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Caffeine intake (200 mg) in the morning affects human sleep and EEG power spectra at night

Hans-Peter Landolt, Esther Werth, Alexander A. Borbély, Derk-Jan Dijk *

Institute of Pharmacology, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich-Irchel, Switzerland

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Abstract

Adenosine has been implicated in the physiological regulation of sleep propensity. The adenosine-receptor-antagonist, caffeine (100 mg), administered immediately prior to a nocturnal sleep episode, has previously been shown to lower sleep propensity as indexed by a reduced sleep efficiency, a reduced EEG power density in low delta frequencies and enhanced power density in the frequency range of sleep spindles. To further investigate the role of adenosine in sleep regulation we administered 200 mg of caffeine at 07.10 h and analyzed the sleep stages and EEG power spectra during the subsequent night in nine healthy men. Caffeine levels in saliva decreased from a maximum of 17 μmol/l one hour after intake, to 3 μmol/l immediately prior to the sleep episode starting at 23.00 h. Compared to placebo, sleep efficiency and total sleep time were significantly reduced. EEG power density in nonREM sleep was suppressed in the 0.25–0.5 Hz band and enhanced in the frequency range of sleep spindles (11.25–12.0 Hz and 13.25–14.0 Hz). In REM sleep EEG power density was suppressed in the frequency range of 0.75–4.5 and 5.25–6.0 Hz. The data indicate that a saliva level of caffeine as low as 3 μmol/l directly affects sleep propensity or, alternatively, that the presence of caffeine in the central nervous system during the waking episode reduces the progressive increase of sleep propensity associated with wakefulness.

Keywords: Adenosine; Electroencephalography; Power spectrum; Non-REM sleep; REM sleep; Sleep-homeostasis

1. Introduction

Adenosine is present throughout the central nervous system (CNS) and is considered a neuromodulator but its specific function is unknown [15]. Adenosine analogs act on at least two different binding sites, i.e. the A_1 and A_2 adenosine receptors, and several lines of evidence suggest that adenosine is involved in the regulation of sleep [23,27]. In rats, adenosine concentration in the CNS exhibits a pronounced variation over the light–dark cycle. High levels of adenosine coincide with the major sleep phase when the activity of the metabolizing enzymes is low [10]. Systemic application of adenosine agonists over a wide range of doses has consistently been shown to prolong the deep stages of non-REM sleep, whereas the effects on REM sleep and wakefulness depend upon the doses administered [24,25]. Intraperitoneal injection of cyclopentyladenosine, an A_1 receptor agonist, induces changes in the spectral power density of the sleep EEG which are similar to those observed after an 'intensification of sleep' by 6 h of sleep deprivation [3,19,37]. Furthermore, adenosine is released in the brain during periods of high metabolic activity [16]. These findings have led to the hypothesis that adenosine mediates the effects of wakefulness on sleep propensity and EEG slow-wave activity [3,26], possibly by its inhibitory action on meso-pontine nuclei involved in the regulation of EEG desynchronization and arousal [27].

Adults living in Western societies have an average daily caffeine intake of about 200–300 mg [11] which leads to a low micromolar blood plasma concentration [2,22]. In this concentration range, competitive antagonism on the level of A_1 and A_2 receptors is likely to be responsible for the well-known effects of caffeine on alertness, performance and sleep propensity [4,32]. In accordance with previous findings (for a recent review see Snel [31]) we recently reported that a low dose (100

* Corresponding author. Fax: (41) (1) 257-5707.

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mg) of caffeine immediately prior to a nocturnal sleep episode prolonged sleep latency, reduced the duration of slow-wave sleep (SWS, i.e. stage 3 + 4 of non-REM sleep) in the first non-REM–REM sleep cycle, and reduced sleep efficiency. Furthermore, EEG spectral power density in some low delta frequencies was decreased, whereas power density in the spindle frequency range was slightly enhanced [20]. Although these effects did not completely mimic the spectral changes observed in physiological conditions of reduced sleep pressure in which EEG activity in both delta and theta frequencies is decreased [39], the caffeine induced changes were, to some extent, similar to those associated with a reduction of sleep pressure.

The aim of the present study was to investigate whether caffeine intake at the beginning of the wake-episode modulates the increase of sleep propensity and slow-wave propensity associated with wakefulness [6,12]. To this end we administered 200 mg caffeine which is the equivalent of one to two cups of regular coffee [11] at the beginning of the wake episode. Since caffeine has a plasma half-life of 3–7 h [2,5,34], by the beginning of the nocturnal sleep episode plasma caffeine levels should have reverted to values below the lowest concentration reported to be effective in alertness and performance tests [21], i.e. approximately 1 μg/ml which equals about 4 μmol/l in saliva [33].

2. Materials and methods

2.1. Subjects

Nine men (mean age: 22.4 ± 0.4 (±S.E.M.) years; range 21–25 years) from the student populations of the University of Zürich and the Swiss Federal Institute of Technology were recruited to participate in this study which was approved by the local ethical committee for research on human subjects. Subjects gave their written informed consent prior to the study and were paid for their participation. Questionnaires revealed that they had no significant medical history, were in good health and had no sleep disturbances. The subjects, all non-smokers with a habitual alcohol intake of less than five drinks per week, were asked to refrain from alcohol for the duration of the experiment. They all reported a habitual consumption of one or two caffeinated beverages (coffee, tea, coke) per day. During the week prior to the study, the subjects were instructed to keep a regular sleep–wake cycle with sleep scheduled from 23.00 to 07.00 h. During the weekend subjects were allowed to deviate from this schedule by not more than one hour. Compliance with this instruction was verified by inspection of the rest–activity plots obtained by an activity monitor worn on the wrist of the non-dominant arm. During the pre-study week, the subjects filled out a caffeine-log which revealed an average intake of 1.5 ± 0.17 (±S.E.M.) caffeinated drinks per day. Subjects were asked to abstain from caffeine during 24 h before the adaptation night and during the entire experiment.

2.2. Study protocol

Subjects slept in completely darkened and sound-attenuated bedrooms of the sleep laboratory on four consecutive nights: an adaptation night followed by two placebo baseline nights and a caffeine night. Ten minutes after awakening, and on completion of a short memory task and a questionnaire assessing self-estimated sleep quality, the subjects were given a capsule. On the morning after the third night, the capsule contained 200 mg of caffeine (caffeine anhydrous; manufacturer: Siegfried Ltd., Zofingen, Switzerland) and mannitol (manufacturer: Siegfried Ltd., Zofingen, Switzerland), whereas on other mornings it contained only mannitol. The subjects were blind to the treatment.

2.3. Polygraphic recording, EEG and ECG analysis

Subjects slept in the sleep laboratory from 23.00 to 07.00 h. Polygraphic recordings of the electroencephalogram (EEG), submental electromyogram (EMG), electrooculogram (EOG) and electrocardiogram (ECG), were obtained during all sleep episodes. EEG electrodes were placed at the locations F3, C3, P3, and O1 and referenced to the A_2 derivation according to the 10–20 system [17]. For the present study, however, only the C3-EEG-derivation was analyzed. Electrophysiological signals were recorded on Grass polygraphs (model 78E and 78D; Quincy, MA, USA). For the EEG signals the half-amplitude, low-frequency high-pass cut off was set at 0.1 Hz. EEG signals were low-pass filtered in different steps, which resulted in a 3 dB attenuation at 27 Hz. Signals were analog to digital converted (256 Hz, 12-bit resolution), digitally low-pass filtered (3 dB attenuation at 25 Hz, 24 dB/octave), and stored on a personal computer with the sampling rate of 128 Hz. The power spectra for consecutive 4-s epochs were computed using a Fast-Fourier transform routine with a 10% tapered-cosine window. Data were reduced by omitting values above 25 Hz and by averaging over two (0.25–5 Hz) or four (5.25–25.0 Hz) adjacent 0.25 Hz bins. With the exception of the adaptation night, the polygraphic records of all nights were visually scored in 20-s epochs according to standard criteria [28]. Four-second epochs with artifacts were visually identified and eliminated. Power spectra were averaged for 20-s epochs and analyzed for sleep stages, non-REM–REM sleep cycles, and across time intervals.

Heart rate was detected off-line by a level-crossing algorithm. All epochs in which the variability of the ECG-amplitude or the R–R intervals exceeded a preset value, were visually inspected and either corrected or eliminated.

2.4. Alertness rating and performance test

During the day, subjects rated their alertness every hour on a 20-point visual analogue scale (VAS) and performed a short memory test using a hand-held computer.

2.5. Caffeine concentration in saliva

Saliva samples collected fifteen minutes prior to all sleep episodes were stored at −20°C and later assayed with an EMIT-Caffeine Test (Syva Co., Palo Alto, CA, USA).

In a separate experiment, the kinetics of 200 mg of caffeine during the habitual wake episode were assessed in saliva samples of five male non-smoking university students (mean age: 23.3 ± 0.8 (±S.E.M.) years; range 21–25 years), three of whom had already participated in the sleep study. Subjects were asked to refrain from dietary caffeine for at least 48 h before the study and reported to the laboratory at approximately 06.45 h. After collection of a saliva sample at 07.00 h, 200 mg of caffeine was administered at 07.10 h whereafter subjects continued with their normal daily activities. Samples were taken at 07.15, 08.15, 10.15, 12.15, 15.15, 18.15, 21.15 and 22.55 h and stored at −20°C.

2.6. Statistical analysis

Statistical significance was assessed with ANOVAs for repeated measures, and comparisons between the placebo and the caffeine condition were performed with paired t-tests. Since the two placebo sleep episodes did not differ significantly for any variable, the caffeine sleep episode was compared to the average of the two placebo sleep episodes. Some variables (sleep latency, EEG power densities) were log-transformed prior to statistical tests.

3. Results

3.1. Caffeine concentration in saliva

Fifteen minutes prior to the first placebo baseline sleep episode (night 2) caffeine concentration in saliva was below the detection limit (1.0 μmol/l) in all nine subjects. Prior to the second placebo baseline sleep episode (night 3) concentrations were below 1.0 μmol/l in eight subjects and 2.5 μmol/l in one subject. After intake of 200 mg caffeine at 07.10 h, saliva levels immediately prior to the sleep episode (night 4) were below the limit of detection in two subjects, and 1.6, 1.6, 2.8, 3.3, 4.2, 4.5 and 6.5 μmol/l in the remaining subjects (mean caffeine concentration: 2.7 ± 0.7 (±S.E.M.) μmol/l; Fig. 1, filled circle at 22.55 h).

The time course of the caffeine concentration in saliva after intake of 200 mg at 07.10 h was assessed in a separate experiment. One hour after administration, a maximum of 17 μmol/l was reached. Subsequently,

Table 1
Sleep parameters derived from visual scoring

	Placebo 1	Placebo 2	Caffeine	$F_{2,16}$ (P)
Sleep episode	467.85 ± 1.57	468.63 ± 1.37	457.81 ± 5.82	3.69 (0.09)
Total sleep time (TST)	452.67 ± 3.13	450.70 ± 3.76	440.7 ± 5.3 *	4.80 (0.05)
Sleep efficiency	94.12 ± 0.65	93.70 ± 0.78	91.64 ± 1.11 *	4.74 (0.05)
Sleep latency (to Stage 2)	13.07 ± 1.60	12.37 ± 1.37	23.07 ± 5.83 **	3.94 (0.05)
Latency to Stage 1	9.85 ± 1.50	7.44 ± 0.77	13.11 ± 2.43	3.17 (0.09)
REMS latency (from Stage 2)	75.19 ± 7.53	83.41 ± 9.17	81.0 ± 11.32	0.88 (0.40)
Stage 1	31.11 ± 4.15	32.59 ± 3.28	31.81 ± 2.98	0.07 (0.92)
Stage 2	231.74 ± 10.11	226.67 ± 11.22	220.63 ± 11.42	1.43 (0.27)
Stage 3	45.44 ± 3.52	48.30 ± 5.50	40.67 ± 4.35	1.70 (0.22)
Stage 4	40.89 ± 7.81	42.74 ± 9.54	39.70 ± 8.91	0.48 (0.63)
SWS	86.33 ± 8.29	91.04 ± 10.71	80.37 ± 9.50	2.84 (0.11)
REMS	103.48 ± 5.43	100.41 ± 5.90	107.89 ± 4.31	1.65 (0.23)
MT	11.37 ± 0.71	12.78 ± 1.19	11.59 ± 0.90	1.35 (0.29)
WASO	3.85 ± 1.73	5.15 ± 2.72	5.52 ± 1.92	1.36 (0.28)

Values are for means ± S.E.M. in minutes. Placebo 1, Placebo 2, and Caffeine refer to respective sleep episodes; Sleep episode: interval between the first occurrence of Stage 2 and the final awakening; Total sleep time (TST): sleep episode − (MT + WASO); MT: movement time; WASO: waking time after sleep onset; Sleep efficiency: TST/TIB (%); TIB: time in bed; REMS: rapid-eye-movement sleep; Stage 1, 2, 3, 4: nonREM sleep stages; SWS: slow-wave sleep.

* $P < 0.05$ compared to Placebo 1, Placebo 2 and Placebo-mean.

** $P < 0.05$ compared to Placebo 2 ($P = 0.08$ compared to Placebo-mean).

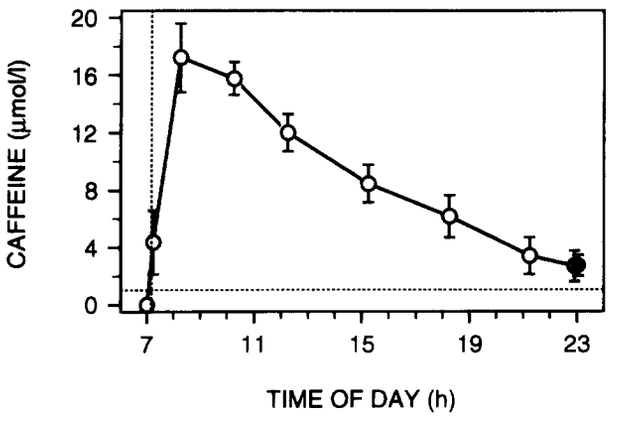

Fig. 1. Time course of saliva caffeine concentration after 200 mg of caffeine administered at 07.10 h (dashed vertical line). Open circles represent mean caffeine levels (±S.E.M.; $n = 5$) assessed in a separate kinetics-experiment. The filled circle at 22.55 h represents the mean saliva caffeine concentration (±S.E.M.; $n = 9$) immediately prior to the caffeine night in the sleep experiment. Samples in which the caffeine concentration was below the detection limit of 1.0 μmol/l (dashed horizontal line) were assigned a value of zero.

the concentration declined to 2.6 μmol/l at 22.55 h (Fig. 1, open circles).

3.2. Alertness and performance, heart rate and subjective sleep quality parameters

No significant effects of the caffeine treatment were detected for the subjective alertness ratings and performance parameters. No significant changes were observed for heart rate, subjective sleep quality, subjective sleep latency and the perceived number and duration of awakenings at night.

3.3. Sleep parameters derived from visual scoring of polygraphic recordings

Total sleep time and sleep efficiency were significantly reduced after caffeine intake while the latency to REM sleep and the duration of REM sleep episodes were not significantly different from placebo (Table 1). Sleep latency was slightly longer after caffeine intake ($P = 0.08$) and was significantly longer when compared to the second placebo sleep episode ($P < 0.05$).

3.4. Changes in EEG power spectra over consecutive non-REM sleep episodes

Power density in the delta (0.25–4.5 Hz) and theta (6.25–9.0 Hz) frequencies decreased over consecutive non-REM sleep episodes, whereas power density in the frequency range of sleep spindles (12.25–15.0 Hz) increased. These changes were very similar in the placebo (Fig. 2a) and the caffeine (Fig. 2b) condition.

3.5. Effects of caffeine on all-night power spectra in non-REM sleep and REM sleep

After caffeine intake EEG power density in non-REM sleep was reduced in the lowest delta band (0.25–0.5 Hz) and enhanced in the 11.25–12.0 Hz and in the 13.25–14.0 Hz band (Fig. 3, upper panel). In REM sleep, spectral power density was significantly reduced in the 0.75–4.5 Hz and 5.25–6.0 Hz range (Fig. 3, lower panel). For no frequency bin a significant difference between the two placebo baseline sleep episodes was observed, neither in non-REM sleep nor in REM sleep.

3.6. Effect of caffeine on EEG power spectra in non-REM sleep episodes

A repeated measures ANOVA with factors 'condition' (placebo, caffeine) and 'non-REM sleep episode' (1–4) revealed a significant effect of 'condition' for power density in the frequency range of 11.25–14.0 Hz ($P < 0.05$ for all bins). Post-hoc comparisons demonstrated that in the first three non-REM sleepepisodes power density was enhanced in the frequency range of

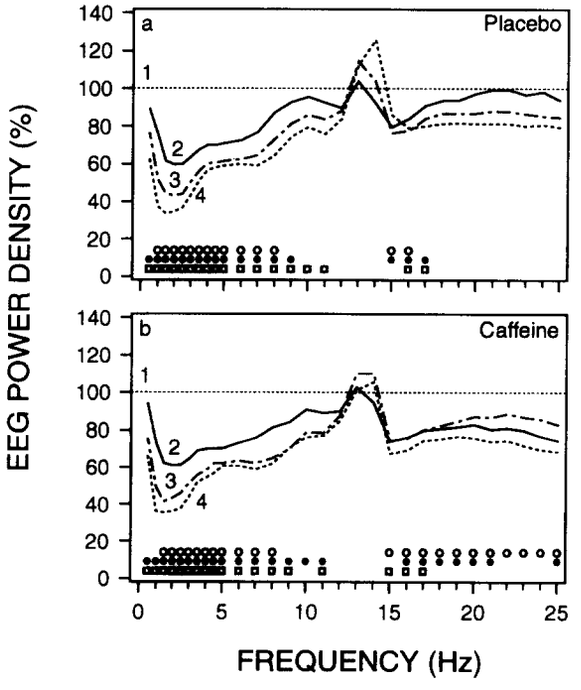

Fig. 2. Changes in EEG power density (C3-A2 derivation) in non-REM sleep over consecutive nonREM sleep episodes. Curves connect mean values, expressed as a percentage of the values in the first non-REM sleep episode, of the placebo: mean values of two placebo sleep episodes (a); and the caffeine condition (b). Filled circles (non-REM sleep episode 2), open circles (episode 3) and open squares (episode 4) indicate frequency bins for which power differed significantly from the value in the first non-REM sleep episode ($P < 0.05$, paired t-test).

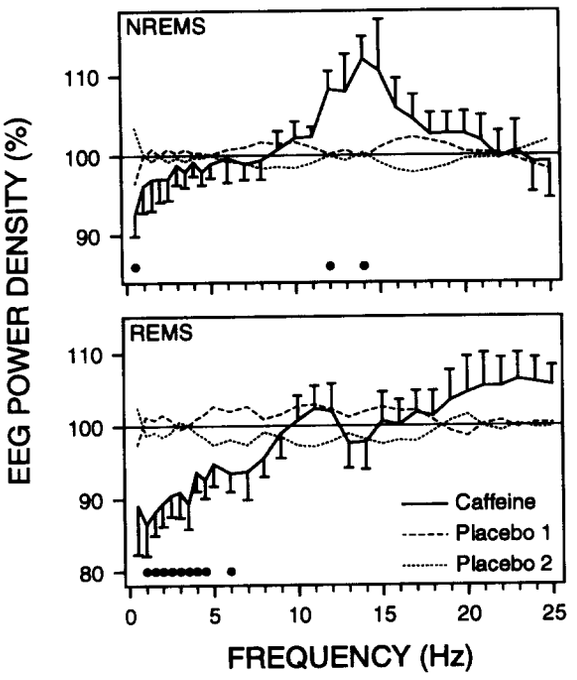

Fig. 3. EEG power density (C3-A2 derivation) in nonREM sleep (upper panel) and REM sleep (lower panel) for the first placebo night, the second placebo night and for the caffeine sleep episode. For each frequency bin, mean values are expressed as a percentage of the corresponding mean value of the two placebo sleep episodes (horizontal line at 100%). Vertical bars represent 1 S.E.M. Filled circles indicate frequency bins for which power following caffeine administration in the morning differed significantly from the corresponding average placebo value ($P < 0.05$, paired t-test).

sleep-spindles (Fig. 4; non-REM sleep episode 1: 11.25–14.0 Hz; non-REM sleep episodes 2 and 3: 13.25–14.0 Hz). The repeated measures ANOVA did not reveal a significant effect of the factor 'condition' for any of the delta frequencies.

3.7. Dynamics of slow-wave activity and sleep spindle frequency activity

The intra-episodic time course of slow-wave activity (SWA, i.e. EEG power density in the 0.75–4.5 Hz band) and spindle frequency activity (EEG power density in the 12.25–15.0 Hz band) were computed by subdividing individual non-REM sleep episodes into 20 equal parts, and individual REM sleep episodes into 4 equal parts (i.e. time-bins). The time course of SWA was very similar in both conditions and showed high values in non-REM sleep and low values in REM sleep (Fig. 5, upper panel). The effects of caffeine were analyzed in each non-REM sleep episode with a repeated measures ANOVA with factors 'condition' (placebo, caffeine) and 'time-bin' (1–20). A significant effect of the factor 'condition' was not observed in any of the non-REM sleep episodes. An analysis of the intra-episodic time course of power density in the lowest frequencies (0.25–0.5 and 0.75–1.0 Hz) also failed to show a significant effect of the factor 'condition'.

Although the typical pattern of spindle frequency activity (i.e. low values in REM sleep, high values and

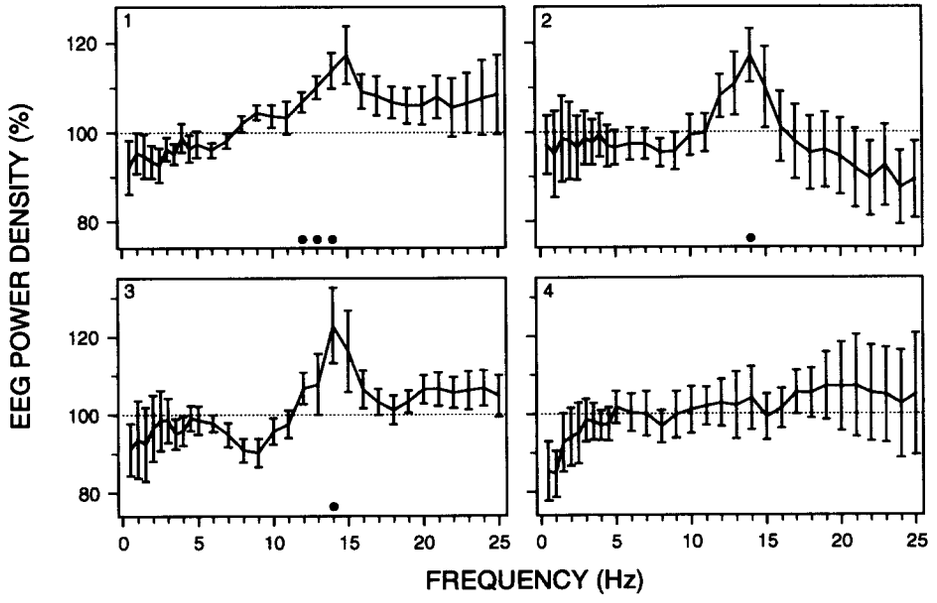

Fig. 4. EEG power density (C3-A2 derivation) in the first 4 non-REM sleep episodes during the sleep episode following caffeine intake at 07.10 h. The number on the top of the panels denotes the non-REM sleep episode. Mean values are expressed as a percentage (±S.E.M.) of the corresponding average placebo value. Filled circles indicate frequency bins for which a repeated measures ANOVA with factors 'condition' (placebo, caffeine) and 'non-REM sleep episode' (1–4) revealed a significant effect of 'condition' and were significantly different from the corresponding average placebo value as assessed by a paired t-test ($P < 0.05$).

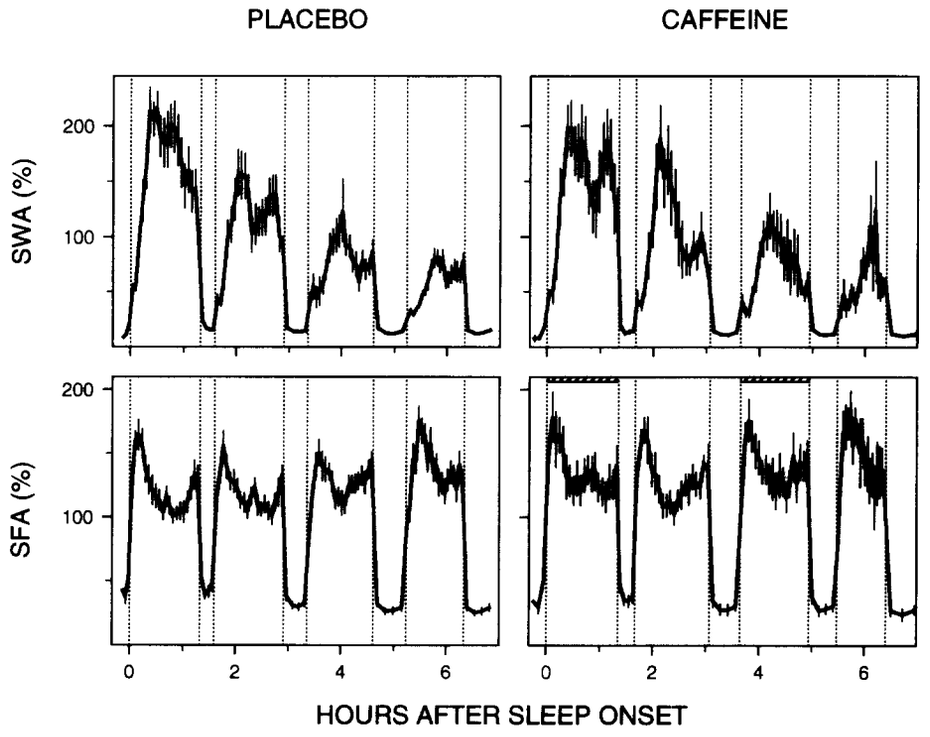

Fig. 5. Dynamics of EEG power density (C3-A2 derivation) in the slow-wave (SWA, 0.75–4.5 Hz; upper panel) and spindle frequency (SFA, 12.25–15.0 Hz; lower panel) range plotted for the placebo (mean values of two placebo sleep episodes) and the caffeine condition. For each subject, individual nonREM sleep episodes were subdivided into 20 equal time-bins, whereas REM sleep episodes as well as the interval between lights out and sleep onset were subdivided into four equal time-bins. For each subject and night, power density values per time-bin were expressed as a percentage of the mean value in non-REM sleep averaged over the two placebo sleep episodes. Data were then averaged across subjects ($n = 9$) and plotted against the mean timing of non-REM and REM sleep episodes. Vertical bars represent ± 1 S.E.M. Dashed vertical lines delimit REM sleep episodes. Hatched horizontal bars indicate non-REM sleep episodes for which a repeated measures ANOVA with the factors 'condition' (placebo, caffeine) and 'time-bin' (1–20) revealed a significant effect of condition.

U-shaped pattern in non-REM sleep) was present in both the placebo and the caffeine conditions the ANOVA revealed a significant effect of 'condition' for non-REM sleep episode 1 and 3 reflecting the higher values of spindle frequency activity in the caffeine condition.

4. Discussion

The present data show that intake of 200 mg of caffeine (the equivalent of approximately 1–2 cups of regular coffee) at 07.10 h, affects sleep propensity and spectral power density of the sleep EEG in the subsequent night. The sleep effects were rather small and not associated with severe disruption of sleep continuity or a deterioration of subjective sleep quality. This study differs from others in the literature in which the interval between caffeine administration and subsequent sleep was much shorter [18] or caffeine was given throughout the wake episode [29,30]. In these earlier studies the dose of caffeine was often higher and no quantitative EEG analysis was applied. Schwertz and Marbach [30] observed a prolonged sleep latency, whereas Saletu et al. [29] did not find any effect on objective or subjective sleep parameters, after administration of several single doses of caffeine (total intake: 800 mg and 450 mg) starting ten hours before sleep. We recently reported that intake of 100 mg caffeine immediately prior to sleep resulted in a reduction of power density in the lowest delta range and an enhancement in the frequency range of sleep spindles in non-REM sleep [20]. The effects of morning caffeine on the non-REM power spectrum are very similar to this previous study, although of a smaller magnitude. The reduction of power density in the delta frequencies in REM sleep was not observed after intake of caffeine immediately prior to sleep. Interpretation of this finding is difficult since power values in the delta frequencies are very low in REM sleep.

The opposite effects of caffeine on EEG slow waves and sleep spindles are in keeping with the inverse relation between these two EEG activities observed under baseline conditions [1], after sleep deprivation [6,14] and after administration of benzodiazepine [7,38] and non-benzodiazepine hypnotics [8,38]. Sleep depri-

vation reduces activity in the frequency range of sleep spindles [6,14], whereas benzodiazepine-receptor agonists (BRAs) and caffeine enhance activity in this frequency range [7,8,20,38]. However, the low EEG frequency range affected by caffeine clearly differs from the frequency range affected by both sleep deprivation and BRAs. Sleep deprivation enhances power density in the range of 0.75–10 Hz [6,14] and BRAs reduce power density in the same frequency range [7,8,38]. In contrast, but in accordance with our previous study [20], caffeine administered in the morning reduced activity in the lowest frequency bin (0.25–0.5 Hz). This may suggest that caffeine affects primarily the slow oscillations (< 1 Hz) recently described by Steriade et al. [35]. Both slow EEG oscillations and EEG activity in the frequency range of sleep spindles are dependent on the hyperpolarization of neurons in thalamo-cortical and cortical circuits. The transition of sleep spindle dominated EEG patterns to slow wave dominated patterns is thought to be associated with a further hyperpolarization of thalamo-cortical neurons related to reduced activating inputs from meso-pontine nuclei and the nucleus basalis [36]. Rainnie et al. [27] recently reported that adenosine inhibits cholinergic neurons in meso-pontine nuclei and the nucleus basalis and suggested that this effect is related to the actions of adenosine and its antagonists on EEG synchronization. The present effects on the sleep EEG, and especially the opposite effects on slow waves and sleep spindles, are in accordance with this hypothesis. The observed effects may be related to the very low levels of caffeine still present immediately prior to the sleep episode, i.e. 16 h after intake of the drug. These levels are, however, lower than the levels previously reported to be effective in alertness and performance tests [21]. An alternative interpretation of the observed effect is that the presence of caffeine in the central nervous system during the waking episode, through an as yet unknown mechanism, attenuates the increase of sleep propensity associated with wakefulness. Although the experimental design did not allow us to exclude an order effect, such an effect appears unlikely in view of the lack of a significant difference between the two placebo nights (Fig. 3) as well as on the basis of previous experiments in which several successive baseline nights have been recorded [9,13].

We conclude that a moderate dose of caffeine taken in the morning affects sleep and the sleep EEG during the subsequent night. However, in accordance with our previous study, the caffeine induced changes in the EEG power spectrum did not exactly mimic the effects of a physiological reduction in sleep pressure. The data nevertheless indicate that the EEG during sleep is much more sensitive to caffeine than previously thought, which warrants further investigation on the role of adenosine in sleep regulation.

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