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ORIGINAL INVESTIGATION

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Distinctive effects of modafinil and *d*-amphetamine on the homeostatic and circadian modulation of the human waking EEG

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Abstract *Rationale:* Modafinil is a wake-promoting agent that affects hypothalamic structures involved in the homeostatic and circadian regulation of vigilance. Administered during sleep deprivation, it reduces the need for prolonged recovery sleep and decreases the rebound in EEG slow-wave activity. These diachronic effects suggest an action of modafinil on a homeostatic sleep regulatory process. *Objectives:* The aim of this study was to determine whether modafinil, in comparison to the *d*-amphetamine reference psychostimulant and to placebo, interferes with the vigilance regulatory processes reflected in the EEG during waking. *Methods:* Thirty-three healthy subjects were investigated during 60 h of sustained wakefulness in a double-blind placebo-controlled parallel-design study. A 4-min maintenance-of-wakefulness test administered hourly allowed the concomitant assessment of alertness and waking EEG activity. The effects of equipotent psychostimulant dosages (modafinil 300 mg and *d*-amphetamine 20 mg) were evaluated at the beginning of the first sleep deprivation night, at the end of the second sleep deprivation night and in the afternoon preceding the first recovery night. *Results:* One hour following ingestion, both psychostimulants increased alertness during 10–12 h, independently of the time of administration. At the level of the waking EEG, *d*-amphetamine attenuated the natural circadian rhythm of the different frequency bands and suppressed the sleep deprivation-related increase in low frequency (0.5–7 Hz) powers. In contrast, modafinil, which exhibited a transient amphetamine-like effect, had slight effect on circadian rhythms. Its selective action was characterized by maintenance of the α_1 (8.5–11.5 Hz) EEG power, which under placebo exhibited a homeostatic decrease paralleling that of alertness with a circadian trough at night. *Conclusions:* These findings demonstrate that the alertness-promoting effects of modafinil and *d*-amphetamine involve distinct EEG activities and do not reside on the same vigilance regulatory processes. While *d*-amphetamine inhibits the expression of a sleep-related process, probably through a direct cortical activation masking EEG circadian rhythms, modafinil, through a synchronic effect, preferentially disrupts the homeostatic down-regulation of a waking drive.

Keywords Alertness · Circadian rhythm · Homeostasis · Sleep deprivation · Psychostimulant · Waking EEG

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Introduction

The neuropharmacological mechanism by which modafinil promotes wakefulness is not fully understood, but it differs substantially from the action of amphetamines (Ferraro et al. 1997). Animal studies have shown that modafinil interacts with a wide variety of neurotransmitter and neuropeptide pathways (monoaminergic, glutamatergic, gabaergic, orexinergic) (Tanganelli et al. 1995; Ferraro et al. 1996, 1999; Perez de la Mora et al. 1999; Scammell et al. 2000), while amphetamines act via monoaminergic mechanisms, preferentially stimulating norepinephrine and dopamine release (Nishino et al. 1998). Unlike amphetamines, which act through widespread brain areas, modafinil has a marked regional brain specificity, its targets being mainly localized in hypothalamic structures involved in the regulation of sleep, wakefulness and circadian rhythms (Lin et al. 1996; Berridge et al. 1999; Scammell et al. 2000).

The wake-promoting effect of modafinil has been successfully employed in excessive daytime sleepiness, especially narcolepsy (Bastuji and Jouvet 1988; Besset et al. 1993; Billiard et al. 1994; Laffont et al. 1994; Broughton et al. 1997). In patients with organic brain syndrome, in the elderly and in air force personnel, modafinil was reported to decrease electroencephalographic (EEG) slow-wave activity, indicating an enhancement of alertness (Saletu et al. 1986, 1993b; Caldwell et al. 2000). In healthy sleep-deprived subjects, modafinil improves psychomotor and cognitive performance as well as subjective alertness (Lagarde et al. 1995; Pigeau et al. 1995; Baranski and Pigeau 1997; Wesensten et al. 2002). Compared to amphetamines, modafinil does not produce the subjective feelings related to drug abuse liability (Warot et al. 1993) and has fewer sympathomimetic side effects (Nicholson and Stone 1980; Pigeau et al. 1995; Fry 1998). In addition, our group demonstrated in humans that modafinil, in contrast to *d*-amphetamine, does not disrupt sleep and reduces the duration of recovery sleep following sleep deprivation (Buguet et al. 1995). Similar decreases in sleep rebound have been evidenced in rats (Edgar and Seidel 1997) and in cats (Lin et al. 2000) following prolonged wakefulness, indicating that modafinil has a diachronic, i.e. time-delayed, effect on the homeostatic sleep regulatory component. Taken together, these elements distinguish modafinil as a true nootropic drug with more selective pharmacological profile and psychophysiological properties than that of amphetamines.

The waking EEG being responsive to psychotropic drugs is widely used to evaluate and predict short-term behavioral effects in human subjects (Fink 1978). Proposed as an objective measure of alertness (Akerstedt and Gillberg 1990), waking EEG activity has been shown (Aeschbach et al. 1997) to be influenced by the two main physiological processes regulating sleep propensity across the sleep-wake cycle (Borbély 1982). Signs for homeostatic control of waking have been identified, with EEG power changes in specific frequency bands occurring in proportion to previous sleep-wake duration (Corsi-Cabrera et al. 1992; Cajochen et al. 1995). In addition, endogenous clock-dependent changes in waking EEG activity have been isolated from distinct frequency bands and have been related either to the circadian rhythm of melatonin or to that of body temperature and subjective alertness (Aeschbach et al. 1999; Dumont et al. 1999).

The effects of modafinil on the neurophysiological aspects of waking have never been characterized in healthy volunteers during sleep deprivation. In view of their distinctive psychopharmacological properties, it was postulated that modafinil and *d*-amphetamine, which both enhance vigilance, would affect differently the homeostatic and circadian processes regulating alertness and EEG activity across the sleep-wake cycle. Thus, by comparing the action of modafinil with that of *d*-amphetamine and placebo on the temporal changes in alertness and EEG activity during extended sleep deprivation, we tested whether the two substances may have distinct EEG "signatures". For this purpose, a short iterative alertness test adapted from the maintenance-of-wakefulness test (MWT; Mitler et al. 1982) was administered hourly to healthy human subjects during 60 h of sustained wakefulness with concomitant and standardized quantitative waking EEG measurements.

Materials and methods

The general protocol of the investigation has been extensively described in two previously published papers (Buguet et al. 1995; Pigeau et al. 1995).

Subjects

Forty-one Canadian Forces reservists (19–47 years old, 39 males and two females) volunteered for the study. They were selected after medical screening and did not suffer from any acute nor chronic pathology or sleep-wake cycle disturbance and were not on any medication or drugs for the 3 weeks prior to the study. The subjects were instructed on the experimental protocol, which had been approved by the Defence and Civil Institute of Environmental Medicine (DCIEM) ethics committee and Health and Welfare Canada, and gave informed written consent to take part in the study. They were required to remove their watches, no time cues being available throughout the investigation. The data from one female subject were discarded because she developed influenza, and those of seven other subjects were discarded due to technical problems (recording failure or insufficient signal quality for quantitative analysis).

Protocol

Each subject underwent a 6-day study composed of a 2-day and 1-night adaptation, followed by 1 control night, 64 h of sustained wakefulness and 2 recovery nights and days (Fig. 1). Based on their regular sleep schedules, the subjects were allowed 8 h of sleep between 2200 and 0600 hours during the adaptation and control nights and the second recovery night. On the first recovery night following sleep deprivation, lights were turned off at 2200 hours and the subjects were instructed to rise after having met their own sleep need, with a maximum allowance of 13 h in bed. During the 64 h of sustained wakefulness, the subjects worked continuously in 105-min sessions devoted to cognitive tasks and subjective questionnaires with 15-min breaks devoted to experimental and individual needs. During the experiment, the subjects lived in a windowless facility with individual dimly lit (<100 lux) rooms, the ambient temperature being maintained at approximately 24°C by central air conditioning. Because only 6 individual rooms were available, the experiment was performed in seven sessions of five to six subjects. In order to avoid any seasonal effect, the entire experiment took place during winter in Toronto, Canada.

Drug administration

The experimental design corresponded to a double-blind placebo-controlled parallel-design study involving three groups of different subjects. Drug administration was randomized and consisted of either a placebo (P) pill, 300 mg modafinil (M) or 20 mg *d*-amphetamine (A); individuals in each group always receiving the same drug. As shown in Fig. 1, drugs were administered thrice during sustained wakefulness: during the first night at 2330 hours on day 1 (D1), to determine whether the psychostimulants would prevent the anticipated decline in vigilance; during the second night at 0530 hours on day 3 (D3), to test whether the stimulants would restore vigilance; and at 1530 hours on D3, to determine their effect

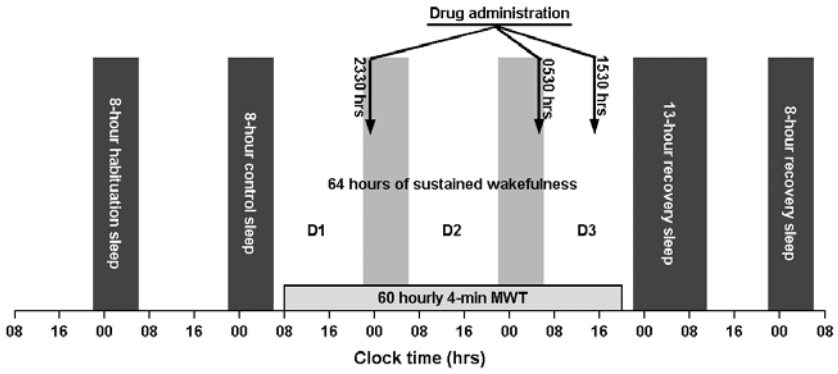

Fig. 1 General design of the experiment: sustained wakefulness with continuous mental work was maintained during 64 h following a habituation period and a control night. Sixty hourly 4-min maintenance-of-wakefulness tests (*MWT*) were administered from D1 at 0800 hours to D3 at 1900 hours. During the first recovery night, the subjects were allowed to stay in bed for 13 h. The *arrows* indicate the time at which the drug administration took place. "Subjective" nights occurring between 2200 and 0600 hours are *shaded in light gray*

on subsequent recovery sleep. Drug dosages were considered as reasonably equipotent (Buguet et al. 1995; Baranski and Pigeau 1997). No major medical side effects were assessed through the measurement of blood pressure, pulse and self-administered questionnaires.

Continuous polygraphic recordings and iterative alertness test

Polygraphic recordings were taken continuously throughout control and recovery nights and the 64 h of sustained wakefulness. Analog signals were recorded with Oxford Medilog 9000 II (Oxford Instruments, Abington, UK) ambulatory recorders. Monopolar EEGs were taken with Ag/AgCl cup electrodes fixed on the scalp with collodion at the standard bilateral central (C_3 and C_4) and parietal (P_3 and P_4) sites (American Electroencephalographic Society 1991), each electrode being referenced to the linked mastoid apophyses (A_{1-2}). These sites on the scalp were selected for the purpose of a standard and objective assessment of vigilance states. One diagonal electro-oculogram (EOG) and one chin electromyogram (EMG) were also recorded for artifact control. The electrodes were checked regularly and replaced when necessary.

To assess alertness, an iterative 4-min MWT was administered hourly throughout the first 60 h of sustained wakefulness (Fig. 1). During each testing sequence, the subjects, comfortably seated in an armchair, were required to relax keeping their eyes closed, staying awake and resisting sleep. They were instructed to start each sequence from their desk video display terminal using a computerized delivery system and were observed through a closed-circuit television network for compliance. Testing sequences ended automatically after 4 min, a duration that was chosen because sleep bouts occurring during this time lapse are not long enough to interfere with the sleep deprivation procedure (Angus et al. 1992).

Standardized waking EEG and iterative alertness test analyses

Polygraphic recordings were digitized with a 12-bit A-D converter at a sampling frequency of 128 Hz using the Oxford Vision® software, and stored on compact disks. The traces were inspected by one expert (A.B.) and did not demonstrate any abnormal or pathologic pattern. The MWT traces were visually scored on a 21" PC screen using the PRANA© software package (PhiTools, Strasbourg, France). Sleep-wake stage scoring, blind as to subject and drug group, was performed in 20-s epochs following classical criteria (Rechtschaffen and Kales 1968). Sleep latency, i.e. the time elapsed from the start of the task to sleep onset, was calculated hourly for each MWT sequence. Sleep onset was defined as the onset of three consecutive epochs of stage I or of one epoch of any deeper sleep stage. If the subject did not fall asleep during the test, sleep onset was ceiled to the 4-min duration of the MWT.

Quantitative EEG analyses of the iterative MWT were also performed with the PRANA© software. Artifacts such as eye blinks, movements and electrode detachments were detected by a method derived from Brunner et al. (1996), which combines digital filtering and background-dependent amplitude thresholds. Automatically detected artifacts were subsequently checked and manually corrected by one expert (F.Ch.) when this was necessary. An EEG power spectral analysis was performed using a Fast Fourier Transform algorithm (Cooley and Tuckey 1965) on 2-s windows yielding a 0.5-Hz spectral frequency resolution. The use of absolute powers (μV^2), which best reflect the activity of EEG generators (Pivik et al. 1993), was chosen for the analysis. A mean estimate of the waking EEG power spectrum was computed for each hourly MWT sequence by averaging the 2-s artifact-free spectra preceding sleep onset. Subject's data were discarded when artifacts represented more than 25% of at least one MWT sequence. Data using the C_3-A_{1-2} derivation happened to be least disturbed and were solely considered in the present study. Incidentally, the resulting experimental groups were composed of 11 subjects for each type of drug administration. To assess the pattern of temporal changes in waking EEG activity, the individual 0.5–30 Hz power spectra were reduced into broad frequency band powers by summing up powers in the adjacent 0.5-Hz frequency bins that belongs to the corresponding frequency band, the upper frequency bin being excluded.

Statistical analysis

Statistical analyses were implemented and performed using the MATLAB© 6.1 statistical toolbox (The MathWorks, Sèvres, France). Before any analysis, all individual 60-sample time series were linearly interpolated to yield strictly regular intervals and then smoothed with a triangular moving average of three samples. To remove the important inter-individual variability in EEG spectral parameters, time series were expressed as percent of changes from a subject- and parameter-dependent baseline average. Baseline levels were chosen to correspond to the means of individual values of the considered parameters between 0800 and 1300 hours on D1, i.e. before the occurrence of any sleep deprivation. All results were expressed as mean±SEM calculated from each 11-subject drug group.

Sleep deprivation- and drug-induced changes

Changes in sleep latency across the first 60 h of sustained wakefulness and between the three drug groups were compared using non-parametric analyses of variance on the ranks. When significant time-of-day or drug effects were observed, post-hoc comparisons were undertaken. Wilcoxon signed rank tests were performed to compare changes from baseline levels. Differences between drug groups were assessed using non-paired Mann-Whitney *U*-tests.

Time-of-day and drug effects on the percent of changes in EEG powers of each frequency bin and each broad frequency band were tested with a series of two-way ANOVA with one within- and one between-factor. Post-hoc non-paired two-tailed Student's *t*-tests were computed for each time sample to compare the three drug groups, using the Bonferroni correction for multiple comparisons. The assessment of time-of-day effect was done in each drug group by comparing each time sample to its corresponding baseline level average (considered as a constant value of 100%) using a one-sample two-tailed *t*-test. The significance level at which the null hypothesis was rejected was $P<0.05$ for time-of-day effect and, according to the Bonferroni correction, $P<0.025$ for drug effect.

Pattern of temporal changes

The pattern of temporal changes in sleep latency and EEG broad frequency band powers throughout the first 60 h of sustained wakefulness were characterized by tests for linear trend and 24-h cosine modulation. The rate of linear change, whether increasing or decreasing, was determined from the slope of the best-fit line, significance level being determined by a slope *t*-test on the individual data. For the 24-h cosine modulation, the percent of accounted variance (PAV), the amplitude and the acrophase, i.e. the time of the maximum, were assessed by regressing the individual data with a 24-h cosine function. Each individual PAV was determined by squaring the cross-correlation coefficient between the original signal and the fitted function and was considered significant when exceeding the 5% confidence level threshold, i.e. 6.4% with 60 time samples. The 24-h modulation was removed from the original data before determining a linear trend and, reciprocally, the linear trend was removed before determining a 24-h modulation. For both the linear trend and 24-h modulation, the number of significant individual results per group was tested with a binomial *t*-test to yield a group statistics. Non-parametric Kruskal-Wallis ANOVA on the ranks and Mann-Whitney *U*-tests were used to assess drug effects on the rate of linear trend and on the amplitude and acrophase of the 24-h modulation.

Results

Alertness during prolonged wakefulness

For each drug group, the average alertness temporal profile during the 60 h of sustained wakefulness, as revealed by sleep latency during the iterative 4-min MWT, is shown in Fig. 2. During the baseline period, between 0800 and 2300 hours on D1, sleep latency averaged around 220 s and showed a minor but significant mid-afternoon decline in all drug groups. Analysis of the pattern of temporal changes revealed that alertness in the P group followed a combined linear decreasing trend with a rate of −1.44±0.17%/h as well as a 24-h modulation with an acrophase at 2112±0030 hours and an amplitude of 20.3±3.1%, both being significant in all subjects (Table 1).

Although alertness still decreased with the duration of sleep deprivation in the A and M groups, it was increased significantly compared to P 1 h after the drugs were administered without significant difference between the A and M groups. Compared to P, the psychostimulants helped to maintain significantly higher alertness levels during 12 h following the first administration at 2330 hours on D1. The second administration of psychostimulants at 0530 hours on D3 restored alertness,

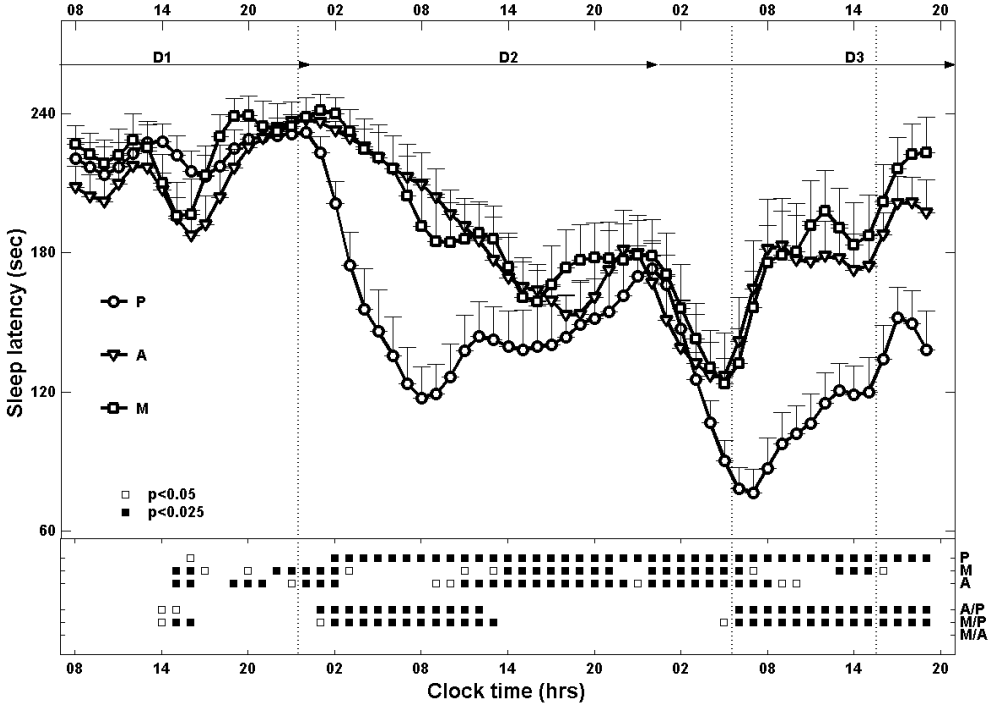

Fig. 2 Average temporal profile (mean±SEM) of the sleep latency obtained from the iterative hourly MWT during 60 h of sustained wakefulness in the placebo (*P*), *d*-amphetamine (*A*) and modafinil (*M*) groups. Significant differences from the baseline level (mean sleep latency between 0800 and 2300 hours on D1; $P<0.05$; Wilcoxon signed rank test) and significant differences between the three drug groups ($P<0.025$; Mann-Whitney *U*-test with Bonferroni correction) are indicated by *squares*. *Vertical dotted lines* represent the time of drug administration

Table 1 Average characteristics (mean±SEM) of the pattern of temporal changes in sleep latency and waking EEG broad frequency band powers during sustained wakefulness in the placebo (*P*), *d*-amphetamine (*A*) and modafinil (*M*) groups. Probability values for drug (*D*), time-of-day (*T*) and interaction (*I*) effects are given (ANOVA). Average changes (%) from baseline levels (D1 between 0800 and 2300 hours) were calculated during the 44 h of effective sleep deprivation (from 0000 hours on D2 to 2000 hours on D3). The average rate of linear change (%/h), the average amplitude (%) and acrophase (h) of the best fitting 24-h cosine modulation were computed during the 60 hours of sustained wakefulness (from 0800 hours on D1 to D3 at 1900 hours)

	ANOVA	Group	Change from baseline (%)	Linear trend		24-h modulation		
				Rate (%/h)	Ss	Amplitude (%)	Acrophase (h)	Ss
Sleep latency	D $P<0.001$	P	61.8±3.8	−1.44±0.17	11*	20.3±3.1	2112±0030	11*
	T $P<0.001$	A	85.9±4.4	−0.60±0.19	8*	8.5±2.1	2236±0148	6
	I $P<0.001$	M	83.7±4.7	−0.57±0.20	8*	8.5±1.6	2100±0118	8*
δ_1: 0.5–3.5 Hz	D $P<0.001$	P	115.5±5.9	0.54±0.16	7	12.1±2.0	1436±0154	8*
	T $P<0.001$	A	100.8±2.8	0.10±0.11	3	10.8±2.7	2006±0206	7
	I $P=0.274$	M	104.7±5.1	0.19±0.13	4	10.7±1.9	1354±0218	8*
δ_2: 3.5–5.5 Hz	D $P<0.001$	P	120.9±5.5	0.46±0.14	6	9.8±1.7	1130±0236	9*
	T $P<0.001$	A	100.5±4.6	0.14±0.13	6	10.5±1.9	1412±0136	9*
	I $P=0.247$	M	108.4±4.7	0.21±0.16	6	10.8±2.1	1412±0036	10*
θ_1: 5.5–7 Hz	D $P<0.001$	P	124.7±4.5	0.40±0.11	7	10.7±2.5	0912±0230	7
	T $P<0.001$	A	93.3±4.5	−0.23±0.13	4	6.7±1.6	1342±0154	6
	I $P<0.001$	M	109.9±6.2	−0.00±0.16	4	10.0±2.4	1518±0112	7
θ_2: 7–8.5 Hz	D $P<0.001$	P	106.9±3.3	−0.05±0.12	3	12.8±1.5	0854±0224	11*
	T $P<0.001$	A	81.8±4.1	−0.71±0.14	9*	8.2±0.7	11.24±0224	9*
	I $P<0.001$	M	103.7±7.4	−0.29±0.20	5	10.9±2.5	1706±0124	8*
α_1: 8.5–11.5 Hz	D $P<0.001$	P	73.2±6.2	−1.15±0.27	9*	14.1±2.6	1624±0206	8*
	T $P<0.001$	A	66.1±3.3	−1.39±0.15	11*	10.9±1.7	1500±0118	8*
	I $P=0.309$	M	89.1±7.3	−0.61±0.22	8*	11.9±2.1	1806±0118	10*
α_2: 11.5–13.5 Hz	D $P<0.001$	P	96.3±4.9	−0.20±0.12	5	15.4±2.1	1654±0148	9*
	T $P<0.001$	A	97.4±4.2	−0.36±0.11	6	9.1±1.0	1736±0154	9*
	I $P=0.998$	M	89.4±5.2	−0.48±0.21	8*	14.4±2.8	1718±0106	10*
β: 13.5–20 Hz	D $P<0.001$	P	99.6±4.7	−0.19±0.14	4	10.4±2.2	2106±0148	8*
	T $P<0.001$	A	91.2±3.4	−0.41±0.15	7	8.8±1.6	0354±0218	7
	I $P=0.999$	M	92.7±4.1	−0.34±0.16	6	10.1±1.3	1730±0148	11*
γ: 20–30 Hz	D $P<0.001$	P	119.5±4.1	0.23±0.14	6	12.9±1.9	0348±0136	9*
	T $P<0.001$	A	107.5±5.4	−0.09±0.19	4	9.8±1.8	0436±0206	7
	I $P=0.877$	M	104.2±3.2	−0.16±0.15	4	9.8±1.4	2206±0206	8*

The number of subjects (*Ss*) among the 11 in each drug group showing a significant linear trend or a 24-h cosine modulation is indicated with an asterisk (*) when it was found to be significant ($P<0.05$; binomial *t*-test)

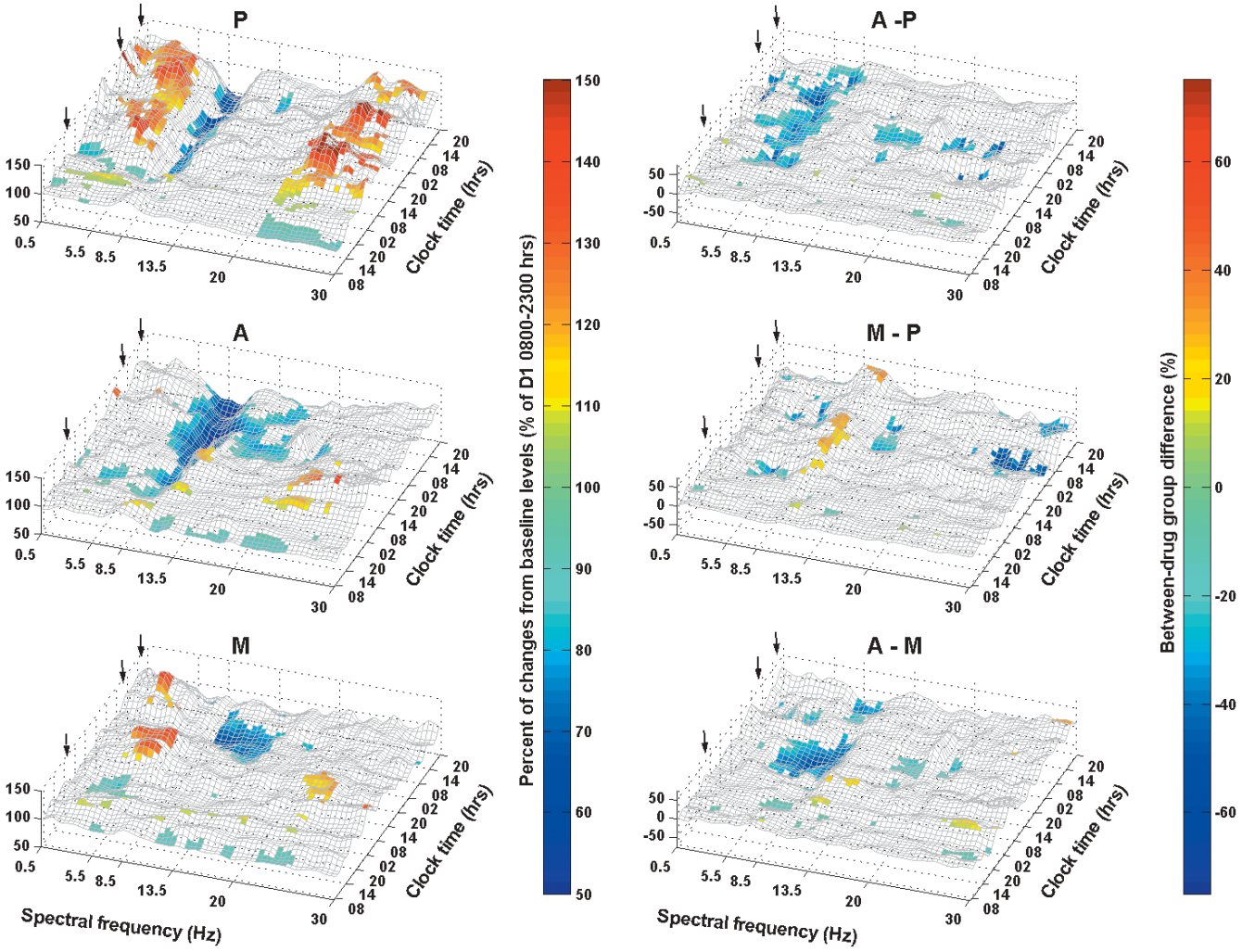

Fig. 3 Average temporal profile (mean±SEM) of the waking EEG power spectrum during 60 h of sustained wakefulness in the placebo (*P*), *d*-amphetamine (*A*) and modafinil (*M*) groups. Waking EEG powers were expressed as relative changes (%) from baseline levels (individual mean of each 0.5-Hz frequency bin power between 0800 and 2300 hours on D1). Differences (%) between *d*-amphetamine and placebo (*A*-*P*), modafinil and placebo (*M*-*P*) and between *d*-amphetamine and modafinil (*A*-*M*) groups are represented in the *right panel*. Only statistically significant changes ($P<0.05$, one-sample *t*-test for time effect; $P<0.025$, non-paired Student's *t*-test with Bonferroni correction for drug effect) are represented with a color code, *warm colors* representing significant increases in EEG power and *cold colors* significant decreases. *Vertical arrows* represent the time of administration of the drugs

sleep latency increasing significantly during the following 10 h, as compared with P. A further increase in alertness lasting until the end of the iterative MWT was observed after the third administration of psychostimulants at 1530 hours on D3. As shown in Fig. 5, the psychostimulants diminished significantly the rate of decrease in sleep latency (from −1.44±0.17%/h in P to −0.60±0.19 and −0.57±0.20%/h in A and M, respectively; all *P* values <0.01) and decreased the 24-h modulation amplitude (from 20.3±3.1% in P to 8.5±2.1 and 8.5±1.6% in A and M, respectively; all *P* values <0.01).

Waking EEG activity during prolonged wakefulness

Baseline

During the first day, before any sleep deprivation had occurred, the average EEG power spectrum of the three drug groups shown in the left panel of Fig. 3 exhibited significant deviations from baseline levels in the lower (0.5–7 Hz) and higher (>21.5 Hz) frequency bins. The lower frequency bin powers were low in the morning, culminated in the afternoon, and then decreased on the evening while the higher frequency bins exhibited increasing powers throughout the first day. Apart from some sparse bins, the three drug groups did not differ significantly during the 16-h baseline period and, as expected, could be considered homogeneous.

Placebo

In the P group during the sleep deprivation phase, the average EEG power spectrum in the upper left of Fig. 3 clearly demonstrates that changes from baseline levels concerned three main frequency bands. The frequency bins over 21.5 Hz increased up to 150% of baseline levels from 2300 hours on D1 to the end of the extended wakefulness phase, except on two instances: in the second afternoon (between 1500 and 1800 hours on D2), and after the second sleep deprivation night (between 0600 and 1200 hours on D3). In the intermediate 8.5–11.5 Hz frequency bins, EEG power decreased continuously from 0100 hours on the first night and reached levels below 50% of baseline levels at the end of the third day of sustained wakefulness. In the low frequency range (0.5–7 Hz), EEG power started to rise around 0400 hours on D2 and remained at higher levels than baseline until the end of sustained wakefulness, peaking at 150%. In this frequency range, the power increase occurred later for the lower frequencies.

d-Amphetamine

The average EEG power spectrum of the A group, as shown in the middle left of Fig. 3, indicated that power in the 8.5–11.5 Hz frequency range decreased even more quickly and deeper than in the P group, reaching 30% of baseline levels at the end of the third day. This effect was also wider in frequency, compared to the P group, extending to lower frequencies down to 6.5 Hz. However, contrary to P, no increase in the lower frequencies did occur. The EEG spectrum difference of the A minus P groups (upper right plot of Fig. 3) demonstrates that, compared to P, the power-decreasing action of A is prominent on a wide range of low to intermediate frequencies from 0.5 to 9.5 Hz. The administration of A at 0530 hours on D3 promoted a new and stronger power decrease in this frequency range. Unlike the power diminution in the 8.5–11.5 Hz frequency range, slight and transient increases (+25%) in the upper 11.5–12.5 Hz frequency bins were observed on D2 between 0600 and 1500 hours in comparison to baseline levels. The power increase in the higher frequency bins over 21.5 Hz observed in the P group was reduced in amplitude (130%) and duration, lasting only 10–11 h after A administration, and was limited to frequency bins between 20 and 24.5 Hz. EEG power also decreased in bins of the 12.5–19 Hz frequency range 17 h after the first administration, this decrease being prolonged after the second A administration.

Modafinil

The decrease in EEG powers of the intermediate 8.5–11.5 Hz frequency bins observed under P was completely absent during the 20 h following the first M administration. After the second M administration, the 8.5–11.5 Hz frequency bin powers stopped decreasing; however, it took 6 h to resume near-baseline levels (Fig. 3, lower left panel). Compared to P (Fig. 3, middle right panel), the power increases (+30%) in the 8.5–11.5 Hz frequency band occurred 2–3 h after the first M administration and lasted 23 h. Following the second administration, this action appeared to be significant only after 9 h, i.e. at the time of the third administration, and lasted until the end of the 60 h of sustained wakefulness. The power increase in the low frequency range (0.5–7 Hz) observed during prolonged wakefulness under P was also observed under M, both in comparison to baseline levels and to the P group. However, a slight and transient (3–6 h) decrease in EEG powers of the 3.5–7.5 Hz frequency bins occurred 1–2 h after the first and second M administrations (Fig. 3, middle right panel). Similar to the P group, power in higher frequencies (20–25 Hz) was increased, although the increase lasted only 14 h after the first M administration.

Pattern of temporal changes in waking EEG activity

According to the observed variations in waking EEG power spectra, the following broad frequency bands were educed: δ_1 (0.5–3.5 Hz), δ_2 (3.5–5.5 Hz), θ_1 (5.5–7 Hz), θ_2 (7–8.5 Hz), α_1 (8.5–11.5 Hz), α_2 (11.5–13.5 Hz), β (13.5–20 Hz) and γ (20–30 Hz). The average time course during the iterative alertness tests of waking EEG power in the educed frequency bands is given in Fig. 4. Statistical analysis of the corresponding data set confirmed the previously described results.

Placebo

As shown in Table 1, the existence of a significant 24-h modulation in waking EEG power of the P group was demonstrated in a majority of subjects for the δ (δ_1 and δ_2), θ_2, α (α_1 and α_2), β and γ frequency bands. The acrophase of the 24-h modulation in EEG power occurred around noon for the δ frequency band (δ_1: 1436±0154 hours and δ_2: 1130±0236 hours), and later in the afternoon for the α frequency band (α_1: 1624±0206 hours and α_2: 1654±0148 hours). The 24-h rhythm in θ_2 EEG activity (acrophase at 0854±0224 hours) occurred in phase opposition to the 24-h oscillation in alertness while the circadian rhythm in β EEG activity (acrophase at 2106±0148 hours) paralleled the circadian evolution of alertness. The circadian oscillation in γ EEG activity exhibited a maximum in the second half of the night with an acrophase at 0348±0136 hours. The existence of a linear tendency was found to be significant only for EEG power in the α_1 frequency band, with a rate of decrease of −1.15±0.27%/h paralleling that of alertness.

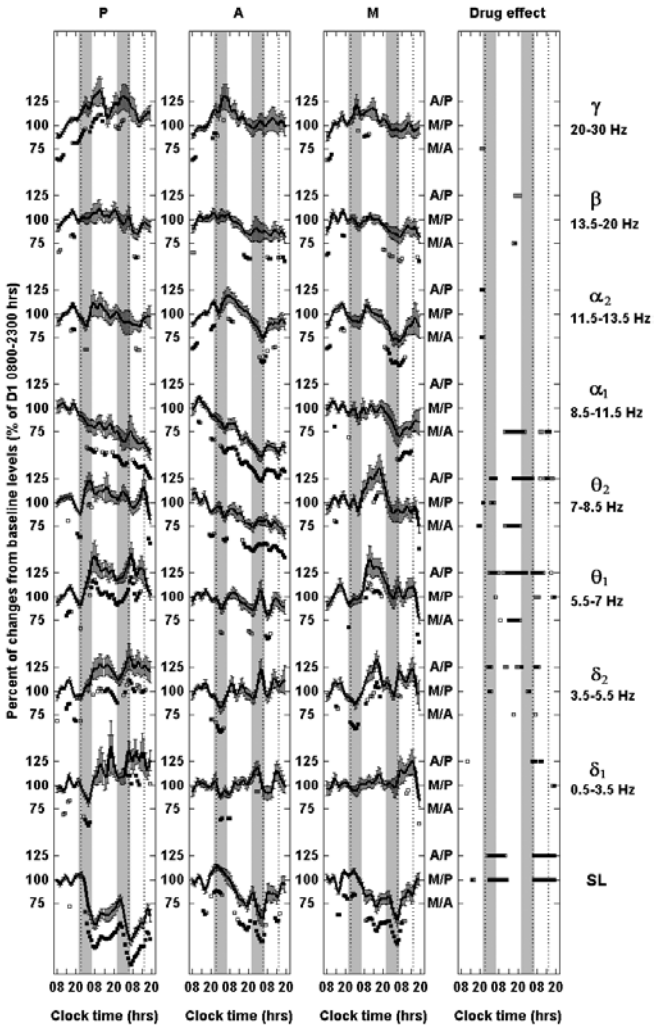

Fig. 4 Average temporal profile (mean±SEM) of the waking EEG broad frequency band powers in regard to sleep latency (*SL*) during 60 h of sustained wakefulness in the placebo (*P*), *d*-amphetamine (*A*) and modafinil (*M*) groups. Each parameter was expressed as relative changes (%) from baseline levels (individual mean of each parameter between 0800 and 2300 hours on D1). For each drug group, significant changes from baseline levels (one-sample *t*-test for EEG powers; Wilcoxon signed rank test for sleep latency) are indicated under each curve by *white* ($P<0.05$) and *black* ($P<0.025$) *squares*. Significant changes between drug groups (non-paired Student's *t*-test with Bonferroni correction for EEG powers; Mann-Whitney *U*-test with Bonferroni correction for sleep latency) are indicated in the right panel by *white* ($P<0.025$) and *black* ($P<0.0125$) *squares*. *Vertical dotted lines* represent the time of drug administration. "Subjective" nights occurring between 2200 and 0600 hours are *shaded in light gray*

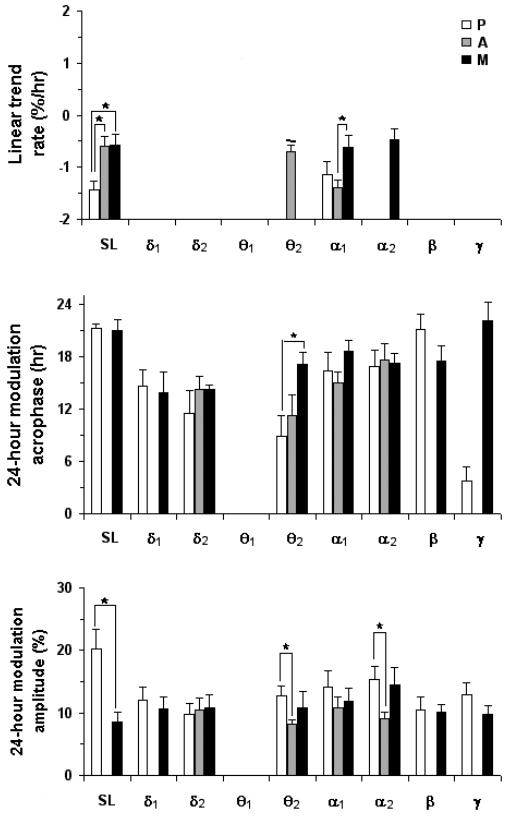

Fig. 5 Average characteristics (mean±SEM) of the pattern of temporal changes in sleep latency (*SL*) and waking EEG broad frequency band powers during 60 h of sustained wakefulness in the placebo (*P*), *d*-amphetamine (*A*) and modafinil (*M*) groups. Linear trend and 24-h modulation were determined individually on data expressed as relative changes (%) from baseline levels (individual mean of each parameter between 0800 and 2300 hours on D1). Only statistically significant patterns over the group of subjects, assessed using the binomial *t*-test, are represented. *Black stars* indicate significant changes between drug groups ($P<0.025$, Mann-Whitney *U*-tests with Bonferroni correction)

d-Amphetamine

In the A group, the rate of decrease in waking EEG power of the α_1 frequency band tended to be lowered from −1.15±0.27%/h in the P group to −1.39±0.15%/h and extended to the θ_2 frequency band with a rate of −0.71±0.14%/h significant in almost every subjects (Table 1). The 24-hour modulations in EEG power of the δ_1, β and γ frequency bands were no longer significant for all subjects. As shown in Fig. 5, the amplitude of the 24-h rhythm in EEG power of the θ_2 and α_2 frequency bands decreased significantly compared with the P group (from 12.8±1.5 to 8.2±0.7% and 15.4±2.1 to 9.1±1%, respectively; all P values <0.05).

Modafinil

In the M group, the rate of linear decrease in waking EEG power of the α_1 frequency band was dampened to −0.61±0.22%/h ($P<0.01$ as compared to the A group). EEG power in the α_2 frequency band exhibited a significant linear decrease in a majority of subjects with an average rate of −0.48±0.21%/h (Table 1). As shown in Fig. 5, the amplitude and acrophase of the 24-h modulations in EEG power of the different broad frequency bands were not significantly affected after the M administration compared to P, except for the θ_2 frequency band whose 24-h rhythm was delayed by approximately 8 h

(acrophase from 0854±0224 to 1706±0124 hours, $P<0.05$).

Discussion

Alertness and waking EEG activity during prolonged wakefulness

The time course of alertness under placebo was similar to that reported previously (Akerstedt and Folkard 1996) and, as anticipated, confirmed Borbély's postulate (Borbély 1982) that sleep propensity reflects both a circadian oscillation and a homeostatic process that depends on the previous sleep-wake duration. In addition to a circadian morning trough around 0900 hours, alertness exhibited a mid-afternoon decrease around 1600 hours, corresponding to the well-known "daytime dip" (Carskadon and Dement 1992).

As previously demonstrated (Corsi-Cabrera et al. 1992), EEG powers in the 0.5–7 Hz low frequency range increased with sleep deprivation, but in contrast with previous findings from shorter 40-h constant routine protocols (Cajochen et al. 1995, 2000, 2001; Aeschbach et al. 1999; Dumont et al. 1999), the δ and θ frequency bands isolated from this 60-h study did not show the monotonic trends, reflecting the homeostatic sleep-wake regulatory process. However, using a 0.5 Hz spectral resolution, our methodology indicated that the increase in low frequency EEG activity occurred later for the lower frequencies. Since low frequencies reflect underlying thalamo-cortical inhibitory processes (Steriade et al. 1990), the progressive EEG slowing is likely to reveal cortical fatigue and the intrusion of a sleep process during waking (Krueger et al. 1999).

In the α_1 frequency band, EEG power decreased linearly with accumulating hours of wakefulness and reached approximately half baseline levels after 60 waking hours. Similar changes in α frequency EEG activity, which decline with drowsiness (Santamaria and Chiappa 1987), have been reported following sleep deprivation (Lorenzo et al. 1995). Discrepancies with previous studies reporting a lack of change (Aeschbach et al. 1999; Dumont et al 1999) arise from the opened- versus closed-eyes differences, the sleep deprivation-related changes in the α band occurring in opposite directions according to the recording situation (Stampi et al. 1993). It is admitted that α EEG activity, generated at cortical and thalamo-cortical levels (Lopes da Silva et al. 1980), represents a salient feature of relaxed waking states (Rechtschaffen and Kales 1968). By exhibiting a rate of decline paralleling that of alertness during prolonged wakefulness, the present study indicates that closed-eyes EEG power in the α_1 frequency band may constitute the accurate reflect of a homeostatic waking maintenance process.

In contrast with other findings (Aeschbach et al. 1999), the sleep deprivation-related increases in waking EEG of the high frequency range involved only the γ frequency band, the β band remaining virtually unaffected. Although the previous studies did not examine frequencies over 25 Hz, the boundary evidenced in the high frequency range best fits the frequency clusters educed by Dumont et al. (1999) using 1-Hz frequency bands. Over and above, a similar boundary around 20 Hz has also been reported by applying the same methodology to another set of daytime EEG recorded at higher sampling rate (Chapotot et al. 2000). While a monotonic increase in EEG power of the 18–25 Hz frequency cluster has been reported (Dumont et al. 1999), our 60-h sustained wakefulness protocol demonstrated that the γ frequency band response to sleep deprivation reached its highest level in the early sleep deprivation phase and declined thereafter. Thus, EEG high frequencies, which traditionally reflect cortical activation (Aston-Jones and Bloom 1981; Steriade et al. 1990), indicated that prolonged waking induced a biphasic physiological response characterized by an initial and transient hyperarousal that is not maintained durably.

The existence of two distinct circadian rhythms in waking EEG activity was first demonstrated from a 40-h constant routine study (Aeschbach et al. 1999). In close agreement with these findings, we found two 24-h rhythms, phase-shifted by 6–7 h, in the θ_2 (acrophase ~0900 hours) and α (acrophase ~1600–1700 hours) frequency bands. In addition, two circadian rhythms mirroring that of the θ_2 and α frequency bands were evidenced from the present study in the β (acrophase ~2100 hours) and γ (acrophase ~0400 hours) frequency bands, respectively. Regarding the sleep latency profile, the minimum of the β band rhythm corresponded to the morning minimum in alertness (~0900 hours) and that of the γ band to the midafternoon dip in alertness (1500–1600 hours). Consequently, high frequency EEG activity in the β and γ bands, which are thought to be controlled by the brainstem ascending reticular activation system (Aston-Jones and Bloom 1981) and to represent direct indices of cortical activation, may reflect different aspects of the circadian rhythm in arousal.

In close agreement with the available literature on this topic, data from the placebo group emphasize the robustness of the homeostatic and circadian processes underlying fluctuations in waking EEG activity, although their interactions could not be determined. The present results further indicate that the homeostatic EEG response to sleep deprivation may demonstrate monotonic but also biphasic patterns depending on the frequency band considered. In addition, our findings reveal the dual nature of circadian rhythmicity previously identified in different EEG frequency bands and suggest the existence of two distinct activatory processes reflected in the high frequency range and differentially influencing cortical arousal under the endogenous influence of the circadian timing system.

Effects of the psychostimulants on alertness and waking EEG activity

Similar to subjective sleepiness and cognitive performance evaluated in the same subjects (Pigeau et al. 1995), the effects of 20 mg of *d*-amphetamine and 300-mg of modafinil on objective alertness, assessed by measuring sleep latency, appeared 1 h after the administration of the drugs and lasted approximately 10–12 h. As expected, the respective dosages of the two drugs were equipotent in their alerting effects, both drugs maintaining alertness when given at the beginning of the first night and restoring alertness when administered at the end of the second night.

The EEG effects of modafinil and *d*-amphetamine were in global agreement with previous reports, although the effects of modafinil, which had been briefly described, appeared more intricate. *d*-Amphetamine, studied under resting conditions, i.e. when subjects were allowed to fall asleep, has been reported to decrease EEG power in the δ, θ and β frequency bands and to increase the α frequency activity (Matejcek 1982; Saletu et al. 1993a; Slattum et al. 1996). Modafinil, as reported in a short summary of a phase I study (Laboratoire Lafon 1997), produced quite similar changes at a 400-mg dosage, while a recent helicopter simulator investigation (Caldwell et al. 2000) indicated a decrease in EEG power concerning the δ and θ frequency band only. Discrepancies with previous findings may be attributable to the different recording situations and particularly to the fact that the present study took exclusively into account the waking portion of EEG recordings, thus excluding the confounding effects of sleep.

As demonstrated in the present study, the 20-mg dose of *d*-amphetamine induced a long-lasting suppression of the sleep deprivation-related increase in EEG power of the δ and θ_1 frequency bands, independently of the time of administration. It also decreased the α_1 activity, limited the increase in the γ band power and abolished, or significantly dampened, the EEG circadian rhythms identified under placebo. In the same subjects, our group previously reported that, in contrast to modafinil, *d*-amphetamine severely disrupted sleep during the 2 consecutive nights of recovery (Buguet et al. 1995). The pharmacological action of *d*-amphetamine resides presumably in directly activating the whole cerebral cortex by massive monoamine release at the cortical neuron terminals (Lin et al. 1996). Accordingly, the present study indicated that *d*-amphetamine enhanced alertness through suppression of the sleep deprivation-related increase in EEG low frequency activity, therefore counteracting cortical fatigue and preventing the intrusion of sleep processes during waking. The dampening of EEG circadian rhythms may subsequently be explained by a possible masking effect rather than by a specific chronobiotic action of *d*-amphetamine on the endogenous timing system.

The 300-mg dose of modafinil produced a short-lasting (3–6 h) EEG power decrease in the δ_2 and θ_1 frequency bands whether the drug was administrated at the beginning of the first night or at the end of the second night of sleep deprivation. It also reduced the sleep deprivation-related increase in the γ band and delayed the circadian rhythm of the θ_2 band, but did not affect circadian rhythms in the other frequency bands. According to the pharmacokinetics of modafinil (Laboratoire Lafon 1997) and considering the low affinity of modafinil for the dopamine transporter site in vitro (Mignot et al. 1994), the ingestion of a 300-mg dose would theoretically elicit blood-brain concentrations that might be in the range interfering with dopaminergic reuptake in vivo. Thus, it is suggested that the transient modafinil-induced power decrease in EEG low frequencies, as well as the apparent circadian delay in the θ_2 frequency band, may result from amphetamine-like dopaminergic effects. A similar experiment with lower doses of modafinil might confirm this interpretation.

Functionally, the enhancement of alertness elicited by the 300-mg dose of modafinil could not solely be related to the observed decrease in low frequency EEG activity since sleep latency was increased during 10–12 h while low frequencies were decreased for a shorter time lapse, lasting only 3–6 h. As compared with placebo and in contrast to 20-mg of *d*-amphetamine, modafinil also prominently increased EEG power in the α_1 frequency range during approximately 24 h following the first evening ingestion. Consequently, the nootropic properties of modafinil, in contrast to that of *d*-amphetamine, may be related to its selective effects on the α_1 frequency band, which is intimately related to waking maintenance, as shown by its linear wake-dependent decline and its circadian minimum at night. Therefore in humans, modafinil may improve alertness over prolonged periods by allowing for the maintenance of an active waking process. However, few significant changes from placebo were noted in the α_1 frequency range between the second and third administrations. Thus at night, when the circadian rhythm in the α_1 EEG activity is at its minimum, the α_1 power increasing action of modafinil may not be efficient enough, the alertness-promoting effect of modafinil thus residing at least partly in its amphetamine-like sleep-suppressing effects.

These mixed short- and long-lasting EEG effects of modafinil have to be considered in regard to a recently reported brain amines microdialysis study (de Saint Hilaire et al. 2001). Indeed, it has been shown in rats that the wake-promoting effect of modafinil was related to an initial amphetamine-like increase in cortical monoamines, followed by a secondary increase in hypothalamic noradrenaline, which may belong to the specific effect of modafinil ensuring the maintenance of wakefulness over longer time lapses.

Summary and conclusions

This comparative study is the first to describe the action kinetics of modafinil and *d*-amphetamine on neurophys-

iological aspects of waking during the course of sleep deprivation. High-resolution spectral analysis of long-term EEG recordings combined with iterative alertness test allowed us to i) to distinguish from the waking EEG spectrum the influence of wake- and clock-dependent regulatory processes underlying fluctuations in brain arousal and alertness, and ii) to differentiate modafinil and *d*-amphetamine, which showed equivalent alertness-promoting effects, on the basis of their selective actions upon the regulatory processes involved in the modulation of waking EEG activity. In summary, the present study indicates that, in addition to a transient amphetamine-like sleep-suppressing effect, modafinil, through a synchronic effect, preferentially counteracted the homeostatic decline of a waking maintenance process.

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