Dynamics of Slow-Wave Activity and Spindle Frequency Activity in the Human Sleep EEG: Effect of Midazolam and Zopiclone

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Electroencephalographic slow-wave activity (SWA; power density in the 0.75 to 4.5 Hz band) and spindle frequency activity (SFA; 11.25 to 15.0 Hz) exhibit a typical time course and a distinct mutual relationship during sleep. Because benzodiazepines (BDZ) suppress SWA and enhance SFA, we investigated the effect of two BDZ-receptor agonists on the dynamics of these EEG parameters. A single dose of midazolam (15 mg), zopiclone (7.5 mg), or placebo was administered before bedtime to healthy young men. Although the two drugs reduced SWA and enhanced SFA, their time course across and within sleep cycles as well as their mutual relationship were little affected. The results constitute further evidence that hypnotics acting as BDZ-receptor agonists do not substantially interfere with the homeostatic aspect of sleep regulation.
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KEY WORDS: *Sleep spindles; Slow-wave activity; $GABA_A$-benzodiazepine-receptor complex; Midazolam; Zopiclone; Spectral analysis; Thalamocortical neurons*

Benzodiazepine (BDZ) hypnotics have long been known to suppress slow-wave sleep and to enhance sleep spindles (Gaillard et al. 1973; Johnson et al. 1976; Feinberg et al. 1977; Azumi and Shirakawa 1981). All-night spectral analysis of the sleep EEG made it possible to study the time course of this effect and to specify the frequency bands of the sleep EEG that are affected. Thus, a reduction of slow-wave activity (SWA; spectral power density in the 0.75 to 4.5 Hz range) and an increase of activity in the spindle frequency range (SFA; spectral power density in the 11.25 to 15.0 Hz range) was documented for four BDZ hypnotics (Borbély et al. 1983, 1985; Dijk et al. 1989). These effects are probably mediated by the $GABA_A$–BDZ-receptor complex because they were shown to be induced also by the non-BDZ hypnotics zopiclone (Trachsel et al. 1990) and zolpidem (Brunner et al. 1991), which act as agonists on this receptor complex. However, despite the considerable changes of the sleep EEG, sleep architecture was remarkably little affected. Thus, both the typical declining trend of SWA over consecutive non-rapid-eye-movement sleep (NREMS) episodes and its cyclic occurrence were shown to persist after the intake of BDZ hypnotics (Achermann and Borbély 1987; Borbély and Achermann 1991). Because slow waves have been postulated to represent an indicator of sleep homeostasis (Webb and Agnew 1971; Feinberg 1974; Borbély 1982; Daan et al. 1984), the results suggest that the homeostatic facet of sleep regulation is little affected by BDZ-receptor agonists.

Whereas EEG slow waves have received substantial attention in recent studies of sleep regulation, the

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changes in higher frequency bands have been less investigated. This is the case in particular for the sleep spindles that constitute transient 11 to 15 Hz oscillations in NREMS. The pattern of their occurrence during sleep corresponds to a large extent to the pattern of spectral SFA (Dijk et al. 1993). Both SWA and SFA rise in the beginning of an NREMS episode and decline prior to the transition to REMS (Aeschbach and Borbély 1993). This positive correlation between the two activities reverses to a negative correlation in the middle part of the NREMS episode where SWA exhibits a peak and SFA a trough. This gives rise to a U-shaped time course of SFA that is most prominent in the early NREMS episodes. An inverse relationship between SWA and SFA had been recognized previously (Ambuehl et al. 1978; Shiotsuka et al. 1988, Shirakawa et al. 1988; Uchida et al. 1988, 1991) and is also evident in sleep deprivation records in which SWA was enhanced and SFA suppressed (Borbély et al. 1981; Brunner et al. 1990; Dijk et al. 1990). The more complex relationship of the two EEG parameters within the NREMS episodes has been analyzed in detail only recently (Aeschbach and Borbély 1993; Dijk et al. 1993; Uchida et al. 1994).

The interest in the changes of SWA and SFA has increased as a result of the evidence that the two types of activity may be generated by common thalamocortical mechanisms (for a recent review, see Steriade et al. 1993). These processes at the neuronal level may account for the typical time course of SWA and SFA in the sleep EEG. Agonistic effects on the $GABA_A$-BDZ-receptor are of particular interest because this receptor appears to be involved in the generation of spindle oscillations (Thomson 1988; Von Krosigk et al. 1993) and in the synchronization of slow-wave oscillations in thalamocortical neurons (Soltesz and Crunelli 1992).

We had previously used the data obtained in this experiment to describe the pharmacological effects on the sleep parameters and the global changes of the sleep EEG (Trachsel et al. 1990). The main objective of the present study was to see whether BDZ-receptor agonists alter the dynamics and the mutual relationship of SWA and SFA.

METHODS

Subjects and Procedure

The subject selection procedure and the experimental protocol have been described elsewhere (Trachsel et al. 1990). In brief, sleep was recorded in nine healthy male subjects (mean age 24.8 years, range 20 to 28) during three blocks of 3 nights. Each block consisted of an adaptation night, a baseline night, and an experimental night. All nights were recorded in the completely darkened, sound-attenuated bedrooms of the sleep laboratory. During both adaptation and baseline nights, time in bed was restricted to 2300 to 0700 hours. On the experimental nights, the subjects went to bed at 1900 hours, after intake of either midazolam (15 mg), zopiclone (7.5 mg), or placebo, 15 minutes prior to bedtime. The subjects were instructed to stay in bed for 12 hours and encouraged to sleep as long as possible. Each subject underwent the three treatments at 1-week intervals. A double-blind crossover schedule was used. Baseline data were not included in the analysis presented here.

Drug

The doses administered (midazolam 15 mg, zopiclone 7.5 mg) corresponded to the hypnotic doses recommended by the manufacturers.

Recording and Data Analysis

Sleep was polygraphically recorded and scored for 20-second epochs according to conventional criteria (Rechtschaffen and Kales 1968). The method of all-night spectral analysis of the EEG has been described previously (Borbély et al. 1981; Dijk et al. 1990). The EEG signal (C3/A2 or C4/A1 derivation) was amplified (time constant 0.9 s), low-pass-filtered (25 Hz, 24dB/oct), digitized (128 Hz), and subjected to on-line spectral analysis based on a Fast-Fourier transform routine. Power spectra were computed for consecutive 4-second epochs (rectangular window) providing a frequency resolution of 0.25 Hz. Values of adjacent frequency bins were collapsed into 0.5-Hz bins in the 0.25 to 5.0 Hz range, and into 1-Hz bins in the 5.25 to 25.0 Hz range. Next, the power spectra were averaged for 20-second epochs and matched with the sleep scores.

Non-rapid-eye-movement–rapid-eye-movement sleep cycles were defined by the succession of an NREMS episode of at least 15 minutes duration and a REMS episode of at least 5 minutes duration (Feinberg and Floyd 1979). No minimal criterion for the REMS duration was applied for the completion of the first and last cycle. Non-rapid-eye-movement-sleep episodes were defined as the interval between the first occurrence of stage 2 and the first occurrence of REMS within a cycle. Rapid-eye-movement-sleep episodes were defined as the intervals between two consecutive NREMS episodes or the interval between the last NREMS episode and the final awakening. Consequently, epochs of stage 1 or waking between REMS and stage 2 were included in the REMS episode. These criteria have proved to be appropriate for calculating average all-night dynamics of the human sleep EEG (Aeschbach and Borbély 1993). In 5 of the 27 nights, episodes of prolonged wakefulness (>15 minutes) instead of REMS episodes were used as a criterion for the completion of a cycle, because the usual criterion would

have yielded largely unequal cycle durations. In 3 nights, waking episodes (>5 minutes) preceding REMS were included in the REMS episode.

Statistics

Power density was calculated for consecutive NREMS episodes as well as for equal subdivisions (percentiles) of the episodes. To standardize the values of different individuals, power density was expressed in each frequency band as the percentage of the mean placebo value of all NREMS epochs (i.e., stages 2+3+4) within that band. Dynamics of relative EEG power density within and across NREM-REMS cycles were analyzed with two-way and three-way analyses of variance (ANOVAs) on log transformed values. Post hoc comparisons between placebo and each of the two drug conditions were performed with paired *t*-tests. The relationship between EEG power density values of different frequency bands was analyzed on the basis of Pearson's product-moment correlations.

RESULTS

A detailed description of the sleep parameters has been published previously (Trachsel et al. 1990). Therefore, only the significant differences between midazolam and placebo, and between zopiclone and placebo ($p < .05$, Wilcoxon matched pairs, signed ranks test, two-tailed) are summarized in this paragraph. After midazolam, the sleep episode defined as the interval between the first occurrence of stage 2 (i.e., sleep onset) and the final awakening was prolonged (705.6 ± 3.1 versus 664.6 ± 26.8 [SEM] minutes), sleep latency was reduced (12.0 ± 1.7 versus 47.6 ± 20.2 minutes), the percentage of stage 2 was increased (54.3 ± 1.4 versus 49.9 ± 1.5% of total sleep time) and the percentage of stage 3 reduced (7.5 ± 0.9 versus 9.6 ± 1.3). Zopiclone induced similar changes. However, only the reduction of stage 3 (7.1 ± 1.0 versus 9.6 ± 1.3% of total sleep time) and the enhancement of movement time (3.2 ± 0.5 versus 2.2 ± 0.4% of sleep episode) were significant.

Midazolam and zopiclone affected the EEG power spectra in NREMS in a similar way. The drugs reduced power density in the 0.75 to 10.0 Hz range and enhanced it in the 11.25 to 14.0 Hz band (two-tailed paired *t*-tests, $p < .05$). The reduction of activity in the delta range was largest in the 1.25 to 1.5 Hz bin (midazolam: 33%, zopiclone: 30%). The largest increase was observed in the 12.25 to 13.0 Hz bin (midazolam: 32%, zopiclone: 19%), which is in the frequency range of sleep spindles.

The time course of SWA and SFA in the first six NREM-REMS cycles of the placebo and the midazolam condition is shown in Figure 1. Spindle frequency activity was calculated for a lower (11.25 to 13.0 Hz) and a higher band (13.25 to 15.0 Hz). The dynamics were computed by subdividing each NREMS episode into 20 equal parts (i.e., percentiles) and each REMS episode into five percentiles. Time midpoints of the percentiles were determined on the basis of the median episode durations. In each condition, SWA and SFA showed high values in NREMS and low values in REMS. The reduction of SWA and the enhancement of SFA in NREMS were evident after both drugs. However, the dynamics of EEG activity *within* NREMS episodes were very similar for placebo and the two drugs. Slow-wave activity increased during a large part of an NREMS episode and decreased rapidly prior to the transition to REMS. Spindle frequency activity exhibited a fast increase at the beginning and a steep decline at the end of an NREMS episode. In the middle part, a U-shaped pattern was present in some of the episodes. It was more prominent in the 13.25 to 15.0 Hz than in the 11.25 to 13.0 Hz band and was particularly evident in the early episodes. In each condition, the trough of SFA in the middle part of an NREMS episode coincided with a high level of SWA. These inverse dynamics were even evident in some minor reciprocal fluctuations (see middle part of NREMS episode 1 after placebo and after midazolam). Three-way ANOVAs with factors "condition" (midazolam and placebo or zopiclone and placebo), "NREMS episode" (1 to 6), and "percentile" (1 to 20) confirmed the robustness of the EEG dynamics in NREMS episodes against the drug action. Slow-wave activity and activity in the two spindle frequency bands were significantly affected by each of the two drugs (factor "condition" $p < .0001$ and interaction "condition" × "episode" $p < .001$ in all cases). By contrast, no significant effect on the *intraepisodic* dynamics of SWA and 13.25 to 15.0 Hz activity was obtained (interaction "condition" × "percentile" NS). The only significant effect was present in the 11.25 to 13.0 Hz band for midazolam ("condition" × "percentile" $p < .05$). However, also in this band the drug primarily enhanced the *level of activity*, whereas the intraepisodic time course was similar to placebo.

The analysis of the first 30 minutes after sleep onset disclosed a similar evolution of SWA for all three treatment conditions (Figure 2). A two-way ANOVA with factors "condition" (placebo, midazolam, zopiclone) and "2-minute interval" (1 to 16) yielded no significant effects of "condition" and "condition" × "2-minute interval" (see legend of Figure 2 for *F* values). In contrast, both drugs enhanced the level of SFA, midazolam being more effective than zopiclone. Nevertheless, the time course of SFA was very similar for the three conditions ("condition" × "2-minute interval," NS). Spindle frequency activity exhibited a peak 6 to 9 minutes after sleep onset, and the time of peak as determined by a 7-point moving average of the original

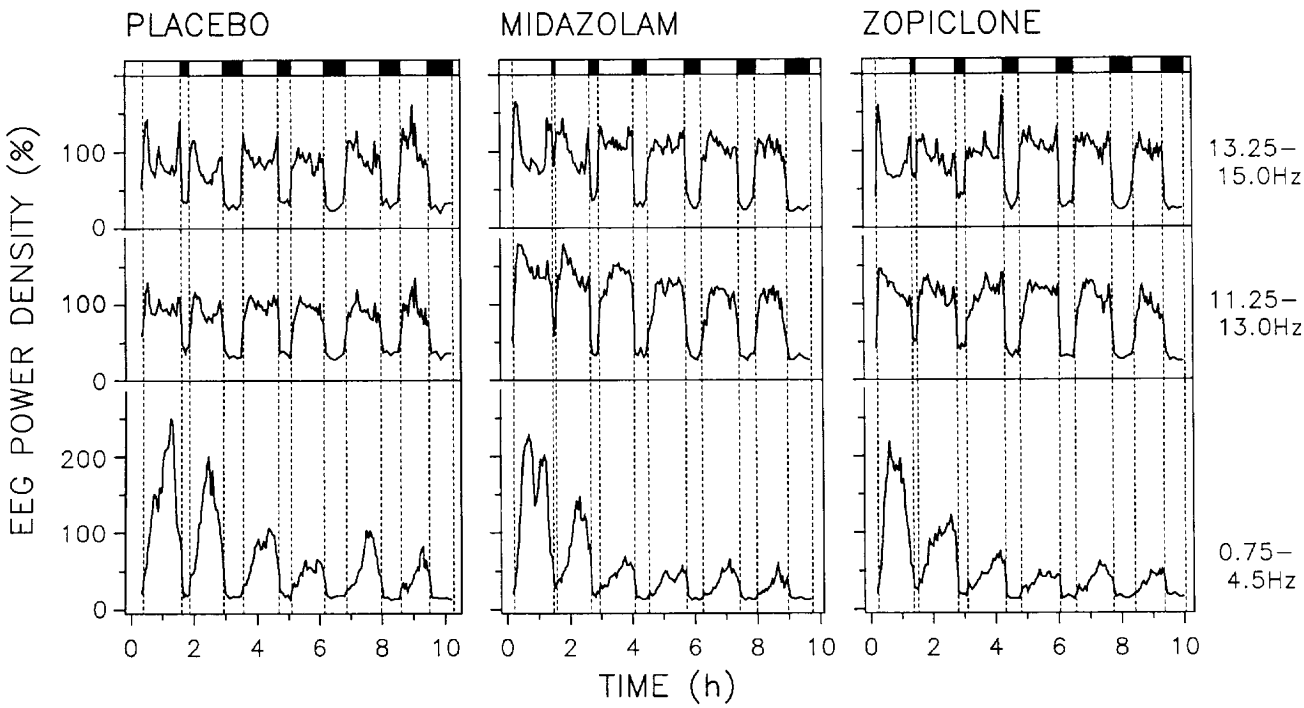

Figure 1. Dynamics of EEG power density in the 0.75 to 4.5 Hz band (SWA) and in two bands in the spindle frequency range plotted for the first six NREM-REMS cycles. NREMS episodes were subdivided into 20 equal parts (percentiles), REMS episodes into five percentiles. The interval between lights off and sleep onset was also subdivided into five percentiles but only the fifth percentile is shown. Dashed vertical lines and top horizontal bars delimit REMS episodes. Power density values per percentile were calculated after excluding 20-second epochs of waking and movement time. For each frequency band and night, values per percentile are expressed as a percentage of the mean value in NREMS of the placebo night (100%). Log transformed values were averaged across subjects and retransformed for plotting. Placebo: NREMS episode 1-4, $n = 9$; episode 5, $n = 8$; episode 6, $n = 7$; midazolam, zopiclone: episode 1-5, $n = 9$, episode 6, $n = 8$. Time 0 corresponds to lights off.

20-second data did not differ between conditions (one-way ANOVA for repeated measures). Thus, the concomitant increase of SWA and SFA in the first minutes of NREMS and the subsequent dissociation (i.e., the persisting rise of SWA and the decline of SFA) were preserved.

To document the global time course, SWA as well as power density within 1-Hz bins in the 10.25 to

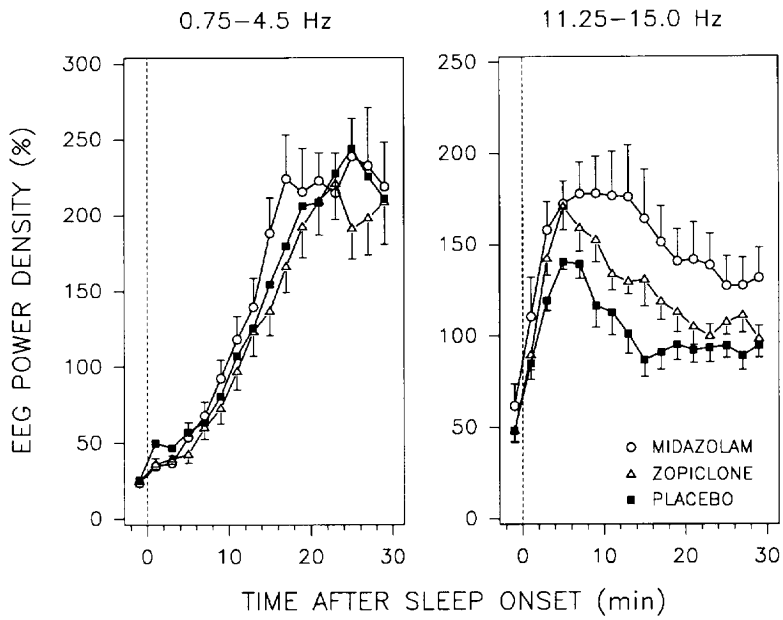

Figure 2. Evolution of SWA (0.75 to 4.5 Hz) and SFA (11.25 to 15.0 Hz) prior to and in the first 30 minutes of the first NREMS episode. The data are expressed as a percentage of the mean power density in NREMS of the placebo night. Mean values ± SEM ($n = 9$) are plotted for consecutive 2-minute intervals. To avoid a superposition of the bars, SEMs of SWA are not plotted for the placebo condition. Results of the ANOVAs on log transformed values: SWA: "condition" $F_{2,384} = 2.4$, NS; "interval" $F_{15,384} = 74.0$, $p < .0001$; "condition" × "interval" $F_{30,384} = 0.53$, NS. SFA: "condition" $F_{2,384} = 40.7$, $p < .0001$; "interval" $F_{15,384} = 20.0$, $p < .0001$; "condition" × "interval" $F_{30,384} = 0.57$, NS.

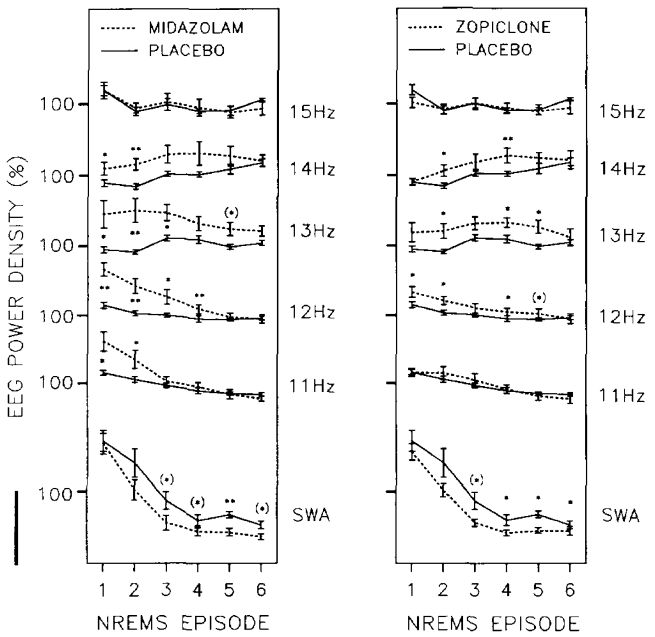

Figure 3. SWA and EEG power density within 1-Hz bins in the 10.25 to 15.0 Hz range are plotted for the first six NREMS episodes. 1-Hz bins are indicated at their upper limits (e.g., 15 Hz represents 14.25 to 15.0 Hz). For each frequency band and night, the values are expressed as a percentage of the mean value in NREMS of the placebo night. Bars represent ± 1 SEM. Tick marks on the left indicate the 100%-level for each pair of curves. Vertical bar at the bottom left corresponds to 100%. Significant differences between drug and placebo are indicated by ** $p < .01$; * $p < .05$; (*) $p < .09$ (two-tailed paired *t*-tests on log transformed percentage values; placebo: episode 1–4, $n = 9$, episode 5, $n = 8$; episode 6, $n = 7$; midazolam, zopiclone: episode 1–5, $n = 9$; episode 6, $n = 8$). For each frequency band, *t*-tests were only calculated if the factor "condition" in a two-way ANOVA (factors "condition" and "NREMS episode") was significant ($p < 0.05$).

15.0 Hz range were averaged for consecutive NREMS episodes (Figure 3). In all conditions, SWA declined over the first three to four episodes. Both drugs reduced SWA mainly in the second part of the night. The manifestation of the drug effect changes as one ascends the frequency scale. In the frequencies between 11.25 and 14.0 Hz, both drugs enhanced power density. The effect of midazolam was strongest at the beginning of the night and then vanished after two to four episodes. Although the enhancement of SFA by zopiclone was not restricted to the early episodes, it was no longer present in the last episode, at a time when SWA was still depressed. Three-way ANOVAs of the values in the 10.25 to 15.0 Hz range with the factors "frequency" (1-Hz bins), "condition" (midazolam and placebo *or* zopiclone and placebo), and "NREMS episode" (1 to 6) revealed significant main effects and significant two-factor interactions (midazolam: $p < .001$ in all cases; zopiclone: $p < .0002$ for "frequency" and "condition," $p < .01$ for "episode," $p < .0001$ for "frequency" × "condition" and "frequency" × "episode," $p < .03$ for "condition" × "episode").

Because the drug-induced reduction of SWA and the enhancement of SFA did not coincide, the question arose whether on a finer time scale the two activities still fluctuated inversely. To examine the relationship between SWA and activity in the various 1-Hz bins during NREMS, correlation coefficients were computed across percentile values. The analysis was performed separately for the first three and the subsequent three NREMS episodes. A positive correlation coefficient in Figure 4 indicates that the dynamics of SWA and EEG activity in a specific 1-Hz bin were similar. In the placebo condition, SWA showed a significant positive correlation with the activity in the 0.25 to 8.0 Hz range. As indicated by the maximum correlation coefficient, SWA was primarily determined by activity in the 1.25 to 2.0 Hz bin. The correlation coefficients decreased monotonically with increasing frequencies up to 14 Hz. A negative correlation was present in the spindle frequency range. In the second part of the night (NREMS 4 to 6), significant negative correlations were absent. The correlations in both drug conditions were similar to those in the placebo condition. In particular, the negative correlation between SWA and SFA was also present in the first part of the night. In all conditions, the negative correlation was highest in the first NREMS episode and diminished progressively over consecutive NREMS episodes (data not shown). However, differences from placebo were present in the alpha range where a peak appeared in the first part of the night following midazolam and zopiclone. In the midazolam condition, a positive correlation was present up to 12 Hz. Also, in the second part of the night positive correlations in the alpha range were observed for the drugs but not for placebo.

DISCUSSION

The present analysis revealed that the time course of SWA and SFA *across and within* NREMS episodes was similar in the two drug nights and in the placebo night (Figures 1 and 2). Although midazolam and zopiclone depressed SWA and enhanced SFA, they did not induce a major modification of the intraepisodic dynamics. Spindle frequency activity invariably exhibited a rapid increase at the beginning of a NREMS episode, a U-shaped pattern in the middle part of the early episodes, and a rapid decrease prior to REMS. Thus, the concomitant increase of SWA and SFA, their subsequent dissociation, and the concomitant decline prior to REMS were observed in the early NREMS episodes of all experimental conditions. Consequently, the corre-

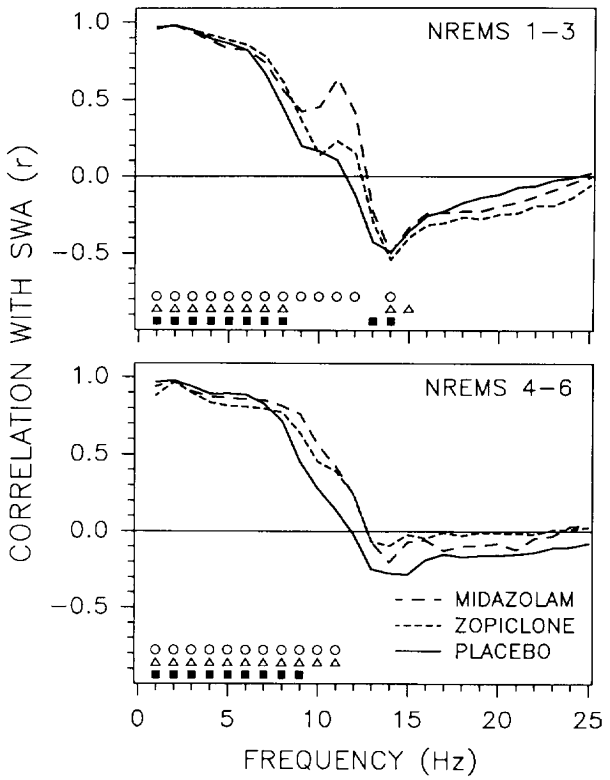

Figure 4. Correlations between SWA and power density values of 1-Hz bins between 0.25 and 25.0 Hz. Correlation coefficients were calculated separately in each night across the first 60 percentiles in NREMS episode 1-3 (*top*) and across the subsequent 60 percentiles in NREMS episode 4-6 (*bottom*). The values were Fisher-Z transformed, averaged over subjects (NREMS episode 1-3, $n = 9$; NREMS episode 4-6, placebo, $n = 7$; midazolam, zopiclone, $n = 8$) and retransformed for plotting. The values are plotted at the upper limit of the frequency bins. Correlation coefficients differing significantly from 0 are indicated by open circles for midazolam, by open triangles for zopiclone, and by filled squares for placebo ($p < .05$; two-tailed Dunnett's t-tests on Fisher-Z transformed values.

lations of SWA to the other frequency bands were similar for drug and placebo nights (Figure 4). In particular, the negative correlation between SWA and SFA in the early NREMS episodes was preserved.

The dissociation between SWA and SFA in the middle part of the initial NREMS episodes that was also observed in EEG recordings from the central lateral thalamus of the cat (Lancel et al. 1992) is consistent with the notion that the establishment of NREMS is associated with a progressive hyperpolarization of thalamocortical neurons (Steriade et al. 1991). According to this view, a gradually increasing number of neurons switches from a spindle mode to a slow oscillatory mode. A reversal of this process could account for the changes in the EEG prior to the transition to REMS. It had been shown that thalamocortical cells are more hyperpolarized in NREMS than in either REMS or waking (Hirsch et al. 1983). It can be assumed that the dissipation of "sleep pressure" over consecutive NREMS episodes corresponds to a reduction in the degree of hyperpolarization of thalamocortical neurons. Thus, neuronal groups in the spindle mode would increasingly coexist with others in the slow oscillatory mode. This could account for the marked dissociation between SWA and SFA in the early episodes and the lack of a clear dissociation in the later episodes. Whatever processes are responsible for the dissociation between SWA and SFA during NREMS, they appear to be robust against the action of hypnotics that bind to the $GABA_A$-BDZ-receptor complex.

The SWA depressing and SFA enhancing effect of hypnotics are likely to be mediated by the activation of GABAergic processes. Thus, a barbiturate that also binds to the $GABA_A$-BDZ-receptor complex was shown to trigger the GABA-dependent spindle oscillations in thalamocortical cells and to depress spontaneously occuring slow-wave oscillations (Curró Dossi et al. 1992; Nuñez et al. 1992). Supporting the involvement of thalamocortical neurons in the pharmacological action of benzodiazepines and barbiturates, a high $GABA_A$-receptor immunoreactivity was found postsynaptic to afferents from the reticular thalamic nucleus (Soltesz et al. 1990). The latter structure is thought to play a pivotal role in synchronizing spindle oscillations (Steriade and McCarley 1990).

The time course of the drug-induced changes of SWA and SFA differed. The attenuation of SWA became prominent and statistically significant only beyond the second NREMS episode, whereas the increase of SFA was present initially and then subsided (Figure 3). Thus, the drug-induced changes of these two EEG parameters do not represent merely an accentuation of their inverse relationship but reflect their temporal dissociation. It has been noted previously that the changes of SFA or sleep spindles correspond more closely to the pharmacokinetics of BDZ hypnotics than those of SWA (Borbély et al. 1983; Johnson et al. 1983; Gaillard and Blois 1989). The longer lasting increase of SFA after zopiclone than that after midazolam is readily explained by the difference in elimination half life (3.5 to 6 hours [Goa and Heel 1986] versus 2 to 3 hours [Brown et al. 1979]). The more prominent relative decrease of SWA in the later parts of sleep had been reported for various other BDZ hypnotics (Borbély et al. 1985; Borbély and Achermann 1991; Aeschbach et al. 1994). Residual concentrations in the brain and changes in the number and sensitivity of receptors are two possible explanations that will have to be examined.

An unexpected result was the presence of a high correlation between SWA and activity in the 9.25 to 11.0 Hz range for the midazolam condition (Figure 4). A concomitant increase of spectral activity in these two

frequency bands has been observed previously during recovery from sleep deprivation when the largest increase in the first NREMS episode was observed in the delta and alpha bands (Borbély et al. 1981; Dijk et al. 1990). Moreover, a concomitant enhancement of delta and alpha activity was induced by ethanol (Dijk et al. 1992). Thus, three different experimental manipulations—sleep deprivation, administration of a BDZ-receptor agonist, and the intake of ethanol—affected activity in these two frequency bands in a similar way. The observations suggest a coupling of the processes underlying these EEG components that becomes more evident upon some experimental manipulations.

In conclusion, the present study demonstrated that despite the attenuation of SWA and the enhancement of SFA by midazolam and zopiclone, their characteristic features and mutual relationship were maintained. The results provide further support for the notion that hypnotics belonging to the class of BDZ-receptor agonists do not interfere seriously with the processes underlying the homeostatic aspect of sleep regulation.

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