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Effects of seganserin, a 5-HT₂ antagonist, and temazepam on human sleep stages and EEG power spectra

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The effects of seganserin, a specific 5HT₂ antagonist, on human sleep were assessed in two experiments and compared to the effects of temazepam and sleep deprivation. During daytime recovery sleep after sleep deprivation, seganserin did not significantly enhance visually scored slow wave sleep (SWS, stages 3 + 4) or the EEG power density in the delta frequencies. Under these conditions temazepam reduced the power density in the delta and theta frequencies. During nighttime sleep after a nap in the evening, seganserin caused an increase in SWS, a reduction in intermittent wakefulness, and an enhancement of the power density in the delta and theta frequencies during non-rapid eye movement (NREM) sleep. Temazepam induced a reduction in the power density in the delta and theta frequencies. It is concluded that the 5HT₂ antagonist, seganserin, can induce SWS. However, since the spectral results showed that the changes in the sleep EEG were not identical to those induced by sleep deprivation it seems premature to conclude that 5HT₂ receptors are primarily involved in NREM sleep regulation.

Seganserin; 5-HT₂ receptor antagonists; Sleep; EEG (human); Spectral analysis

1. Introduction

The development of specific 5HT₂-receptor antagonists (Leysen et al., 1985) has provided new tools to study the involvement of the serotonergic system in sleep regulation. In man a massive enhancement of stages 3 and 4 of non-rapid eye movement (NREM) sleep after a single dose of ritanserin has been reported (Idzikowski et al., 1986; DeClerck et al., 1987). This effect persisted during two weeks of treatment (Idzikowski et al., 1987). Ritanserin also causes an enhancement of deep NREM sleep (SWS2) in rats (Dugovic and

Wauquier, 1987). Seganserin, a closely related 5HT₂ receptor antagonist, enhances SWS in dogs (Wauquier and Van den Broeck, 1987) and man (Idzikowski, 1989). These data are in accordance with the hypothesis that 5HT₂ receptors are primarily involved in the regulation of SWS (Dugovic and Wauquier, 1987).

In man, SWS can be reliably manipulated by non-pharmacological interventions. Numerous sleep deprivation studies have shown that stages 3 + 4 are enhanced after extended wakefulness (for references see Borbély, 1982) whereas stages 3 + 4 are reduced after a nap in the afternoon (Karacan et al., 1970; Feinberg et al., 1985; Tilley et al., 1987). These data suggest that the amount of stage 3 and 4 NREM sleep is a monotonic function of prior waking and sleep. Spectral analysis of the sleep EEG by means of fast Fourier transformation allows a more detailed description

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of the effects of drugs or of waking and sleeping on the NREM sleep EEG. During NREM sleep, power densities in the delta and theta frequencies increase monotonically as a function of the duration of prior wakefulness (Dijk et al., 1987a) and decrease monotonically during sleep (Borbély et al., 1981). Powers were, however, not affected equally over the mentioned frequency range. In several studies it was shown that power values between 1.25 and 2.0 Hz were most strongly affected whereas power values of the adjacent delta and theta frequencies responded to a lesser extent (Borbély et al., 1981; Dijk et al., 1987a,b; Dijk and Beersma, 1989). In addition, evidence has accumulated that power densities in the frequency range of the sleep spindles are attenuated after extended waking (Borbély et al., 1981; Dijk et al., 1987a; Dijk and Beersma, 1989). If the effects of prior waking and the effects of 5HT₂ antagonists on the NREM sleep EEG have a common underlying mechanism, it could be hypothesized that the effects of 5HT₂ antagonist on sleep EEG power spectra closely resemble those of sleep deprivation. The major aim of the present study was to investigate this possibility. To this end the effects of seganserin on sleep stages and EEG power spectra were assessed during enhanced and reduced sleep pressure. The effects were compared with the effects of manipulations of sleep pressure under placebo conditions as well as after temazepam, a benzodiazepine hypnotic. Benzodiazepine hypnotics are known to affect sleep EEG spectra (Borbély et al., 1985) and therefore the temazepam treatment was expected to provide a suitable set of pharmacological control data.

2. Materials and methods

2.1. Experiment 1: recovery sleep after sleep deprivation

After an adaptation night in the laboratory, baseline night sleep was recorded from 00:00 to 08:00 h. The following evening the subjects came to the laboratory at approximately 22:00 h and stayed awake till 11:00 h the next morning. During this sleep deprivation night (and preceding

and following baseline and recovery sleep), the subjects filled out several mood scale forms and carried out performance tasks during which the EEG was recorded. These data will be presented in a separate paper.

To avoid differences in power densities due to small differences in the placement of the EEG electrodes, these were not removed between baseline night and recovery sleep. Recovery sleep was initiated at 11:00 h. The subjects were instructed to try and sleep their normal quatum of sleep. No watches or clocks were available in the bedroom, which was completely darkened and quiet. After they had decided to rise they could call an experimentator to end the recording. Ten subjects followed this protocol three times. The interval between two consecutive sessions was at least two weeks. The sessions only differed in the pharmacological treatment. Drugs were administered 30 min before the start of recovery sleep.

2.2. Experiment 2: sleep after a nap in the early evening

After an adaptation night, baseline sleep was recorded from 00:00 to 08:00 h. The subjects returned to the laboratory at approximately 17:00 h. They went to bed at 18:00 h for a nap. Sleep duration was designed to be 2 h. If at 21:00 h the subjects had not slept for 2 h they were awakened anyway to prevent the interval between the nap and the subsequent night sleep from becoming too short. The subjects went to bed again at 00:00 h and were instructed to sleep until they felt refreshed. EEG electrodes were not removed between the baseline night and the recovery sleep after the nap. Ten subjects followed this protocol three times. The interval between two consecutive sessions was at least one week. The sessions only differed in the pharmacological treatment. Drugs were administered 30 min before the start of recovery sleep after the nap.

2.3. Drugs

Seganserin (R56413, Janssen Pharmaceutica, N.V.) is a highly specific 5HT₂ antagonist devoid of dopaminergic activity (Kennis et al., 1986). The

plasma half-life is 26.1 ± 12.9 (S.D.) h. After oral administration maximal plasma levels are reached after 1.0 ± 0.5 h (Van de Velde et al., 1986). In the present experiments 10 mg of seganserin was given in capsules. Identical capsules were available as placebo.

Temazepam (Normison[®], Wyeth B.V.) is a benzodiazepine with a plasma half-life of 8.5 ± 1.5 h. After oral administration maximal plasma levels were reached after 0.8 ± 0.6 h (Fuccella, 1979). In the present experiments 20 mg of temazepam was given in soft gelatin capsules. Identical capsules were available as placebo. The order of drug treatment was randomized. Both experiments were double blind, cross-over designs. At each session two capsules were provided. Possible combinations were: (1) placebo-temazepam and placebo-seganserin capsules; this will be called the placebo condition. (2) Placebo-temazepam and seganserin capsules; this is the seganserin condition. (3) Temazepam and placebo-seganserin capsules; this is the temazepam condition.

2.4. Subjects

Twenty males, age range 21-26 years, were selected on the basis of a questionnaire. They all had regular sleep-wake habits and were apparently in good health. During the experiments they refrained from drinking alcohol and were not allowed to do sports. All subjects gave their written informed consent. No subject participated in both experiments.

2.5. Polygraphic recordings and processing

EEG, EMG and EOG signals were preamplified in the bedroom and sent to the computer room by means of telemetry. The EEG was derived from C3-A2 and C4-A1. The EEG, submental EMG, EOG and a time signal were recorded on paper. After low-pass filtering at 30 Hz (24 dB/oct), the EEG signals were digitized with a sampling rate of 128 Hz. The EMG and the time signal were also digitized. Power spectra between 0.25 and 30 Hz were computed off-line per 4 s epochs, on a PDP11/34 computer, by using a DEC laboratory FFT subroutine. The resulting

frequency bin width amounts to 0.25 Hz. The lowest frequency (0.25 Hz) was omitted from the analysis. The power of the 0.5 Hz bin was stored separately. Power values of the 0.75 and 1.0 Hz bin were added. The remaining power spectra were reduced to 1 Hz bins by adding power values of four adjacent frequencies. Bins will be referred to by mentioning their upper limit, so 3 Hz refers to 2.25-3.0 Hz.

The paper recordings were scored per 30 s epochs according to the criteria of Rechtschaffen and Kales (1968). All EEG recordings obtained from an individual subject were scored by one and the same investigator, who was blind to the pharmacological treatment. Visual scores were stored in the computer and synchronized with the temporal series of power spectra. This allowed the calculation of power spectra per NREM sleep (stage 1 included) and REM sleep separately, and the automatic omission of epochs which were scored as wakefulness or movement time.

2.6. Statistics

2.6.1. Sleep stages and related parameters

In both experiments sleep latency, REM latency, stage 0, 1, 2, 3, 4, REM, SWS, movement time and total sleep time (TST) of three baseline nights were compared with Friedmans non-parametric ANOVA for repeated measures. In both experiments the three baseline nights were very similar (out of 22 ANOVAs only one was significant: this concerned sleep latency in experiment 1). Therefore in each experiment the three baseline nights were averaged. Then the four sets of data (baseline, placebo recovery, seganserin recovery and temazepam recovery) were subjected to Friedman's non-parametric ANOVA for repeated measures. If a significant effect of condition was present, significances of differences between conditions were further analyzed by Wilcoxon's matched pairs signed ranks test.

2.6.2. Power spectra

Since the absolute values of the power densities of the higher frequencies are several orders of magnitude lower than those of the lower frequencies and the interindividual variation is consider-

able, absolute values are not very suitable for a visualization of sleep deprivation or drug effects. Therefore power values were expressed relative to power values of the preceding baseline night. Data were log-transformed before being averaged over subjects to avoid effects of the non-gaussian distribution of ratios. Differences between recovery nights and baseline nights were tested with Wilcoxon's matched pairs signed ranks test. For the comparisons of the pharmacological conditions, the power densities were first expressed as a percentage of the power density of the preceding baseline night. The values were then log-transformed. Subsequently, Wilcoxon's matched pairs signed ranks test was used to assess the significance of differences between the pharmacological conditions.

3. Results

3.1. Experiment 1: sleep deprivation

3.1.1. Sleep stages

Parameters obtained by visual scoring of the EEGs and corresponding statistics are summarized in table 1. Placebo recovery sleep showed all the characteristics of drug-free daytime recovery sleep after sleep deprivation. The sleep latency was reduced from 23.6 to 7.2 min. Compared to baseline sleep, TST was significantly shorter. This reduction of sleep duration was mainly at the expense of REM sleep and stage 2 NREM sleep. The amount of stage 3 NREM sleep was not significantly different from that of the baseline but stage 4 NREM sleep was significantly enhanced. When the sleep stages were expressed as a percentage of TST these differences persisted. After seganserin administration TST was not significantly different from the placebo condition. However, the interindividual variation was remarkable: of all daytime recovery sleep periods, both the shortest (71.0 min) and the longest TST (623.0 min) were obtained after seganserin; four subjects woke up and decided to end the registration before they had entered REM sleep. Compared to the placebo condition no significant differences emerged. There was only a tendency for

the percentages of stage 3 NREM sleep and SWS to be higher than in the placebo condition ($P < 0.1$).

Compared to placebo, temazepam caused a further reduction of the sleep latency and an increase in the REM latency. The percentage of stage 4 NREM sleep was significantly lower than in the placebo condition although it still tended to be above the baseline night-sleep levels ($P < 0.1$).

3.1.2. Power spectra

Since the shortest sleep duration was 71 min in the seganserin condition, only the first hour of sleep was used for the comparison of the effects of sleep deprivation and drug treatment on the power spectra. For the three recovery conditions, the power spectra during NREM sleep were expressed for each subject as percentages of the spectra in the first hour of the corresponding baseline sleep. The values were then log-transformed, averaged and retransformed. The resulting values are plotted in fig. 1. In the placebo condition, sleep deprivation resulted in a significant enhancement of the power densities from 0.5 to 11.0 Hz. This increase was most pronounced in the 2 Hz bin. The power

Fig. 1. Effects of sleep deprivation on the EEG power densities during NREM sleep in the first h of recovery sleep. All values are expressed relative to the power densities recorded in the first h of baseline sleep (=100%). Symbols: ■ placebo recovery; ▲ seganserin recovery; ● temazepam recovery. Horizontal lines at the bottom of the figure indicate significant differences between the recovery condition as marked in the margin and baseline ($P < 0.05$; two-sided Wilcoxon matched pairs signed ranks test). $n = 10$ in all cases.

TABLE 1

Sleep stages and related variables of the sleep deprivation experiment. All values are expressed in min except when indicated otherwise. Stages refer to time spent in each stage between the start of sleep (i.e. the first occurrence of stage 2) and the end of sleep; % are percentages of total sleep time (TST). Values in parentheses represent 1 standard deviation. MT = movement time, B = baseline night (average of 3 nights), PR = placebo recovery, SR = seganserin recovery, TR = temazepam recovery; n = 10 in all cases, except for whole night variables of PR where n = 9. The column labelled effect of condition contains probabilities derived from Friedmans non-parametric ANOVA. All other P values were derived from Wilcoxon matched pairs signed ranks test (two-sided). REM latencies were not subjected to ANOVA since in the SR condition REM sleep did not occur in four subjects. Not significant is given by ns.

	B	PR	SR	TR	P <			
					Effect of condition	PR vs. B	SR vs. PR	TR vs. PR
Sleep latency	23.6 (4.8)	7.2 (2.7)	6.7 (1.8)	3.9 (2.4)	0.001	0.001	ns	0.05
REM latency	87.4 (31.9)	83.6 (44.0)	97.4 (53.6)	136.4 (56.1)	—	ns	ns	0.05
Stage 0	2.6 (2.8)	2.1 (4.0)	2.3 (6.8)	0.9 (1.5)	0.05	ns	ns	ns
Stage 1	22.8 (12.3)	11.2 (8.6)	6.9 (10.9)	7.3 (4.5)	0.05	0.01	ns	ns
Stage 2	228.2 (20.9)	122.5 (76.5)	99.9 (82.8)	152.7 (58.6)	0.05	0.01	ns	ns
Stage 3	47.7 (10.0)	41.6 (23.4)	58.1 (39.9)	65.9 (24.2)	ns			
Stage 4	30.5 (17.8)	52.7 (21.9)	49.0 (25.0)	35.8 (31.9)	(0.06)	0.01	ns	(0.08)
SWS	78.3 (18.5)	94.3 (29.5)	107.0 (54.7)	113.5 (51.9)	ns			
REM	108.2 (21.8)	39.4 (27.3)	36.7 (47.8)	42.5 (23.6)	0.01	0.01	ns	ns
MT	11.5 (4.3)	8.4 (6.4)	4.9 (4.0)	7.4 (5.6)	ns			
TST	437.4 (7.6)	267.5 (130.2)	251.5 (190.2)	304.2 (91.3)	0.05	0.05	ns	ns
Stage 1%	5.2 (2.9)	4.1 (2.2)	2.1 (1.9)	2.3 (1.3)	0.01	ns	ns	0.05
Stage 2%	52.2 (5.2)	43.9 (7.5)	38.1 (10.3)	49.0 (10.8)	0.01	0.05	ns	0.05
Stage 3%	10.9 (2.3)	16.0 (7.4)	23.7 (8.9)	23.4 (9.8)	0.01	ns	(0.06)	ns
Stage 4%	6.9 (4.0)	21.9 (10.2)	27.2 (16.8)	12.3 (10.0)	0.01	0.01	ns	0.05
SWS %	17.9 (4.2)	37.9 (8.5)	50.9 (16.0)	38.6 (14.0)	0.001	0.01	(0.08)	ns
REM %	24.7 (4.8)	14.1 (5.0)	8.7 (9.5)	13.0 (5.3)	0.001	0.01	ns	ns

densities in the 14 Hz bin were significantly below baseline levels. The power densities were also significantly enhanced in the three highest frequency bins analyzed (28-30 Hz).

After administration of seganserin, the power densities in the delta and theta frequencies were also significantly enhanced as compared to the baseline night frequencies. However, no signifi-

Fig. 2. Effects of seganserin and temazepam on the NREM sleep EEG power densities during the first h of recovery sleep after sleep deprivation expressed relative to the power spectra recorded in the first h of placebo recovery sleep (=100%). Symbols: Δ seganserin recovery; $\bullet$ temazepam recovery. Horizontal lines at the bottom of the figure indicate significant differences between the recovery condition as marked in the margin and placebo recovery ($P < 0.05$ two-sided Wilcoxon matched pairs signed ranks test). $n = 10$ in all cases.

cant reduction in the 14 Hz bin was observed. From 15 to 25 Hz the power densities were significantly higher than during baseline sleep.

Except for the 0.5 Hz bin, the sleep deprivation-induced enhancements of the power densities in the delta and theta frequencies were blocked by temazepam. In the 7 Hz bin the power densities were even significantly lower than in the first hour of baseline sleep. In the frequencies from 9.25–13.0 Hz the power densities were significantly higher. In the other frequencies no significant changes were observed.

The effects of seganserin and temazepam on the power spectra were evaluated further by comparing the power densities of the drug sleep periods with the placebo recovery sleep periods (fig. 2). With seganserin the power densities in all frequencies were very close to the placebo values. Only in the 14, 15 and 16 Hz bin did the power densities significantly exceed those of the placebo condition. The picture that emerged for temazepam was quite different. Compared to placebo, the power densities in the delta and theta frequencies were significantly suppressed, whereas between 10.25 and 13.0 Hz they significantly exceeded those of the placebo recovery sleep.

3.2. Experiment 2: effects of a nap on subsequent sleep

3.2.1. Sleep stages

In table 2 the TST and the time (min) of SWS obtained in the naps preceding recovery sleep are presented for the three pharmacological conditions. The mean TST was less than 120 min in all three naps. ANOVA revealed no significant differences between naps for either TST or SWS. So, the differences between the pharmacological conditions are unlikely to be caused by differences between the duration or SWS content of the naps.

Placebo sleep after a nap was different from baseline sleep in several respects (see table 3). The latency to stage 2 NREM sleep was almost doubled, whereas the interval between the start of sleep and the first occurrence of REM sleep was reduced. SWS and within SWS, especially stage 4 NREM sleep, were reduced. These changes in SWS were accompanied by opposite changes in REM sleep. The total time spent in REM sleep, REM % and REM sleep in the first 6 h of sleep (6 h being the longest common sleep duration of all recovery sleep periods) were significantly elevated above baseline levels. The sleep latency after the administration of seganserin was not significantly different from the placebo sleep latency but was also not significantly different from baseline sleep. The REM latency was significantly longer than in the placebo condition and was not significantly different from baseline values. In the seganserin condition, whole night stage 4 NREM sleep tended to be somewhat higher (although not significantly; $P < 0.1$) and SWS was significantly higher than in the placebo nights. These effects of seganserin

TABLE 2

Total sleep time and slow wave sleep (in min) in the naps preceding recovery sleep. NP = nap preceding placebo recovery sleep, NS = nap preceding seganserin recovery sleep, NT = nap preceding temazepam recovery sleep. Values in parentheses represent 1 standard deviation; $n = 10$ in all cases.

	NP	NS	NT	Friedman statistic	P
TST	81.2 (44.9)	69.3 (48.2)	88.5 (51.2)	1.28	0.527
SWS	12.6 (13.4)	12.8 (12.4)	19.6 (14.2)	2.12	0.347

TABLE 3

Sleep stages and related variables of baseline nights and the nights after a nap. All values are expressed in min except when indicated otherwise. Stages refer to the time spent in each stage between the start of sleep (i.e. the first occurrence of stage 2) and the end of sleep, % are percentages of total sleep time (TST). Values in parentheses represent 1 standard deviation. MT = movement time, B = baseline night (average of 3 nights), PR = placebo recovery, SR=seganserin recovery, TR = temazepam recovery; n = 10 in all cases. For further details legend of table 1.

	B	PR	SR	TR	P <			
					Effect of condition	PR vs. B	SR vs. PR	TR vs. PR
Sleep latency	34.7 (18.1)	68.8 (48.2)	44.7 (23.7)	21.7 (12.8)	0.001	0.05	ns	0.01
REM latency	89.8 (31.8)	64.7 (21.2)	88.3 (30.9)	93.1 (50.6)	(0.08)	0.05	0.05	(0.08)
Stage 0	14.0 (10.8)	17.8 (13.7)	10.1 (7.0)	25.4 (24.9)	0.05	ns	0.05	ns
Stage 1	32.0 (14.0)	44.9 (19.8)	36.6 (22.3)	57.9 (25.5)	0.01	0.05	ns	ns
Stage 2	238.3 (16.6)	246.3 (45.8)	293.5 (63.0)	290.6 (50.8)	ns			
Stage 3	35.8 (7.5)	28.4 (10.3)	53.6 (30.9)	37.2 (15.4)	ns			
Stage 4	24.2 (9.2)	9.2 (7.7)	16.8 (17.2)	5.5 (8.0)	0.001	0.01	(0.08)	ns
SWS	59.9 (9.4)	37.6 (17.7)	70.3 (41.7)	42.6 (20.5)	0.05	0.05	0.05	ns
REM	91.6 (17.4)	123.6 (19.8)	112.7 (30.6)	131.8 (20.2)	0.01	0.01	ns	ns
MT	9.0 (3.6)	13.3 (7.8)	18.2 (27.1)	14.9 (9.9)	ns			
TST	421.8 (20.6)	452.4 (45.1)	514.0 (94.7)	524.1 (65.6)	0.05	(0.053)	ns	0.05
Stage 1%	7.6 (3.3)	10.0 (4.4)	6.9 (3.7)	10.9 (4.7)	0.05	0.05	0.05	ns
Stage 2%	56.6 (4.1)	54.1 (6.1)	57.6 (10.5)	55.3 (4.9)	ns			
Stage 3%	8.5 (1.6)	6.5 (2.8)	10.3 (5.5)	7.3 (3.6)	ns			
Stage 4%	5.7 (2.2)	2.1 (1.9)	3.2 (3.1)	1.1 (1.5)	0.01	0.01	ns	ns
SWS %	14.2 (2.1)	8.6 (4.6)	13.5 (7.4)	8.4 (4.5)	0.05	0.05	0.05	ns
REM %	21.6 (3.6)	27.3 (3.6)	21.9 (4.2)	25.2 (2.9)	0.01	0.01	0.05	ns

were not due to the somewhat longer TST in the seganserin recovery condition since there was more SWS in the first 6 h of the seganserin recovery nights than in the corresponding interval of the placebo-recovery nights, although the difference was not statistically significant ($P < 0.1$).

REM sleep was also affected by seganserin. Although whole night REM sleep was not significantly below the placebo values, REM % was significantly reduced. Furthermore, there was less REM sleep during the seganserin condition than in the comparable interval of the placebo nights

($P < 0.05$). No significant differences between seganserin and baseline nights were detected for either REM % or REM sleep in the first 6 h of sleep although whole night REM sleep tended to be elevated above baseline levels ($P < 0.1$).

Intermittent wakefulness was significantly reduced in the seganserin condition as compared to the placebo condition. In fact, it was even significantly ($P < 0.05$) reduced when compared to baseline sleep. Compared to the placebo condition, temazepam significantly reduced the interval between lights-off and the first occurrence of stage 2 NREM sleep. In the temazepam condition the sleep latencies were even somewhat shorter than in the baseline nights, although this difference failed to reach statistical significance. No other significant effects on whole night variables were detected except that, compared to the placebo condition, TST was significantly longer in the temazepam condition. When the comparison between the placebo and temazepam nights was restricted to the first 6 h of sleep, temazepam significantly reduced REM sleep ($P < 0.05$) but did not reduce SWS or stage 4 NREM sleep.

Fig. 3. NREM sleep EEG power densities during the first 6 h of sleep after a nap in the early evening. All values are expressed relative to values of the corresponding interval of the preceding baseline night (=100%). Symbols: ■ placebo recovery; ▲ seganserin recovery; ● temazepam recovery. Horizontal lines at the bottom of the figure indicate significant differences between the recovery condition as marked in the margin and baseline ($P < 0.05$; two-sided Wilcoxon matched pairs signed ranks test); temazepam: $n=10$; placebo and seganserin: $n=9$.

Fig. 4. Effects of seganserin and temazepam on the NREM sleep EEG power densities during the first 6 h of sleep after a nap in the early evening. All values are expressed relative to the power densities recorded during the first 6 h of the placebo sleep period (=100%). Symbols: ▲ seganserin recovery; ● temazepam recovery. Horizontal lines at the bottom of the figure indicate significant differences between the recovery condition as marked in the margin and placebo recovery ($P < 0.05$ two-sided Wilcoxon matched pairs signed ranks test); $n=9$ for both seganserin and temazepam.

3.2.2. Power spectra

Since the longest common sleep duration of all conditions was 6 h, the evaluation of the effects of the different treatments was restricted to the first 6 h of sleep. Power densities were dealt with in the same way as in experiment 1.

In fig. 3 the power spectra during NREM sleep in the first 6 h of sleep after a nap in the early evening are expressed relative to the power spectra of the preceding baseline night.

Compared to the baseline night, the power densities from 2.25-4.0 Hz and from 6.25-8.0 Hz were significantly attenuated. No other significant differences between baseline and placebo recovery emerged. The power spectrum during NREM sleep of subjects who had received seganserin was not significantly different from the baseline power spectrum. This effect contrasts with the effect of temazepam. With this drug the power values in the delta and theta frequencies were much lower than in the preceding baseline night. The power values were also significantly attenuated in the 18, 19 and 20 Hz bin.

The effects of seganserin and temazepam on the power spectra during NREM sleep were fur-

Fig. 5. Effects of seganserin and temazepam on the power densities during REM sleep in the first 6 h of sleep after a nap in the early evening. All values are expressed relative to the power densities in REM sleep during the first 6 h of the placebo condition (=100%). Symbols: Δ seganserin recovery; $\bullet$ temazepam recovery. Horizontal lines at the bottom of the figure indicate significant differences between the recovery condition as marked in the margin and placebo recovery ($P < 0.05$ two-sided Wilcoxon matched pairs signed ranks test); $n = 9$ for both seganserin and temazepam.

ther evaluated by comparing the drug nights with the placebo nights (fig. 4). The data were treated in the same way as in experiment 1. Seganserin induced significantly higher power values in the 0.5 Hz bin and in the 7 and 8 Hz bin. Also the power values in the frequency range of 0.75-1.0 and 5.25-6.0 Hz tended to exceed those of the placebo recovery night ($P < 0.1$). With temazepam the power values between 1.25 and 7.0 Hz were lower than under placebo. No significant differences were observed in the remaining frequencies.

In order to investigate whether the drug-induced changes were sleep state dependent, the effects on the power spectra during REM sleep were calculated for the first 6 h of sleep of baseline and recovery nights. During the placebo recovery sleep, only the power density in the 28 Hz bin was significantly higher than the baseline. All other values were very close to 100%. The drug effects are shown in fig. 5. Data for the seganserin and the placebo condition did not differ significantly, but in the temazepam condition the power values from 0.5 to 13 Hz and from 25 to 30 Hz were lower than in the placebo condition.

4. Discussion

The data of the present sleep deprivation study confirm that when recovery sleep after sleep deprivation is initiated in the morning, recovery sleep is only of short duration (Åkerstedt and Gillberg, 1982) and SWS is enhanced (Dijk and Beersma, 1989). These data are in accordance with the hypothesis that EEG slow wave activity is under homeostatic control, and that the duration of sleep is to a large extent determined by the circadian phase during which sleep takes place (Borbély, 1982; Daan et al., 1984). Spectral analysis of the recovery sleep EEG demonstrated the differential response of EEG frequencies to sleep deprivation. In accordance with previous studies (Borbély et al., 1981; Dijk and Beersma, 1989), the power densities in the delta and theta frequencies were enhanced, and within these frequencies the largest increase was present between 1.25 and 2.0 Hz. In contrast, the power densities in the spindle frequencies were reduced. It should be kept in mind that in the study of Borbély et al. (1981) recovery sleep was initiated at 23:00 h, whereas in the present study and in a previous study (Dijk and Beersma, 1989) recovery sleep was initiated at 11:00 h. Obviously, the sleep deprivation-induced changes in the EEG power spectra are a robust phenomenon, and do not depend strongly on the circadian phase.

A nap in the early evening, albeit only of short duration, proved to be a powerful tool to disturb subsequent sleep. In the placebo condition, SWS was significantly reduced and REM sleep enhanced. Furthermore, the sleep latency was almost doubled, and the latency to REM sleep reduced. These data are in accordance with data from previous studies (Karacan et al., 1970; Feinberg et al., 1985; Tilley et al., 1987) although the effects on REM sleep were not statistically significant in all of these studies. This could be due to smaller number of subjects. The effects of a nap on the EEG power spectra during NREM sleep were more or less a mirror image of those induced by sleep deprivation. Also these data support the hypothesis that slow wave activity is determined by homeostatic control mechanisms. The absence of any significant effects on the power spectra

during REM sleep further indicates that reducing sleep pressure to below normal baseline levels leads mainly to changes in the NREM EEG power spectra. It has been reported previously that sleep deprivation increases the delta power density in REM sleep (Borbély et al., 1981; Dijk and Beersma, 1989).

Both seganserin and temazepam modulated, although in opposite directions, the changes in the NREM sleep EEG induced by manipulating sleep and wakefulness. Temazepam reduced the power densities in the delta and theta frequencies and enhanced the power densities in the spindle frequencies. These effects were similar in both experiments and closely resembled the changes in the power spectra induced by other benzodiazepines (Borbély et al., 1985). These findings suggest that sleep pressure and/or circadian phase are of little importance for benzodiazepine-induced changes of the sleep EEG. Furthermore, the data show that although temazepam reduces the power density of the delta and theta frequencies, changes in sleep pressure are still seen in the sleep EEG. The observed attenuations of the power densities in the delta and theta frequencies during REM sleep further indicate that the actions of temazepam on the EEG are to a large extent independent of the sleep state (cf. Borbély et al., 1985).

Seganserin counteracted several of the effects of a nap in the early evening. SWS was no longer below the baseline levels and exceeded values in the placebo condition. The REM latency was longer than in the Placebo condition, and the sleep latency, although not significantly shorter than in the placebo condition, did not exceed the baseline values. Obviously, like other 5HT₂-antagonists (Oswald et al., 1984; Idzikowski et al., 1986; DeClerck et al., 1987; Clarenbach et al., 1988; Idzikowski et al., 1986), seganserin can induce SWS in man. The present results are in agreement with recent experiments (Idzikowski, 1989) in which the effects of seganserin on the sleep EEG were studied under baseline conditions. The reduction of REM sleep duration after the administration of seganserin was not found in studies with ritanserin by Clarenbach et al. (1988) and Idzikowski et al. (1986) although in the latter

study and in the study of DeClerck et al. (1987) REM sleep tended to be suppressed. The effects of seganserin on SWS during recovery sleep after sleep deprivation were less pronounced and only tended to be significant if SWS was expressed as a percentage of total sleep time. The discrepancies between the two experiments can be explained along several lines. Firstly, seganserin could have induced changes in slow wave activity, but these changes went unnoticed during the visual scoring. This explanation is unlikely since spectral analysis of the first hour of sleep also failed to find an enhancement of slow wave activity although effects of seganserin were detected in the higher frequencies. Secondly, it would probably not be possible to elevate slow wave activity above the already very high levels present after sleep deprivation. Thirdly, the slow wave sleep-inducing properties of seganserin may depend on the circadian phase. Dugovic et al. (in press) showed that ritanserin only induced SWS in the rat during its normal rest phase. Finally, the daytime sleep periods may have been too short for seganserin to induce SWS. There is some support for this explanation since in the three subjects who slept longer than 180 min in both the placebo and seganserin condition, SWS was longer after seganserin administration. In contrast to temazepam, the effects of seganserin on the power spectra of the EEG were confined to NREM sleep, indicating that the effects are sleep state dependent.

The present results allow a comparison of the effects of sleep deprivation and seganserin on the NREM EEG power spectra. After a nap, seganserin enhanced the power densities in the delta and theta frequencies in NREM sleep, as did sleep deprivation. However, a comparison of figs. 1 and 4 reveals that sleep deprivation induced, as in other studies (Borbély et al., 1981; Dijk and Beersma, 1989), a unimodal response pattern in this frequency range, with the largest increase in the 1.25-2 Hz bin. This unimodal response pattern was not only present after total sleep deprivation but also after selective SWS deprivation (Dijk et al., 1987; Dijk and Beersma, 1989). In contrast, the response pattern after seganserin administration was bimodal, with peaks at 0.5-1 Hz and at

5.25-8 Hz (fig. 4). The enhancement of the power densities in the two lowest frequency bins must have undoubtedly contributed to the results of scoring. The presence of more SWS is in accordance with the hypothesis that 5HT₂ receptors are involved in the regulation of SWS. However, the different response patterns of the NREM power densities after sleep deprivation and after seganserin show that seganserin does not completely mimic the spectral concomitants of an increased need of NREM sleep. A similar conclusion was reached by Borbély et al. (1988). They compared the ritanserin-induced changes in the sleep EEG power spectra with those induced by sleep deprivation in rats. In view of these findings, some caution is needed in attributing a critical role to 5HT₂ receptors in NREM sleep regulation (Dugovic and Wauquier, 1987).

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