013*</td>
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<td>19.2 ± 4.3</td>
<td>18.4 ± 4.0</td>
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<td>REM total (%)</td>
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<td>3.7 ± 0.8</td>
<td>2.1 ± 0.8</td>
<td>0.191</td>
<td>0.070</td>
</tr>
<tr>
<td>REM day (%)</td>
<td>2.9 ± 1.4</td>
<td>1.2 ± 0.5</td>
<td>0.8 ± 0.5</td>
<td>0.0 ± 0.0</td>
<td>0.203</td>
<td>0.032*</td>
</tr>
<tr>
<td>REM night (%)</td>
<td>12.6 ± 3.0</td>
<td>10.8 ± 2.1</td>
<td>8.8 ± 1.8</td>
<td>5.8 ± 2.3</td>
<td>0.305</td>
<td>0.127</td>
</tr>
<tr>
<td>No. of awakenings</td>
<td>50.5 ± 10.5</td>
<td>35.0 ± 4.8</td>
<td>35.5 ± 7.1</td>
<td>16.3 ± 1.7</td>
<td>0.256</td>
<td>0.005**</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>66.9 ± 7.0</td>
<td>81.5 ± 4.9</td>
<td>81.2 ± 4.0</td>
<td>81.9 ± 6.0</td>
<td>0.097</td>
<td>0.963</td>
</tr>
</tbody>
</table>

Percentages of sleep stages during the 24 hours of study, before and after SXB administration. Data are shown as mean ± SEM. Unpaired t tests were used to assess differences between the two groups. Mixed-effects models were applied to assess the effect of treatment and potential interaction effects between group (i.e. narcolepsy or control) and treatment. * p < 0.05 and ** p < 0.01.
### Table 3. Deconvolution analysis of 24-hour serum GH concentrations.

<table>
<thead>
<tr>
<th></th>
<th>Narcolepsy</th>
<th>Controls</th>
<th>Narcolepsy vs. controls (baseline)</th>
<th>Narcolepsy vs. controls (SXB)</th>
<th>Treatment effect</th>
<th>Interaction (group × treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>SXB</td>
<td>Basal</td>
<td>SXB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half-life (min)</td>
<td>13.9 ± 1.0</td>
<td>15.4 ± 0.8</td>
<td>13.1 ± 0.9</td>
<td>15.5 ± 0.6</td>
<td>0.59</td>
<td>0.92</td>
</tr>
<tr>
<td>Pulse half-duration (min)</td>
<td>17.6 ± 2.4</td>
<td>17.9 ± 1.0</td>
<td>26.9 ± 3.6</td>
<td>19.8 ± 1.1</td>
<td>0.051</td>
<td>0.22</td>
</tr>
<tr>
<td>Pulse frequency (no./24 h)</td>
<td>20.8 ± 2.3</td>
<td>18.0 ± 1.5</td>
<td>19.0 ± 1.7</td>
<td>16.4 ± 1.5</td>
<td>0.55</td>
<td>0.47</td>
</tr>
<tr>
<td>Mean secreted mass/pulse (mU/L)</td>
<td>3.5 ± 1.0</td>
<td>6.7 ± 2.4</td>
<td>6.3 ± 1.2</td>
<td>6.1 ± 0.8</td>
<td>0.099</td>
<td>0.81</td>
</tr>
<tr>
<td>Mean value (mU/L)</td>
<td>1.0 ± 0.3</td>
<td>1.8 ± 0.6</td>
<td>1.6 ± 0.2</td>
<td>1.6 ± 0.2</td>
<td>0.19</td>
<td>0.75</td>
</tr>
<tr>
<td>24 h basal production rate (mU/L&lt;sub&gt;L&lt;sub&gt;dv&lt;/sub&gt;&lt;/sub&gt;)</td>
<td>2.4 ± 0.43</td>
<td>1.9 ± 0.44</td>
<td>5.5 ± 0.19</td>
<td>2.7 ± 0.66</td>
<td>0.13</td>
<td>0.32</td>
</tr>
<tr>
<td>24 h pulsatile production rate (mU/L&lt;sub&gt;L&lt;sub&gt;dv&lt;/sub&gt;&lt;/sub&gt;)</td>
<td>69 ± 21</td>
<td>109 ± 36</td>
<td>112 ± 18</td>
<td>98 ± 12</td>
<td>0.14</td>
<td>0.77</td>
</tr>
<tr>
<td>24 h total production rate (mU/L&lt;sub&gt;L&lt;sub&gt;dv&lt;/sub&gt;&lt;/sub&gt;)</td>
<td>73 ± 21</td>
<td>112 ± 36</td>
<td>120 ± 19</td>
<td>102 ± 12</td>
<td>0.11</td>
<td>0.79</td>
</tr>
<tr>
<td>Percent pulsatile (%)</td>
<td>93 ± 1.8</td>
<td>96 ± 1.0</td>
<td>93 ± 1.7</td>
<td>96 ± 0.8</td>
<td>0.95</td>
<td>0.84</td>
</tr>
<tr>
<td>Amount of GH secreted in the first secretory burst after 23:00 h (mU/L)†</td>
<td>8.3 ± 7.7</td>
<td>20.2 ± 7.8</td>
<td>12.6 ± 6.3</td>
<td>41.7 ± 7.3</td>
<td>0.673</td>
<td>0.063</td>
</tr>
<tr>
<td>Amount of GH secreted in the first secretory burst after 03:00 h (mU/L)†</td>
<td>1.3 ± 0.6</td>
<td>6.0 ± 3.9</td>
<td>4.9 ± 3.5</td>
<td>12.5 ± 5.8</td>
<td>0.331</td>
<td>0.369</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SEM. Unpaired t tests were used to assess differences between the two groups. Mixed-effects models were applied to assess the effect of treatment and potential interaction effects between group (i.e. narcolepsy or control) and treatment. * p < 0.05 and ** p < 0.01. L<sub>dv</sub>: Liter distribution volume
A) Narcolepsy

- Basal
- Sodium oxybate
B) Control

- Basal
- Sodium oxybate

Growth hormone (mU/L)

Clock time (hours)
C) Narcolepsy

- Basal
- Sodium oxybate

Slow Wave Sleep (%)

Clock time (hours)