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ORIGINAL INVESTIGATION

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The $GABA_A$ agonist THIP produces slow wave sleep and reduces spindling activity in NREM sleep in humans

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Abstract Recent studies in the rat demonstrated that systemic administration of muscimol and THIP, both selective $GABA_A$ receptor agonists, elevates slow wave activity in the EEG during non-rapid eye movement (NREM) sleep. In this placebo-controlled study, we assessed the influence of an oral dose of 20 mg THIP on nocturnal sleep in young healthy humans. Compared to placebo, THIP increased slow wave sleep by about 25 min. Spectral analysis of the EEG within NREM sleep revealed significant elevations in the lower frequencies (<8 Hz) and reductions in the spindle frequency range ($\approx$10–16 Hz). In accordance with previous findings in the rat, these data imply that $GABA_A$ agonists promote deep NREM sleep, without suppressing REM sleep. These effects are opposite to those induced by agonistic modulators of $GABA_A$ receptors such as benzodiazepines and are at variance with established mechanisms according to which $GABA_A$ agonists and modulatory agonists would have similar effects. The sleep response to $GABA_A$ agonists is highly similar to that evoked by sustained wakefulness, suggesting that $GABA_A$ receptors may be implicated in the homeostatic regulation of sleep.

Key words Gaboxadol · GABA · $GABA_A$ receptor · Sleep state · Spectral analysis · Human

Introduction

Peripheral administration of muscimol and gaboxadol [4, 5, 6, 7-tetrahydroisoxazolo (5, 4-c) pyridin-3-ol, THIP], both analogues of the neurotransmitter gamma-aminobutric acid (GABA) and selective agonists of $GABA_A$ receptors, has recently been found to increase the time spent in non-rapid eye movement (NREM) sleep and to increase the duration of the NREM- and REM-sleep episodes in the rat. Furthermore, spectral analysis of the EEG showed that both substances enhance slow wave activity (SWA, 0.5–4 Hz) during NREM sleep and increase the rise rate as well as the maximal level of SWA attained within the NREM sleep episodes (Lancel and Faulhaber 1996; Lancel et al. 1996). These findings are intriguing for two reasons. First, the sleep effects of muscimol and THIP are very different from those induced by the extensively studied agonistic modulators of $GABA_A$ receptors, the benzodiazepines, zolpidem and zopiclone. The latter are well established to shorten sleep latency and promote NREM sleep, but tend to suppress REM sleep and markedly attenuate SWA, while enhancing spindling/sigma activity ($\approx$11–15 Hz) in the EEG within NREM sleep in humans and rats (Borbély et al. 1985; Dijk et al. 1989; Trachsel et al. 1990; Brunner et al. 1991; Aeschbach et al. 1994; Lancel et al. 1996). Secondly, the sleep alterations evoked by THIP and muscimol are reminiscent of the sleep changes observed after prolonged vigilance in both humans and other species. In animals with a polyphasic sleep-wake pattern such as rats and cats, sleep deprivation reduces sleep latency, increases the total amount of NREM sleep, increases sleep episode duration, elevates NREM sleep-specific SWA, which is generally thought to reflect an increase in NREM sleep intensity and is associated with a rise in the build-up rate of SWA and with an enhancement of the highest SWA levels reached within the NREMS episodes (Borbély and Neuhaus 1979; Lancel and Kerkhof 1989; Trachsel et al. 1989; Tobler and Borbély 1990; Lancel et al. 1992). In humans the effects of sustained wakefulness on the EEG during NREM sleep are to a large extent similar to those observed in these animals: it increases

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slow wave sleep (SWS, stages 3 and 4), enhances SWA and decreases spindling activity (Borbély et al. 1981; Dijk et al. 1990; Dijk and Czeisler 1993).

In the present study we investigated the sleep response to THIP in young healthy male subjects and compared it with published results of the effects of agonistic modulators of $GABA_A$ receptors and extended wakefulness on sleep in humans.

Materials and methods

Subjects

The experimental protocol was approved by the Ethics Committee for Human Experiments of the Max Planck Institute of Psychiatry. Ten paid healthy male volunteers (age 22–31 years) gave written informed consent to participate in the study. They underwent extensive psychiatric, physical and laboratory examinations. Reasons for exclusion from the study were a personal or family history of psychiatric disorders, recent stressful life events, medical illness, sleep disorders, substance abuse, shiftwork or a transmeridian flight during the preceding 3 months.

Study design

In this double-blind study the subjects slept in the sleep laboratory during two sessions, separated by at least 1 week. Each session consisted of 2 consecutive nights. The first night served for adaptation to the laboratory conditions. On the second night the subjects took a gelatine capsule at 2230 hours containing placebo (lactose) or THIP (20 mg, Research Biochemicals International, Natick, Mass., USA) according to a randomized schedule. During both the adaptation and treatment nights the subjects went to bed at 2300 hours (lights off) and were awoken at 0700 hours during the adaptation nights. To assess possible effects on total sleep time, time in bed was unrestricted during the treatment nights. Shortly after arising the subjects were asked whether they had noticed physical or psychological changes and if so, which.

Data analysis

Throughout the treatment nights EEG (C3–A2 and C4–A1; high-pass filtering at 0.53 Hz, −3 dB; low-pass filtering at 70 Hz, −3 dB; −12 dB/octave; band stop between 42 and 62 Hz, -3 dB), EMG and EOG were recorded on a Schwartzer ED 24. Sleep stages were visually scored per 30-s epoch according to conventional criteria (Rechtschaffen and Kales 1968) by experienced raters who were unaware of the treatment. The digitized signals (eight-bit A/D converter, sampling rate 100 Hz) were stored on disk and calibrated with a 50 μV, 10 Hz sine wave. The C3–A2 EEG derivation was submitted to a fast Fourier transformation. EEG power spectra were computed for consecutive rectangular windows of 256 samples (≈2.56 s), resulting in a frequency resolution of about 0.39 Hz between 0 and 50 Hz. EEG spectra were averaged over epochs of 12 consecutive windows (≈30.72 s). For the following epoch, the procedure stepped back 72 samples (0.72 s) to permit synchronization with the 30-s epochs of the visual scores. Epochs with excessive low-frequency (cumulative power between 0 and 4.30 Hz) or high-frequency power (10.16–19.14 Hz) were labelled as EEG artefacts by employing individual thresholds for each frequency band and separate NREM and REM sleep episodes. Epochs labelled as artefacts or scored as movement time were excluded from further analysis. Either power was cumulated across the slow wave (0.78–4.29 Hz) and sigma (12.5–14.84 Hz) frequency ranges (Dijk et al. 1990; Aeschbach and Borbély 1993; Dijk and Czeisler 1993) or power of 49 frequency bins (0.39–19.14, 0.39 Hz bins) was used. Mean SWA and sigma activity during NREM sleep (S2, S3 and S4) were computed for the first four 2-h intervals. To analyse changes in the dynamics of SWA and sigma activity, the first four NREM-REM cycles were defined according to criteria of Feinberg et al. (1980). In our analysis the first NREM episode started at sleep onset and the following NREM episodes with the occurrence of a NREM sleep stage (S1 included). SWA and sigma activity were computed per 2-min interval for the 2 min preceding, the first 30 min and last 30 min of the NREM episodes and for the first 2 min of REM sleep. Sleep state-specific power in each of the 49 frequency bins was computed per 2-h interval for NREM sleep (S2, S3 and S4) and, to avoid missing values, per 4-h interval for REM sleep. Because of large inter-individual differences in absolute power, EEG power in NREM and REM sleep were normalized by expressing them as percentage of the average power in the same frequency range and sleep state during the entire placebo night. Statistical differences of the sleep states between the placebo and THIP nights were assessed with a Wilcoxon matched pairs signed rank test. The EEG data were analyzed by means of a two-factor repeated measures ANOVA (Greenhouse-Geisser correction, factors time and treatment) and two-sided, paired *t*-tests.

Results

Sleep stages

The subjects reported neither physical nor psychological changes during the placebo and THIP nights. THIP significantly increased sleep efficiency from 89 to 92% (Table 1). Moreover, it significantly enhanced SWS by about 25 min, due to increases in both stage 3 and 4. Figure 1 depicts the accumulation of SWS over 2-h intervals and shows that increases in SWS occurred throughout the THIP night. THIP did not affect REM sleep latency or the total amount of (Table 1) and the cumulation of REM sleep over the night (Fig. 1).

Table 1 Sleep parameters after placebo and THIP administration

	Placebo	THIP	*P*
TIB	554.0 (52.0)	576.6 (30.0)	NS
TST	493.5 (50.1)	530.7 (45.5)	NS
SEI (%)	89.1 (6.5)	92.0 (4.9)	<0.05
SOL	12.7 (8.5)	13.5 (8.5)	NS
Wakefulness	31.3 (35.1)	24.4 (26.4)	NS
Stage 1	38.7 (22.1)	36.0 (21.9)	NS
Stage 2	275.1 (30.2)	283.6 (38.7)	NS
Slow wave sleep	56.1 (29.2)	80.3 (45.2)	<0.01
Stage 3	38.6 (20.1)	49.8 (26.8)	<0.01
Stage 4	17.6 (12.9)	30.5 (21.6)	<0.01
REM sleep	116.6 (19.8)	122.4 (36.6)	NS
REM latency	69.8 (18.2)	71.4 (25.6)	NS

Data are mean ($n = 10$) (±SD) *TIB* time in bed; *TST* total sleep time; *SEI* sleep efficiency index (% TST of TIB); *SOL* sleep onset latency. All values, except SEI, are in minutes. Statistical significance of differences between placebo and THIP were tested with a Wilcoxon matched pairs signed rank test. *NS* not significant

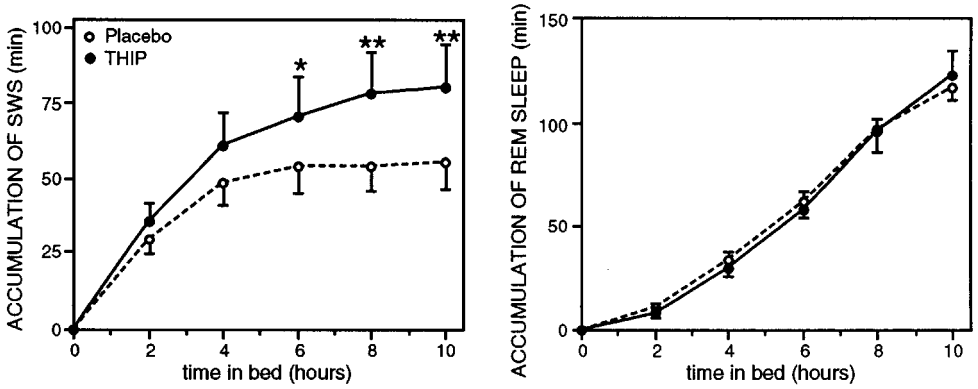

Fig. 1 Cumulation of SWS and REM sleep after administration of placebo and THIP. Values are means ± SEM ($n = 10$) and are plotted at the upper limit of each 2-h interval. During placebo and THIP, respectively, eight and nine subjects were still asleep after 8 h in bed. Significant differences between the treatments are indicated by $*P < 0.05$ and $**P < 0.01$, Wilcoxon matched pairs, signed rank test

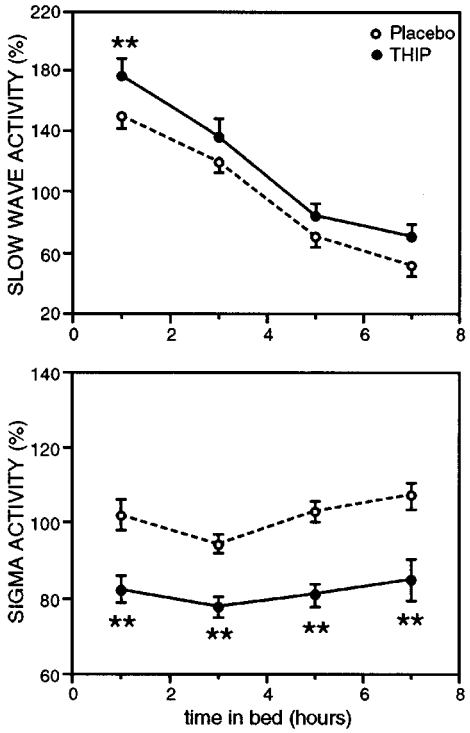

Fig. 2 Time course of average slow wave activity and sigma activity during NREM sleep (stage 2, 3 and 4) after administration of placebo and THIP. Values are means ± SEM ($n = 10$) and are plotted in the middle of the 2-h intervals. For each subject the data were expressed as percentage of the average slow wave and sigma activity in NREM sleep during the entire placebo night. Significant differences between the treatments are indicated by $**P < 0.01$, two-sided, paired t-test)

Average slow wave activity and sigma activity during NREM sleep

Analysis of SWA in NREM sleep across the first 8 h yielded a significant effect of time ($F_{3,27} = 44.9$, $P < 0.0001$) and treatment ($F_{1,9} = 7.3$, $P < 0.02$). Irrespective of the treatment, SWA was maximal during the first 2-h interval and monotonically declined thereafter (Fig. 2). Computed over the first 8 h, THIP enhanced SWA to 120.1% (±23.3 SD) of the placebo values. The enhancement was significant during the first 2-h interval. For sigma activity ANOVA found a significant treatment effect ($F = 61.4$, $P < 0.0001$). Over the first 8 h, THIP reduced sigma activity to 80.5% (±6.5) of the placebo values and reductions were significant during all 2-h intervals (Fig. 2).

Dynamics of slow wave activity and sigma activity within NREM sleep episodes

Analysis of SWA during the initial and final 30 min of the first four NREM episodes revealed significant time effects for all four episodes (see legend to Fig. 3 for results of the ANOVA). Independent of the treatment, SWA typically exhibited a gradual increase after NREM sleep onset and the highest levels attained decreased over successive NREMS episodes. SWA declined rapidly shortly before the onset of REM sleep (Fig. 3). THIP significantly elevated SWA both during the initial and final phase of the first NREM sleep episode. To analyse whether THIP affected the rise rate of SWA, we calculated for each individual subject the median of the differences in SWA of adjacent 2-min intervals over the 2 min prior to and the first 22 min of NREM sleep episode 1. THIP tended to increase the rise rate from 17.5%/2 min (±8.6) to 23.4 (±12.9) ($P < 0.09$, two-sided, paired t-test). THIP significantly elevated SWA during the last 30 min of NREM sleep episodes 2 and 3.

Analysis of the intraepisodic time course of sigma activity yielded significant time effects for all four NREM sleep episodes and a significant interaction effect between time and treatment for the final phase of episode 1 (see legend to Fig. 3 for results of the ANOVA). In the first episode of both treatments, sigma activity initially increased rapidly, which was followed by a decline (Fig. 3). Only during the placebo condition is the sharp drop in sigma activity at the transition to REM sleep preceded by a transient increase. During the other episodes of both placebo and THIP, sigma activity increased, then remained on a rather stable level and declined towards the end of NREM sleep. THIP significantly reduced sigma activity during the end of NREM sleep episode 1

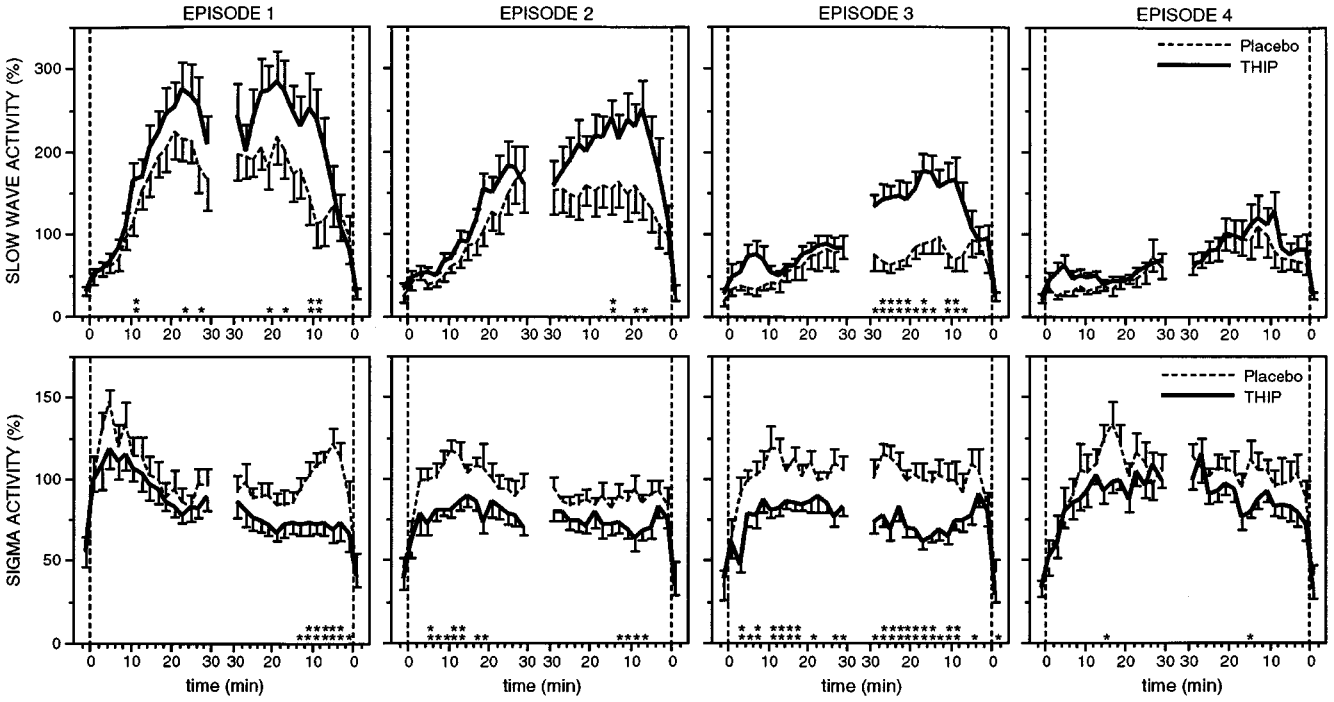

Fig. 3 Evolution of slow wave activity and sigma activity during the first 30 min and last 30 min of the first four NREM sleep episodes after administration of placebo and THIP. Values are means ± SEM ($n = 10$) and are plotted in the middle of the 2-min intervals. For each subject the data were expressed as percentage of the average slow wave and sigma activity in NREM sleep during the entire placebo night. *Dashed vertical lines* indicate the beginning and end of the NREM sleep episodes. Significant results of the ANOVA follow (effects of the factor time were always significant and have been omitted). Slow wave activity: *episode 1*: initial phase: effect of treatment $F_{1,9} = 14.6$, $P < 0.004$: final phase: treatment $F = 5.7$, $P < 0.04$. *episode 2*: final phase: treatment $F = 5.1$, $P < 0.05$. *episode 3*: final phase: treatment $F = 16.5$, $P < 0.003$; interaction $F15{,}135 = 3.2$, $P < 0.02$. Sigma activity: *episode 1*: final phase: treatment $F = 18.7$, $P < 0.002$; interaction $F = 3.8$, $P < 0.005$. *episode 2*: initial phase: treatment $F = 44.0$, $P < 0.0001$: final phase: treatment $F = 14.1$, $P < 0.005$. *episode 3*: initial phase: treatment $F = 27.3$, $P < 0.0005$: final phase: treatment $F = 44.4$, $P < 0.0001$. *episode 4*: initial phase: treatment $F = 6.0$, $P < 0.04$: final phase: treatment $F = 9.1$, $P < 0.01$. Significant differences between placebo and THIP are indicated at the bottom of the graphs by $^*P < 0.05$) and $^{**}P < 0.01$, two-sided, paired *t*-test

and during both the first and last 30 min of episodes 2, 3 and 4.

EEG power during NREM and REM sleep

ANOVA run on the 2-h mean values of NREM sleep-specific power in each of the 0.39 Hz bins found a significant effect of the factor time for all frequencies, except 12.89 and 13.28 Hz. Irrespective of the treatment, EEG power in most frequency bands decreased significantly across the first 6 h and the most prominent reductions were present in the slow wave frequencies (Fig. 4). Power in some high frequency bands (≥14 Hz) increased significantly from interval 5–6 to interval 7–8. Moreover, ANOVA yielded a significant treatment effect for the frequency ranges 0.78–2.73, 5.08–6.64 and 9.77–15.63 Hz and a significant interaction effect for the frequencies between 7.03 and 7.81 Hz. During the first 2 h low-frequency power was generally enhanced, the largest increases occurring in the frequencies between 0.78 and 2.34 Hz, and power was significantly reduced from 9.77 up to 15.63 Hz. During the second 2-h interval power was significantly enhanced in the frequencies between 5.47 and 7.81 Hz. As a consequence, power in the frequencies between 7.03 and 7.81 Hz did not decline over the first 4 h. Reductions in the higher frequency range remained evident throughout the 8 h.

Analysis of EEG power during REM sleep revealed a significant time effect for all frequencies >1 Hz, due to a decline over the consecutive 4-h intervals (Fig. 5). A significant treatment effect emerged for the frequencies 1.56, 2.34, 3.12, 4.69–9.38, 14.45–14.84 and 16.41–17.97 Hz and a significant interaction effect for the frequencies between 2.73 and 8.98 Hz. During the first 4-h interval THIP generally enhanced EEG power in the frequencies <10 Hz. This initial increase resulted in a significant decrease over the 8-h period, which was not present during placebo. Furthermore, THIP slightly decreased EEG power in some higher frequency bands during both 4-h intervals.

Discussion

The present study shows for the first time that the potent, selective $GABA_A$ receptor agonist THIP

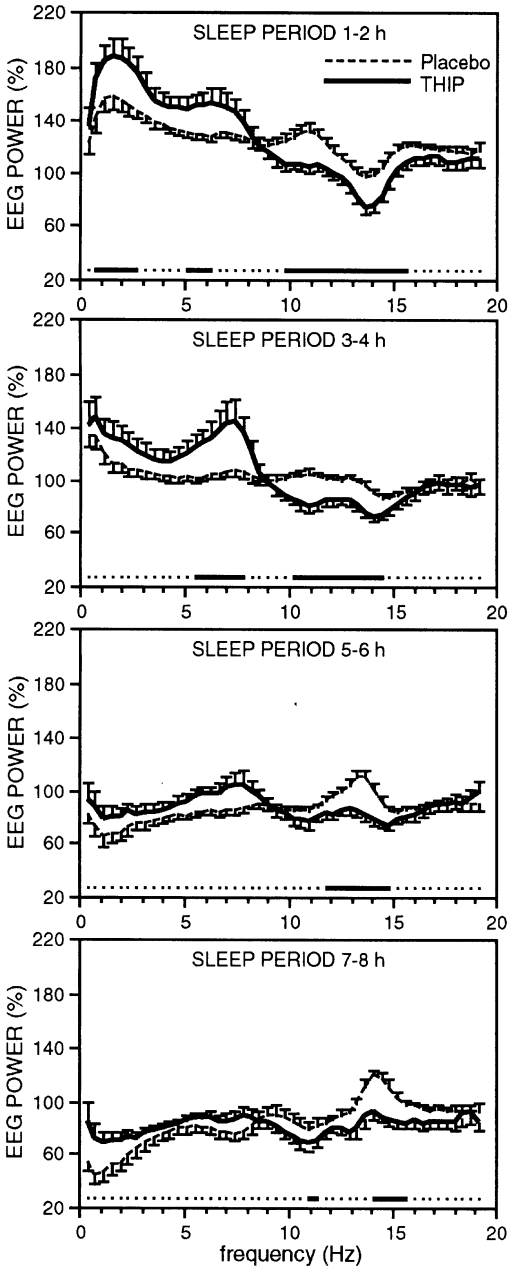

Fig. 4 Average power in the frequencies between 0.39 and 19.14 Hz (0.39 Hz bins) during NREM sleep (stages 2, 3 and 4) per 2-h interval after administration of placebo and THIP. Values are means ± SEM ($n = 10$). For each subject the data were expressed as percentage of the average power in the same frequency band in NREM sleep during the entire placebo night. The frequency bands in which power differed significantly between the treatments are indicated by bars at the bottom of the graphs ($P < 0.05$, two-sided, paired t-test)

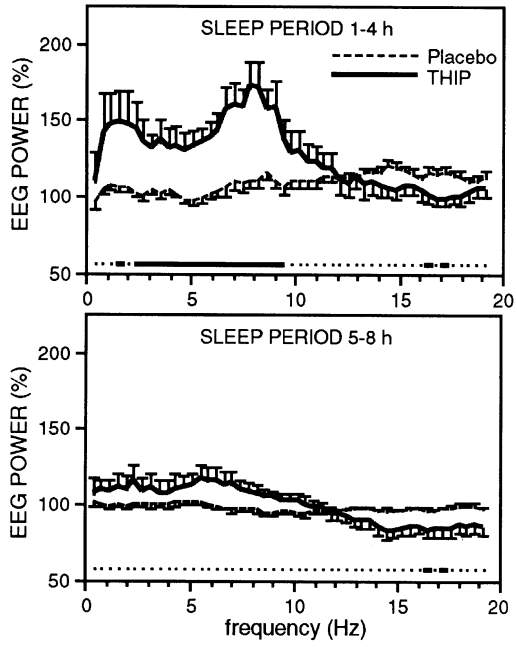

Fig. 5 Average power in the frequencies between 0.39 and 19.14 Hz during REM sleep per 4-h interval after administration of placebo and THIP. Values are means ± SEM ($n = 10$). The data of each subject were expressed as percentage of the average power in the same frequency band in REM sleep over the entire placebo night. The frequency bands in which power differed significantly between the treatments are indicated by bars at the bottom of the graphs ($P < 0.05$, two-sided, paired t-test)

influences sleep in humans. Although the young subjects typically exhibited high quality sleep, THIP increased sleep efficiency, prominently promoted the deep NREM sleep stages and enhanced SWA during NREM sleep.

The amount of the vigilance states, the time course of sleep stage-specific EEG power as well as the intraepisodic dynamics of SWA and sigma activity obtained for the placebo night are in good agreement with the literature (Borbély et al. 1981; Dijk et al. 1990, 1993; Aeschbach et al. 1993; Dijk and Czeisler 1993). None of the subjects reported side effects of THIP. This is in accordance with previous studies in which comparable doses of THIP administered during the day time mainly induced sleepiness (Hoehn-Saric 1983; Peyron et al. 1994). Albeit THIP is rapidly absorbed (Schultz et al. 1981), it did not reduce sleep latency (Table 1). This is consistent with earlier reports on systemically administered $GABA_A$agonists in the rat (Mendelson and Martin 1990; Lancel and Faulhaber 1996; Lancel et al. 1996) and supports the notion that $GABA_A$ agonists do not affect the generation of NREM sleep. THIP significantly increased the time spent in SWS by $\approx$25 min (Table 1, Fig. 1) and elevated low-frequency EEG activity in NREM sleep (Figs. 2 and 4). These results are in accordance with the earlier observed THIP- and muscimol-induced enhancement of SWA during NREM sleep in the rat (Lancel and Faulhaber 1996; Lancel et al. 1996). Since awakening thresholds reportedly vary in parallel with SWA (Blake and Gerard 1937; Grahnstedt and Ursin 1980; Neckelmann and Ursin 1993), these data may indicate that $GABA_A$ agonist increase the intensity of NREM sleep. Analysis of the intraepisodic dynamics of SWA showed that the enhancement of SWA was

associated with a slight increase in build-up rate during NREM episode 1 and with an increase in maximal levels attained in the course of NREM episodes 1, 2 and 3 (Fig. 3). THIP persistently reduced power in the sigma frequencies (Fig. 2), most prominently around 13–14 Hz (Fig. 4), which suggests a decrease in spindle activity. Analysis on a smaller time scale revealed a general NREM sleep-specific decrease of sigma activity, especially during episode 2 and 3 (Fig. 3). THIP and muscimol had minimal effects on sigma activity in the rat (Lancel and Faulhaber 1996; Lancel et al. 1996). This contradiction may be explained by high non-spindle background activity in epidural cortical EEG recordings in this species. The present data are in accordance with the reciprocal relation between overall SWA and spindle frequency activity previously observed in the human cortical EEG (Aeschbach and Borbély 1993; Dijk et al. 1993). Electrophysiological experiments on thalamocortical neurons in the cat revealed that spindle oscillations occur near the resting membrane potential (V_m), while slow wave oscillations are generated at a V_m more negative (for review, see Steriade et al. 1993). Thus, the effects of $GABA_A$ agonists on NREM sleep may be mediated by a hyperpolarization of thalamic neurons. THIP did neither affect the latency nor the total amount and time course of REM sleep (Table 1, Fig. 1). This is an intriguing finding, since other substances known to enhance SWS and/or SWA, such as the 5-HT_2 antagonists ritanserin (for references, see Borbély et al. 1988) and seganserin (for references, see Dijk et al. 1989), glucocorticoids (for review, see Friess et al. 1995) and adenosine agonists (Benington et al. 1995), all inhibit REM sleep. THIP did influence the EEG activity within this state: EEG power in the lower frequencies (<10 Hz) was significantly enhanced during the first 4-h interval (Fig. 5). It is at present unclear whether these changes are REM sleep-specific or due to spill over from or intrusion of NREM sleep.

The $GABA_A$ receptor complex forms a transmembrane ligand-gated anion channel and contains recognition sites for GABA and various modulatory binding sites such as the benzodiazepine receptor. Upon activation by GABA or GABA analogues the membrane permeability for anions, mainly chloride, increases, which usually results in a slight, short lasting hyperpolarization. The most frequently used hypnotics, the benzodiazepines, zolpidem and zopiclone, are agonistic modulators of $GABA_A$ receptors. By binding to the benzodiazepine receptor, these compounds allosterically increase the efficacy of GABA to open the $GABA_A$-associated chloride channels (for review, see Sieghart 1995). It is therefore generally assumed that these agonistic modulators have similar effects as agonists of $GABA_A$ receptors. It is well established that both benzodiazepines, zolpidem and zopiclone, tend to shorten sleep latency, promote stage 2 and suppress SWS and REM sleep (Gaillard et al. 1973; Johnson et al. 1976; Borbély et al. 1985; Dijk et al. 1989; Trachsel et al. 1990; Brunner et al. 1991; Kim et al. 1993). The studies in which a spectral analysis of the EEG was made showed that these substances consistently decrease low-frequency (<10 Hz) EEG activity during NREM and REM sleep and enhance activity in the spindle frequency range during NREM sleep (Borbély et al. 1985; Dijk et al. 1989; Trachsel et al. 1990; Brunner et al. 1991; Kim et al. 1993). The present data substantiate the information from previous studies in the rat (Lancel and Faulhaber 1996; Lancel et al. 1996), indicating that agonists and agonistic modulators of $GABA_A$ receptors have opposing effects on sleep. This may be explained by the fact that both THIP and muscimol, in contrast to GABA, are poor substrates for uptake mechanisms. They are therefore likely to produce more tonic hyperpolarizations and thereby affect neuronal electric activity in a different fashion than GABA.

Nevertheless, the sleep effects of THIP in humans are highly similar to the effects elicited by sustained wakefulness. Ample sleep deprivation studies showed that prolonged vigilance tends to reduce sleep latency, markedly promotes SWS and hardly affects REM sleep (Borbély et al. 1981; Dijk and Czeisler 1993). Moreover, sleep deprivation consistently enhances EEG activity in the lower frequencies (<10 Hz), most prominently in the slow wave bands, during both NREM as well as REM sleep and decreases sigma activity/spindle density during NREM sleep (Borbély et al. 1981; Dijk et al. 1990; Dijk and Czeisler 1993). Time course analyses revealed that sleep deprivation increases the rise rate of SWA, mainly during the first NREM sleep episode, and more persistently enhances SWA in the course of NREM sleep episodes (Dijk et al. 1990, 1993). With a longer onset latency, sleep deprivation generally reduces sigma activity within NREM sleep episodes, without affecting its time course (Dijk et al. 1993). Thus, except for the fact that THIP is devoid of a sleep latency reducing effect, the influence of THIP on the time spend in each vigilance stage, on sleep-stage-specific EEG power and even on the temporal development of the changes in power within NREM episodes are reminiscent of the effects of extended wakefulness. These findings are in accordance with previous observations on $GABA_A$ agonists in the rat (Lancel and Faulhaber 1996; Lancel et al. 1996). Taken together, these data indicate that the influence of $GABA_A$ agonists on NREM and REM sleep mimics the effect of a physiological increase in sleep need. This may suggest that $GABA_A$ receptors are implicated in the homeostatic regulation of sleep. However, it remains to be established whether the effects of sleep deprivation are mediated by $GABA_A$ receptors. Nevertheless, $GABA_A$ agonists and other substances that produce a stimulation of the $GABA_A$ receptor-associated GABA binding site may have therapeutic prospects in the

treatment of sleep disorders characterized by frequent awakenings and reduced sleep intensity.

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