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

Claire E. H. M. Donjacour,1 N. Ahmad Aziz,1 Ferdinand Roelfsema,2 Marijke Frölich,3 Sebastiaan Overeem,4,5 Gert Jan Lammers,1 and Hanno Pijl2

Departments of 1Neurology, 2Endocrinology, and 3Clinical Chemistry, Leiden University Medical Centre, Leiden; 4Department of Neurology, Donders Institute for Neuroscience, Radboud University Nijmegen Medical Centre, Nijmegen; and 5Sleep Medicine Center “Kempenhaeghe,” Heeze, The Netherlands

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Donjacour CE, Aziz NA, Roelfsema F, Frölich M, Overeem S, Lammers GJ, Pijl H. Effect of sodium oxybate on growth hormone secretion in narcolepsy patients and healthy controls. Am J Physiol Endocrinol Metab 300: E1069–E1075, 2011. First published March 29, 2011; doi:10.1152/ajpendo.00623.2010.—Hypocretin deficiency causes narcolepsy and may affect neuroendocrine systems and body composition. Additionally, growth hormone (GH) alterations influence weight in narcolepsy. Symptoms can be treated effectively with sodium oxybate (SXB; γ-hydroxybutyrate) in many patients. This study compared growth hormone secretion in narcolepsy patients and controls and established the effect of SXB administration on GH and sleep in both groups. Eight male hypocretin-deficient patients with narcolepsy and 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 two times 3 g/night for 5 consecutive nights. Both groups underwent 24-h blood sampling at 10-min intervals for measurement of GH concentrations. The 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-h 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 nonsleep effects of SXB, including body weight reduction.

hypocretin; orexin; γ-hydroxybutyrate

Classically, narcolepsy is defined as a sleep disorder with excessive daytime sleepiness and cataplexy as the main symptom (31). However, in recent years, there has been increasing attention paid 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 fueled 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. Therefore, recent research has 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-h 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 (SXB) has evolved into a first-line treatment for narcolepsy (39, 42, 50–52). SXB is a short-acting hypnotic that is dosed twice at night, at bedtime, and 2.5–4 h later. It significantly consolidates nighttime sleep and 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-h GH secretion patterns in both patients with hypocretin-deficient narcolepsy and matched healthy controls. GH secretion was assessed during a 24-h 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 eight male narcolepsy patients who fulfilled the diagnostic criteria for narcolepsy with cataplexy according to International Classification of Sleep Disorders: Second Edition (17). All patients were hypocretin-1 deficient, using a standardized cerebrospinal fluid assay (34). All patients were free of medication for ≥2 wk 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) and anemia as well as hepatic and renal failure. Furthermore, we excluded recent weight change (>3 kg weight gain or loss within the last 3 mo), 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-h 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 g of SXB in the evening (2300) and during the night (0300). Subjects were Fasted ≥2.5 h before drug intake, since 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 3 nights. The 5th night with subjects 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-h blood sampling. A cannula was inserted into an antecubital vein 45 min before the start of blood sampling at 1200. 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 both IGF-I and IGF-binding protein-3 (IGFBP-3) were taken just before sleep disruption by investigative manipulations. Samples for both NaCl and heparin (1 U/ml) infusion (500 ml/24 h) to keep the cannula antecubital vein 45 min before the start of blood sampling at 1200.

Center for 24-h blood sampling. A cannula was inserted into an antecubital vein 45 min before the start of blood sampling at 1200. Subjects were admitted to the Clinical Research Center during the next sampling occasion.

Sleep analysis. Sleep was recorded polygraphically throughout both sampling occasions, using an Embleta X100 recorder (Embla, Broomfield, CO). The recordings were scored visually at 30-s intervals according to the American Academy of Sleep Medicine criteria (16) by an experienced sleep technician. To allow assessment of the individual associations between changes in serum GH levels (measured every 10 min) and sleep stages (scored every 30 s), sleep profiles were divided into the 10-min segments separating consecutive GH measurements, as described previously (44). Each 10-min segment was divided into non-rapid-eye-movement (REM) sleep, stage II/IV SWS, and REM sleep.

Assays. Serum GH was measured by a time-resolved fluororomunnoassay (Delfia; 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 controls were handled in the same run. Total serum IGF-I (Serono; Biomedica, Milan, Italy) and IGFBP-3 concentrations (Nichols, San Juan Capistrano, CA) were measured by radioimmunoassay. Glycosylated hemoglobin (Hb A1c) levels were measured with a high-performance liquid chromatography system (Variant; Biomed, Hercules, CA). Urinary epinephrine, norepinephrine, and dopamine concentrations were measured with high-performance liquid chromatography with electron capture detection (ESTA-Coulchem, Chelmsford, MA).

Deconvolution analysis. A recently developed, fully automatic, multiparameter deconvolution procedure, AutoDecon, was used to estimate various specific measurements of secretion and serum disappearance rate of GH, considering all serum hormone concentrations and their dose-dependent intrasample 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, both of which 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 one-half of the data-sampling interval, and 2) a starting value for the elimination parameter or hormone half-life. Thus, for 10-min sampled data, the SecretionSD was initialized to 5 min together with a starting value for the GH half-life of 16 min. 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 Auto Decon, as described earlier (19).

Approximate entropy. Approximate entropy (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 intraseries standard deviation were used, the statistical suitability of which has been established previously (32).

Statistical analyses. Results are expressed as means ± SE unless otherwise specified. Unpaired t-tests were used to assess differences in means between the two groups. 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 SWS 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 the small number of subjects in each group, paired parametric (paired-sample t-test) and nonparametric 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, San Jose, CA) and SPSS

Table 1. Demographics, body composition, and baseline parameters

<table>
<thead>
<tr>
<th>Value</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Age, yr</td>
<td>38.0 ± 4.7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.1 ± 1.6</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.92 ± 0.03</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>23.6 ± 2.1</td>
</tr>
</tbody>
</table>

Data are shown as means ± SE. BMI, body mass index.
Table 2. Sleep patterns before and after SXB administration

<table>
<thead>
<tr>
<th>Narcolepsy</th>
<th>Controls</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>SXB</td>
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<tr>
<td>Baseline</td>
<td>SXB</td>
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</table>

<table>
<thead>
<tr>
<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>0.044*</td>
<td>0.013*</td>
<td>0.584</td>
<td>0.565</td>
</tr>
<tr>
<td>0.004**</td>
<td>0.001**</td>
<td>0.098</td>
<td>0.597</td>
</tr>
<tr>
<td>0.310</td>
<td>0.999</td>
<td>0.396</td>
<td>0.087</td>
</tr>
</tbody>
</table>

Data are shown as means ± SE. SXB, sodium oxybate; REM, rapid eye movement. Percentages of sleep stages during the 24 h of study before and after SXB administration. Unpaired t-tests were used to assess differences between the 2 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; **P < 0.01.

RESULTS

Patients and controls were well matched for age, BMI, WHR, and body fat content (Table 1). Serum Hb A1c and glucose concentrations were similar in narcolepsy patients (5.3 ± 0.08 vs. 5.3 ± 0.03 mmol/l; P = 0.80) and controls (4.9 ± 0.21 vs. 5.1 ± 0.12 mmol/l; P = 0.47). 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-I remained similar in both patients (16.1 ± 1.4 vs. 16.5 ± 0.9 nmol/l) and controls (20.7 ± 2.5 vs. 21.7 ± 3.1 nmol/l); P = 0.14 and P = 0.30 for group and treatment effect, respectively. However, after SXB treatment, IGFBP-3 levels decreased significantly in both patients (4.05 ± 0.46 vs. 3.9 ± 0.3 mg/l) and controls (4.06 ± 0.31 vs. 3.84 ± 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, and P for treatment effect in controls = 0.024).

Sleep analysis. On average, compared with 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 0730 and 2300), narcolepsy patients also spent significantly less time awake, whereas 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 h in both groups

Table 3. Deconvolution analysis of 24-h serum GH concentrations

<table>
<thead>
<tr>
<th>Narcolepsy</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>SXB</td>
</tr>
<tr>
<td>Basal</td>
<td>SXB</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Basal SXB</th>
<th>Basal SXB</th>
<th>Basal SXB</th>
<th>Basal SXB</th>
<th>Basal SXB</th>
</tr>
</thead>
<tbody>
<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>
</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>
</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>
</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>
</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>
</tr>
<tr>
<td>24-h Basal production rate, mU/l, Basal</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>
</tr>
<tr>
<td>24-h Pulsatile production rate, mU/l, Basal</td>
<td>69 ± 21</td>
<td>109 ± 36</td>
<td>112 ± 18</td>
<td>98 ± 12</td>
</tr>
<tr>
<td>24-h Total production rate, mU/l, Basal</td>
<td>73 ± 21</td>
<td>112 ± 36</td>
<td>120 ± 19</td>
<td>102 ± 12</td>
</tr>
<tr>
<td>%Pulsatile</td>
<td>93 ± 1.8</td>
<td>96 ± 1.0</td>
<td>93 ± 1.7</td>
<td>96 ± 0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amount of GH secreted in the 1st secretory burst, mU/l†</th>
<th>After 2300</th>
<th>After 0300</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.3 ± 2.7</td>
<td>20.2 ± 7.8</td>
<td>12.6 ± 6.3</td>
</tr>
<tr>
<td>1.3 ± 0.6</td>
<td>6.0 ± 3.9</td>
<td>4.9 ± 3.5</td>
</tr>
</tbody>
</table>

Data are shown as means ± SE. GH, growth hormone; Ldv, liter distribution volume. Unpaired t-tests were used to assess differences between the 2 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; **P < 0.01; †SXB was administered at 2300 and 0300.
(P = 0.011 and P = 0.009, respectively), whereas the time spent in SWS increased significantly (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), although 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), whereas sleep efficiency was not affected (P = 0.082) (Table 2).

Fig. 1. Mean serum growth hormone concentrations and slow-wave sleep in narcolepsy and matched control subjects. Blood sampling started at 1200 and was continued at 10-min intervals for 24 h, whereas sleep electroencephalogram was recorded continuously. Sodium oxybate (SXB) administration induced an immediate rise in growth hormone levels in both narcolepsy patients (A) and controls (B). Similarly, after 5 consecutive days of SXB treatment (including the 2nd 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 (2300–0730). The gray arrows indicate the timings of the lunch, dinner, and breakfast at 1300, 1800, and 0830, respectively. The black arrows indicate the timings of SXB administration during the 2nd occasion at 2300 and 0300. Error bars show means ± SE.
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-h GH secretion rate in narcolepsy patients [73 ± 21 vs. 112 ± 36 mU/liter distribution volume (ldv)] but not in controls (120 ± 19 vs. 102 ± 12 mU/ldv); \( P = 0.047 \) 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, \( P = 0.47 \)). However, SXB administration 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 (Fig. 1).

We also compared the first GH secretory burst right after SXB administration (at 2300 and 0300). Compared with the baseline condition, the first dose of SXB at 2300 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; Fig. 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. The increases in both 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-h concentrations of GH in a previous study but rather a more dispersed pattern with a shift toward 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 shown previously 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 g) 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 et al. (46), Gerra et al. (11), and Takahara et al. (39) did find an increase in GH secretion after administration of a single dose of SXB in healthy controls. As a putative explanation of our findings, we believe that subchronic administration of SXB may elevate GH levels to induce feedback 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 feedback inhibition, which explains the fact that other authors did not report a reduction of GH release in healthy humans. Because 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 suggested previously (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 growth hormone-releasing hormone (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 \( \gamma \)-hydroxybutyrate 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 GABA\(_B\) 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 SXB simultaneously promotes endogenous somatostatin release, since 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, since 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 body weight, such as leptin (1, 7, 20, 36). Obesity in narcolepsy is notoriously difficult to treat. This lends particular interest to the 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, whereas GH deficiency leads to decreases in lean body mass and increased fat mass (5, 35). Therefore, it is 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, 5 nights of SXB administration may not correctly reflect the long-term effects of SXB. Therefore, our results need confirmation in future long-term studies. Nevertheless, our results suggest that future prospective long-term studies should focus especially on the effects of SXB on body weight, since 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 SWS. 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 nonsleep effects of SXB, including body weight reduction.

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DISCLOSURES

G. J. Lammers and S. Overeem have served as paid members of the UCB advisory board and received lecture fees from UCB. None of the other authors have financial conflicts of interest.

REFERENCES


