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Slow release caffeine and prolonged (64-h) continuous wakefulness: effects on vigilance and cognitive performance

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SUMMARY Some long work or shift work schedules necessitate an elevated and prolonged level of vigilance and performance but often result in sleep deprivation (SD), fatigue and sleepiness, which may impair efficiency. This study investigated the effects of a slow-release caffeine [(SRC) at the daily dose of 600 mg] on vigilance and cognitive performance during a 64 h continuous wakefulness period. Sixteen healthy males volunteered for this double-blind, randomised, placebo controlled, two-way crossover study. A total of 300-mg SRC or placebo (PBO) was given twice a day at 21:00 and 9:00 h during the SD period. Vigilance was objectively assessed with continuous electroencephalogram (EEG), the multiple sleep latency tests (MSLT) and wrist actigraphy. Cognitive functions (information processing and working memory), selective and divided attention were determined with computerised tests from the AGARD-NATO STRES Battery (Standardised Tests for Research with Environmental Stressors). Attention was also assessed with a symbol cancellation task and a Stroop's test; alertness was appreciated from visual analogue scales (VAS). Tests were performed at the hypo (02:00–04:00 h, 14:00–16:00 h) and hypervigilance (10:00–12:00 h, 22:00–00:00 h) periods during SD. Central temperature was continuously measured and safety of treatment was assessed from repeated clinical examinations. Compared with PBO, MSLT showed that SRC subjects were more vigilant from the onset ($P = 0.001$) to the end of SD ($P < 0.0001$) whereas some cognitive functions were improved till the thirty third of SD but others were ameliorated through all the SD period and alertness was better from the thirteenth hour of SD, as shown by Stroop's test ($P = 0.048$). We showed that 300-mg SRC given twice daily during a 64-h SD is able to antagonize the impairment produced on vigilance and cognitive functions.

KEYWORDS cognitive performance, sleep deprivation, slow release caffeine, vigilance

INTRODUCTION

In everyday life, prolonged sleep deprivation (SD) and wakefulness-sleep rhythm disruptions occur frequently. These situations often lead to an impairment of vigilance and performance, which in turn lead to a decrease in efficacy (Cajochen *et al.* 1995; Lagarde and Batéjat 1994; Linde and Bergström 1992; Lorenzo *et al.* 1995). The degradation in alertness and performance which occurs during the early morning hours can be alleviated by the ingestion of psychostimulants such as caffeine (Bonnet and Arand 1992, 1994; Bonnet *et al.* 1995; Linde 1994; Lorist *et al.* 1994; Muelbach and Walsh 1995; Walsh *et al.* 1990). However, the results obtained with the use of caffeine to enhance vigilance and performance level vary greatly. Sometimes, the results are very positive; an increase in performance mainly in visual vigilance tasks (Fine *et al.* 1994) can be observed as well as an increase

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in the level of vigilance – measured by electrophysiological techniques (Walsh *et al.* 1990) – for unusual situations such as shift work. Other studies reported an absence of effects or heterogeneous results (Hasenfratz and Bättig 1994) and also negative effects such as tachycardia, tremor, anxiety or tolerance during repeated intake of caffeine (Evans and Griffith 1992). Moreover, the alerting effect of caffeine has a limited power – especially compared with amphetamine – and duration (Quinlan *et al.* 1997).

Only few studies have reported the impact of caffeine on alertness and sustained cognitive performance during sleep loss. In shiftworkers, a 200-mg dose of caffeine taken at 22:30 h maintains vigilance during 4–6 h, but the authors did not measure cognitive performance (Walsh *et al.* 1990). It has also been shown that during 48 h of SD, the impact of a single 400-mg dose of caffeine taken at 1:30 h each night or of repeated lower doses (150/300 mg) taken every 6 h starting at 1:30 h is less pronounced than the effect of prophylactic naps; moreover, these effects of caffeine were observed on the first night only (Bonnet *et al.* 1995). Another study investigated the efficiency of caffeine on alertness and performance following 49 h of SD (Penetar *et al.* 1994). Results showed that a large dose (600 mg) of caffeine is able to enhance performance for up to 12 h and alertness for up to 4.5 h only. Finally, the impact of caffeine also depends on the timing of its administration (Wright *et al.* 1997b): the efficiency is better when the intake is at 20:00 h, prior to the onset of melatonin secretion, rather than at 1:00–2:00 h during the peak of the melatonin curve.

A new formulation of caffeine, slow release caffeine (SRC) at the single dose of 300 mg, has been demonstrated to have positive effects on alertness and performance during 9–13 h without any major side-effects (Lagarde *et al.* 2000). Indeed, the release of the active principle by SRC makes it possible to reach plasmatic plateau of caffeine within approximately 4 h and to remain at this level for 4–6 h, without overshooting the threshold of side-effects. (Fig. 1). These beneficial effects have been confirmed across a 36-h SD period with a daily dose of 600 mg (Lagarde *et al.* 2000; Patat *et al.* 2000). To summarise, a single daily (600 mg) or a twice daily dose (300 mg) of SRC seems to be superior than repeated moderate or single larger doses of caffeine to enhance performance and alertness for a period of SD longer than 24 h.

But in some long work or shift-work schedules, workers may be subjected to more stressful conditions with a SD in excess of 36 h. The specific pharmacokinetics of SRC would allow them to extend its psychostimulant effects by a twice daily intake. The aim of this study was to assess the effects of SRC on vigilance and cognitive performance during a 64-h SD period.

METHODS

Subjects

Sixteen healthy male volunteers aged 19–27 [mean age: 23 ± 2 years, (SD); height: 178 ± 7 cm (SD), weight: 73.3 ± 3.7 kg (SD)] participated in this study. All were submitted to thorough medical and biological examinations before participation in the experimentation and completed the questionnaire designed by Horne and Ostberg (1976) to verify that they were neither 'morning' nor 'evening' types. Selected subjects were non or low consumers of xanthic-based beverages on a regular basis (coffee, tea and coke: equivalent to less than three cups of coffee per day) and they also were non-smokers with no antecedent of sleep disorders. The study was carried out in compliance with the Helsinki agreements. The subjects were informed of the objectives and conditions of the experiment and gave their written informed consent after having been included in the study which had been approved by our ethical committee (Hospital Robert Ballanger, Aulnay-sous-Bois, France).

Treatment

The caffeine used in this study was a new pharmacological form of caffeine called SRC. We performed a controlled, double-blind, cross-over study to compare SRC (daily dose: 600 mg) with placebo (PBO). Each subject was given one of the two treatments (300-mg SRC or PBO) twice a day (at 21:00 and 09:00 h) over the 50 first hours of continuous wakefulness (Fig. 2) in a randomized order at two experimental sessions separated by a washout period of at least 2 weeks.

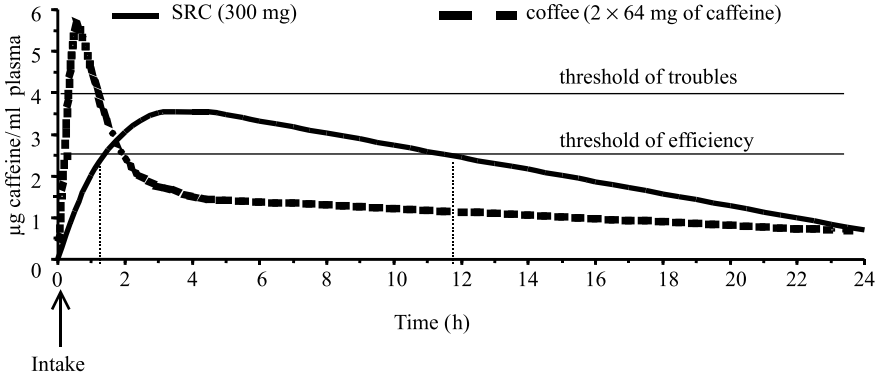

Figure 1. Pharmacokinetics profile of slow release caffeine (SRC 300 mg) vs. two espresso coffee cups (caffeine 128 mg). Whereas with espresso coffee, there is a plasma peak of caffeine concentration overshooting quickly the threshold of efficacy but also the threshold of troubles, the level efficacy of SRC is reached about 90 min after its intake but lasts about 10 h, and the threshold of troubles is never overshot.

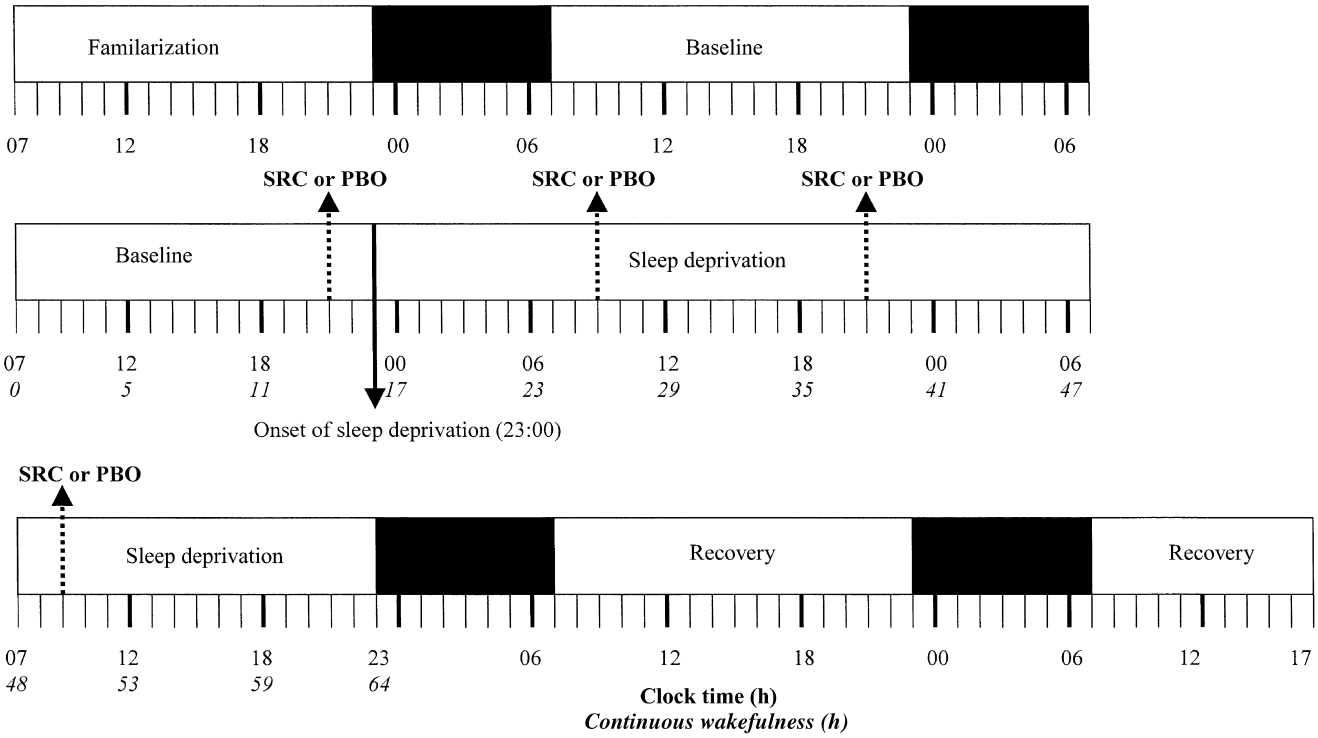

Figure 2. Experimental protocol. Placebo (PBO) and slow release caffeine (SRC), respectively. Treatments were taken twice a day (21:00 h, 9:00 h) over the first 50 h of a 64-h continuous wakefulness period. Start of SD is at 23:00 h of the day following the last baseline night. Nights: dark rectangles.

Methods of measurements

Vigilance

Vigilance level was objectively assessed from continuous EEG recordings, multiple sleep latencies tests (MSLT) and wrist actigraphy.

Continuous EEG recording is the most objective and reliable method to assess vigilance, by scoring microsleep episodes which are defined as stage 1 or 2 (even stages 3 or 4) episodes of a 3–14 s duration by epoch. Episodes longer than 15 s were scored as sleep. Episodes shorter than 3 s were counted as a unique microsleep episode if the sum of these microsleep episodes over a same epoch ranged between 3 and 14 s. Moreover, each microsleep episode to be scored had to be preceded by a wakefulness period of at least 15 s. To be able to compare different objective and subjective data and taking into account the hour of drug intake and test session scheduling, daytime was 'shared' in four time periods (7:00–9:00 h, 9:00–13:00 h, 13:00–17:00 h, 17:00–21:00 h) over the entire study. Afterwards, cumulative duration of sleep (CDS) over a given time period (from one time share to the totality of time shares in a same day) was calculated as the sum of duration of sleep and microsleep (DS) obtained in each time share constituting the considered time period.

Sleepiness was also determined by MSLT according to classical criteria (Carskadon *et al.* 1986).

Wrist actigraphy was used as an objective but indirect criteria of alertness as described and validated by several authors (Brown *et al.* 1990; Lockley *et al.* 1999; Reid and Dawson 1999). Subjects wore a piezoelectric accelerometer (Gaehwiler Electronic, sensitivity: 0.1 Gz, sampling rate: 8 Hz, band-pass filter: 0.25–3 Hz, data acquisition period: 15 s) on their non-dominant wrist throughout the protocol. Number of movements with a force > 0.1 ***g*** was counted hour by hour.

Cognitive functions and attention

Cognitive performance level was assessed from the seven tests from the NATO AGARD STRES Battery (Advisory Group for Aerospace Research and Development – Standardised Tests for Research with Environmental Stressors). The tests were selected among the most commonly used tests which met validity, reliability and sensitiveness conditions (Lagarde *et al.* 2000). The first test was a choice reaction time task, comprised of five blocks of trials corresponding to five different experimental conditions which facilitated the evaluation of five stages of information processing: stimulation analysis, choice of response, motor activation and response realization with four variables related to the visual characteristics of the stimulation, compatibility between stimulation and response, inter-stimulation delay and response complexity. The second test was a mathematical processing task with research of information in long-term memory and sequential treatment in short-term memory also named working memory. The third

test was a Sternberg memory scanning task and included the following steps: detection and recognition of a target stimulus, research in memory and comparison, and selection of the response. The fourth test consisted of a spatial processing task measuring the short-term visual memory performance. The fifth test was a visual tracking test aimed at measuring the resources used to perform a continuous manual control task. The sixth test was a grammatical reasoning test measuring the skills to handle grammatical data using working memory. Finally, the seventh test was a divided attention task simultaneously involving a visual tracking task and a memory search test which made it possible to assess divided attention abilities (Batéjat and Lagarde 1992). Response time, percentage of errors and percentage of response failures were measured in all the tests except for the tracking task where the parameters measured were an index of deviation of the cursor from the screen's centre (calculated as root mean square deviation summed for each second) and the number of control losses recorded when the cursor reached the edges of the display.

For all tests, the main parameters for analysis are the time of response and/or the percentage of errors as subjects were asked to perform the tests as fast and right as possible; a secondary parameter of interest is the number of omissions that is related to sleepiness.

The attention level was also measured from a symbol cancellation test (Batéjat *et al.* 1999) and a computerized form of the Stroop's test which allows one to evaluate cognitive performance with an emotional component induced by a conflicting situation (Patat *et al.* 2000). Score of symbol cancellation test was calculated from number of cancelled symbols, number of errors and number of omissions; score of Stroop's test was calculated from number of right responses. All these tests were used previously during SD experiments and were found to be sensitive to sleep loss (Lagarde *et al.* 1995).

Subjective aspects of alertness

Subjective aspects of alertness were evaluated from Bond and Lader visual analogue scales (VAS) (Bond and Lader 1974).

Central temperature

Central temperature was continuously measured by telemetry (Cor-Temp system®, Human Technologies Inc., FL, USA). Each subject ingested one transmitting capsule, and data was collected by means of a receiving aerial attached to a computer. Absolute temperature values were averaged over 2-h periods for each subject. This method of telemetry over a prolonged period could potentially induce variations of absolute values (artefacts) at the time of change of the capsule. Consequently we calculated relative values of temperature as the difference between the absolute data and a baseline value which was representative of a given time period, for each period over the nycthmeron (baseline and recovery) and each subject.

Subjects' tolerability

Psychiatric and clinical tolerability was assessed every evening by a psychiatrist and with side-effect questionnaires and a classical examination performed by a general practitioner (GP).

Procedure

During the week before the beginning of the experimental conditions, all participants were trained on the performance tests to minimize improvement of performance resulting from learning. Subjects were required to repeat each test until their performance reached a plateau.

The experiment took place in individual rooms of the Aster Institute, Paris, France. Ambient temperature was maintained at about 23 °C by air conditioning.

Each experimental session lasted 1 week (Fig. 2). Subjects were scheduled for a laboratory adaptation night on Saturday. During the Sunday evening time period, the subjects were fitted out with the actigraphs, core temperature monitors and EEG/EMG/EOG electrodes to obtain baseline reference data. At 07:00 h on Monday, they were awakened and placed under surveillance to keep them awake up to 23:00 h on Wednesday and to insure that they were subjected to a real 64-h sleep loss.

Except EEG and actigraphy which were continuously recorded, all tests were performed during hyper (10:00–12:00 h, 22:00–0:00 h) and hypovigilance (14:00–16:00 h, 02:00–04:00 h) periods (Lavie 1986) throughout SD. Between test sessions, subjects were kept awake by verbal stimulation and were allowed to recreational activity (reading, watching TV, playing cards…).

Statistical analysis

All results were expressed from the onset of SD, meaning from 23:00 h, the first day following baseline period.

The different criteria were separately analysed and compared using a two-way ANOVA (drug: PBO and SRC; period and time) with repeated measurements over time. The level of significance P was set at 0.05. In case of significant interaction between time and treatment for a given criteria, the treatment effect was analysed at each time interval, using pair-wise comparison tests and comparisons between the 10 time intervals over SD were performed for each treatment, using a Newman–Keuls test.

RESULTS

None clinical or psychological impairment was observed under SRC throughout SD.

Effects of SRC on vigilance

EEG recordings

The EEG recordings made it possible to identify the time of vigilance impairment. As an interaction drug-time period was

observed during SD (DS: $F_{(9,300)} = 4.24$, $P < 0.001$; CDS: $F_{(9,300)} = 25.28$, $P < 0.0001$), drug effect and time interval effects were shown for, respectively, each time interval and each treatment.

Concerning time effect, we observed in PBO subjects that duration of microsleep per time interval (DS, see Fig. 3a) and cumulative duration of sleep (CDS, see Fig. 3b) started to significantly increase from the sixth hour of SD, compared with values obtained at the preceding time interval (DS: + 245 s, $F_{(9,31)} = 9.41$, $P < 0.0001$; CDS: 265 s, $F_{(9,31)} = 31.1$, $P < 0.0001$). It is interesting to note that DS and CDS of SRC subjects increased from the thirty fourth hour of SD only, meaning from 9:00 h of the second day of wakefulness (DS: + 68 s, $F_{(9,31)} = 7.69$, $P < 0.0001$; CDS: + 197 s, $F_{(9,31)} = 20.2$, $P < 0.0001$).

Concerning the drug effect, DS and CDS were significantly shorter in SRC subjects compared with PBO from the sixth hour of continuous wakefulness (DS: –265 s, $F_{(1,31)} = 8.90$, $P = 0.009$, see Fig. 3a; CDS: –282 s, $F_{(1,31)} = 9.88$, $P = 0.007$, see Fig. 3b).

Analysis of MSLT showed an interaction between time intervals and drugs ($F_{(9,300)} = 3.53$, $P < 0.001$), so that time and drug effects were assessed for each drug and time period, respectively.

Multiple sleep latency tests (MSLT) showed a significant decrease in sleep latency 11 h after the onset of SD (time interval: 10:00–12:00 h) for both drug groups ($F_{(9,31)} = 49.23$, $P < 0.0001$).

Sleep latencies of SRC subjects were significantly greater than PBO from the onset ($F_{(1,31)} = 13.2$, $P < 0.001$) to the end of SD ($F_{(1,31)} = 21.87$, $P < 0.0001$) (Fig. 4).

The results of actigraphy were concordant with those of the MSLT (Fig. 5). The mean motor activity with SRC was superior to the one observed with PBO from the third hour following SD ($F_{(1,126)} = 9.59$, $P = 0.002$) to the end of SD ($F_{(1,1342)} = 58.27$, $P < 0.0001$).

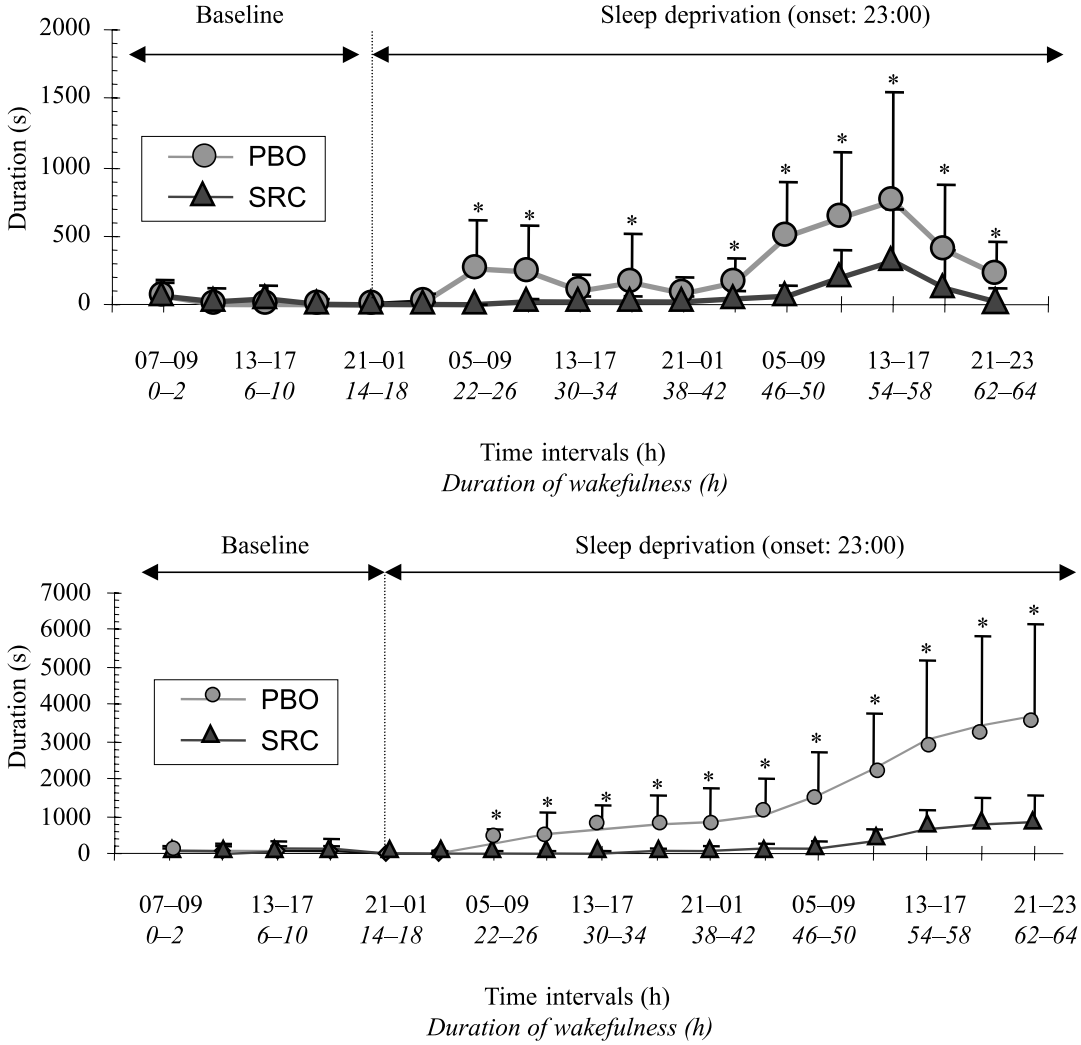

Figure 3. The EEG recording in baseline and SD conditions. Top (Fig. 3a): duration of microsleep episodes per time interval (mean value ± SD); bottom (Fig. 3b): cumulative duration of sleep throughout baseline and SD periods (mean value ± SD). Placebo (PBO), slow release caffeine (SRC). *Significant difference between SRC and PBO conditions, $P < 0.05$.

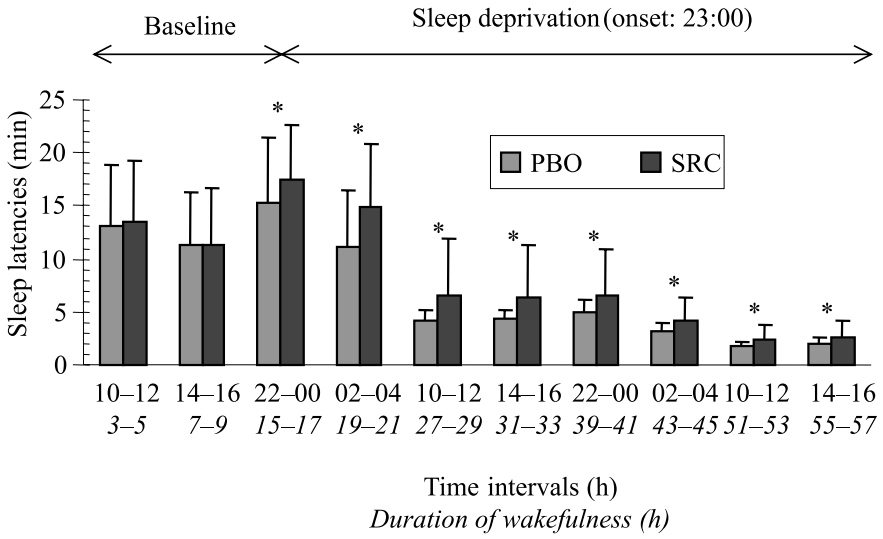

Figure 4. Evolution of the sleep latencies (mean value ± SD) in baseline and SD conditions. Placebo (PBO), slow release caffeine (SRC). *Significant difference between SRC and PBO conditions, $P < 0.05$.

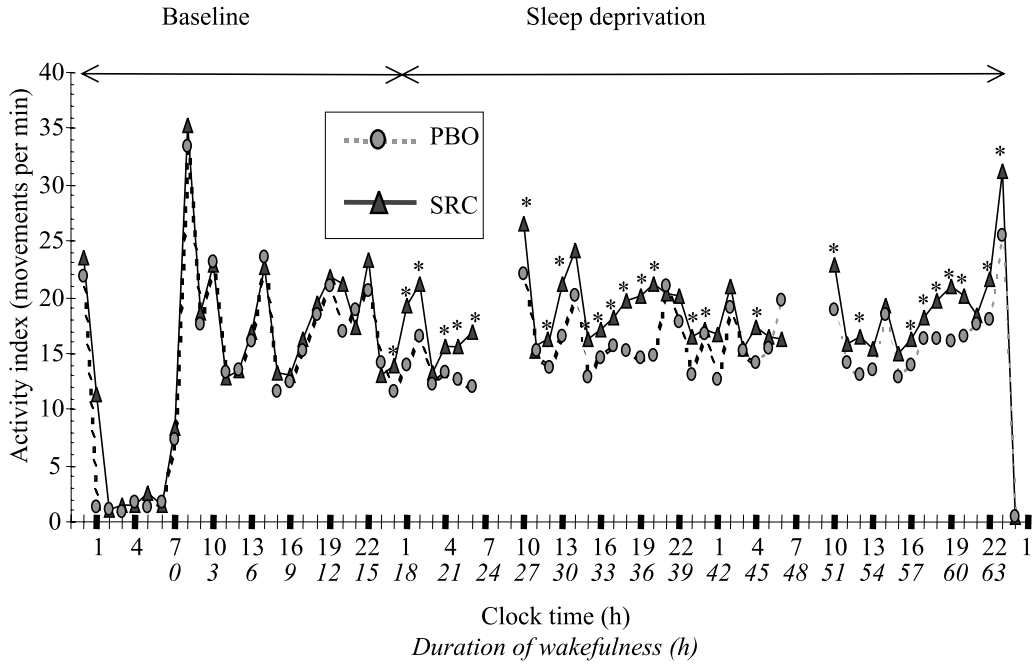

Figure 5. Evolution of the activity index (mean value ± SD) in baseline and SD conditions. Placebo (PBO), slow release caffeine (SRC). *Significant difference between SRC and PBO conditions, $P < 0.05$.

Effects of SRC on cognitive performance

Sleep deprivation produced a decrease in performance levels in both drug groups for all parameters evaluated.

The different STRES battery tasks showed globally a performance impairment for the first time from the ninth hour of SD and an accentuation of this effect 18 h later.

Concerning the attention task and the Stroop's test (Fig. 6a and 6b, respectively), the score was significantly lower for all subjects after 27 and 29 h of SD, respectively ($F_{(9,31)} = 13.98$, $P < 0.0001$ and $F_{(9,31)} = 20.74$, $P < 0.0001$, respectively).

These negative effects caused by SD were less marked under SRC but the duration of SRC's efficacy varied as a function of the STRES battery task. Cognitive tests showed that the lower performance as a result of SD, the better the efficacy of SRC.

- Regarding the reaction time task, the percentage of errors was lower with SRC than with PBO for the block with coded stimuli between 11 and 27 h of SD ($F_{(1,30)} = 4.44$, $P = 0.041$); for the block with uncertain time limit between 11 and 37 h of SD ($F_{(1,30)} = 4.36$, $P = 0.043$); for the block with complex response between 23 and 41 h of SD ($F_{(1,30)} = 4.17$, $P = 0.047$); for the block with inverted response between 3 and 37 h of SD ($F_{(1,30)} = 5.13$, $P = 0.029$).

Similarly, the percentage of response failures obtained with the reaction time task was lower with SRC than with PBO

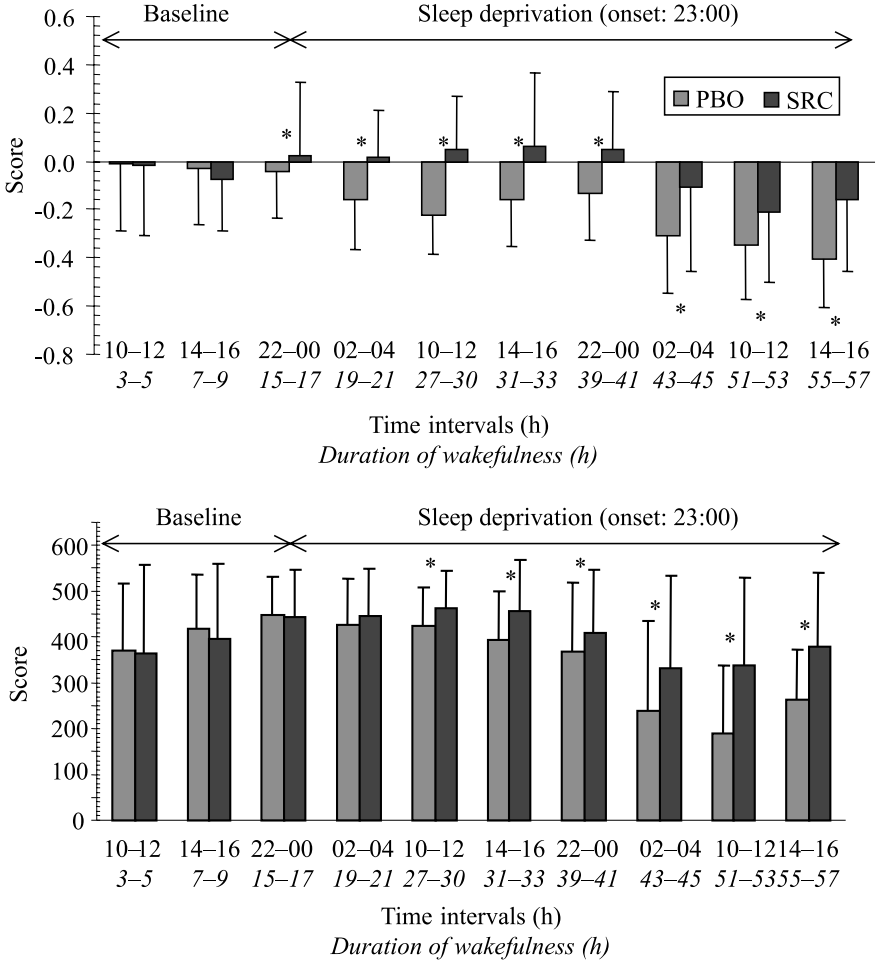

Figure 6. Assessment of the capacity of attention in baseline and SD conditions. Top (Fig. 6a): score of the symbol cancellation test (mean value ± SD); bottom (Fig. 6b): score of the Stroop's test (mean value ± SD). Placebo(PBO), slow release caffeine (SRC). For calculation of scores, see text. *Significant difference between SRC and PBO conditions, $P < 0.05$.

for the basic block after 23 h of SD ($F_{(1,30)} = 5.28$, $P = 0.027$); for the block with coded stimuli for the period between 35 and 41 h of SD ($F_{(1,30)} = 5.65$, $P = 0.022$); for the block with complex response between 11 and 37 h of SD ($F_{(1,30)} = 6.42$, $P = 0.015$) and for the block with inverted response between 3 and 37 h of SD ($F_{(1,30)} = 5.13$, $P = 0.029$).

- The mathematical processing task was globally sensitive to SRC: response time (Fig. 7a) was shorter ($F_{(1,30)} = 4.81$, $P = 0.034$) between 3 and 17 h of SD and percentage of errors (Fig. 7b) was lower ($F_{(1,30)} = 4.11$, $P = 0.048$) between 11 and 29 h of SD compared with PBO.
- Concerning the Sternberg memory scanning task, the response time of SRC subjects was shorter with two and four letters from 3 h of SD ($F_{(1,30)} = 4.26$, $P = 0.045$ and $F_{(1,30)} = 4.09$, $P = 0.049$, respectively), the percentage of errors was lower with four letters between 3 and 41 h of SD ($F_{(1,30)} = 7.97$, $P = 0.008$) and the percentage of response failures was lower with two letters throughout SD ($F_{(1,30)} = 5.42$, $P = 0.025$).
- For the spatial processing task, only percentages of errors between from the onset to the twenty sixth hour of SD ($F_{(1,30)} = 6.03$, $P = 0.019$) and of response failures over all the SD period ($F_{(1,30)} = 4.71$, $P = 0.036$) were lower with SRC than with PBO.
- For the tracking task (Fig. 8), control losses were less numerous with SRC than with PBO period from the onset to the thirty seventh hour of SD ($F_{(1,30)} = 5.13$, $P = 0.029$).
- For the grammatical reasoning task, percentage of errors was lower with SRC than with PBO from the onset to the twenty ninth hour of SD ($F_{(1,30)} = 7.34$, $P = 0.01$).
- For the divided attention task, the same results were observed in memory search task only: the percentages of errors with two and four letters and of response failures with four letters were less impaired with SRC than with PBO ($F_{(1,30)} = 4.51$, $P = 0.039$; $F_{(1,30)} = 5.62$, $P = 0.023$ and $F_{(1,30)} = 5.64$, $P = 0.022$, respectively).

The symbol cancellation test (Fig. 6a) showed a significant difference between SRC and PBO groups across all SD period ($F_{(1,30)} = 7.35$, $P = 0.01$), whereas the Stroop's test (Fig. 6b) showed a positive effect of SRC from the thirteenth hour of SD ($F_{(1,30)} = 4.12$, $P = 0.048$).

Regarding the subjective aspects of wakefulness, a positive effect of SRC was observed, compared with PBO, for only two items of the Bond and Lader's scale: 'Awake/Drowsy' and 'Confused/Clear ideas'. The SRC subjects felt less drowsy than

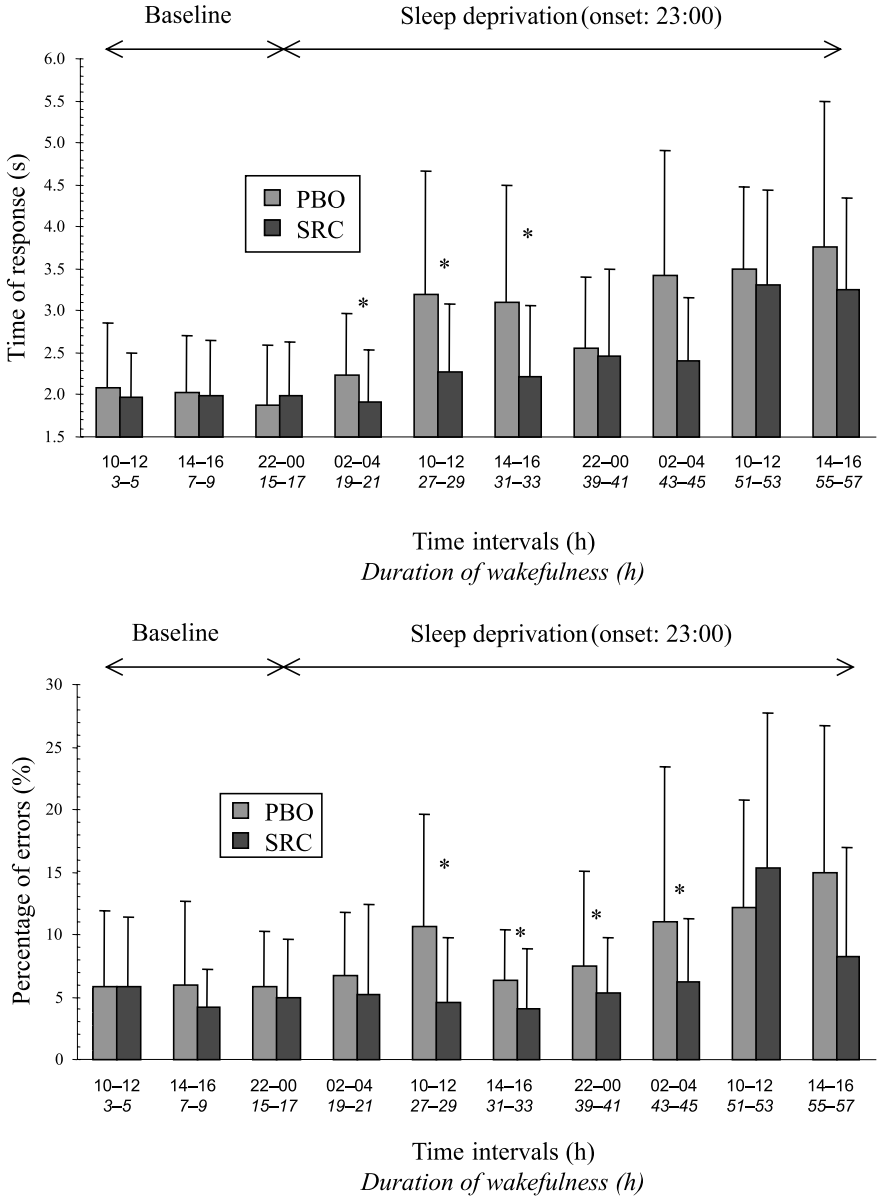

Figure 7. Mathematical processing task in baseline and SD conditions. Top (Fig. 7a): response time (mean value ± SD); bottom (Fig. 7b): percentage of errors (mean value ± SD). Placebo(PBO), slow release caffeine (SRC). *Significant difference between SRC and PBO conditions, $P < 0.05$.

PBO ($F_{(1,30)} = 4.89$, $P = 0.032$) up to 30 h of SD and less confused ($F_{(1,30)} = 4.46$, $P = 0.04$) up to 37 h of SD. No significant effect of caffeine treatment could be observed for the other items.

Core temperature

The core temperature evolution (Fig. 9) showed some differences between the two groups of treatment. Relative temperature of SRC subjects was higher compared with PBO between 4 and 8 h of SD ($F_{(1,186)} = 9.74$, $P = 0.002$), meaning during the first night without sleep. This difference was abolished the following morning, reappeared between 14 and 16 h of SD, meaning in the early afternoon ($F_{(1,15)} = 8.18$, $P = 0.011$) then vanished during all the second night without sleep. Subsequently, the results were inverted: temperature of SRC subjects was decreased compared with PBO during the second day at 09:00–11:00 h ($F_{(1,15)} = 5.19$, $P = 0.036$), 11:00–13:00 h ($F_{(1,13)} = 12.18$, $P = 0.004$), 13:00–15:00 h ($F_{(1,14)} = 9.91$, $P = 0.007$), 15:00–17:00 h ($F_{(1,13)} = 5.23$, $P = 0.037$) and at 21:00–23:00 h ($F_{(1,14)} = 5.70$, $P = 0.03$), meaning between 34 and 40 and between 46 and 48 h of SD.

DISCUSSION

Two recent studies including 32 and 36 h of SD in healthy humans reported the positive effects of SRC on vigilance and cognitive performance. Lagarde *et al.* demonstrated that a 300-mg dose of SRC given at midnight is efficient for maintaining a good level of performance and vigilance during 13 h after intake without any major side-effects, because of its pharmacokinetics (Lagarde *et al.* 2000). With a single 600-mg

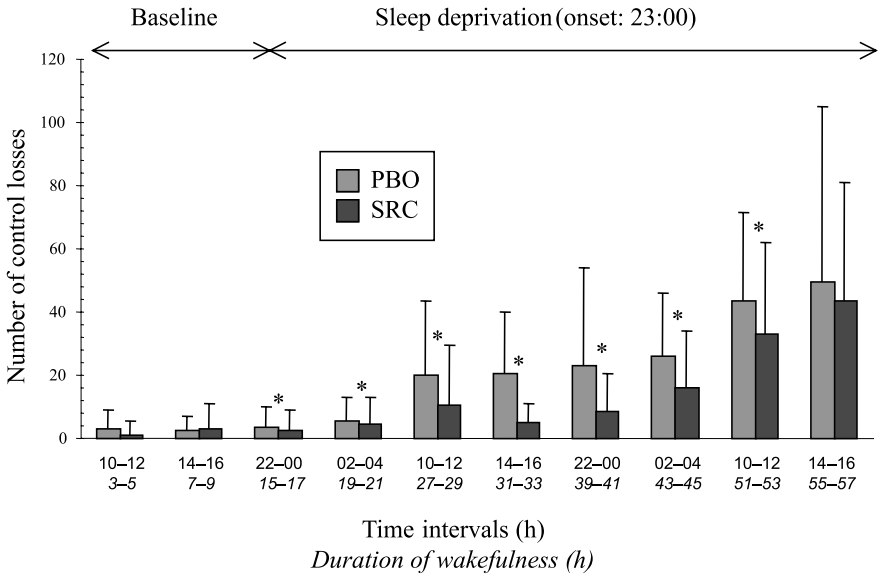

Figure 8. Tracking test number of control losses (mean value ± SD) in baseline and SD conditions. PBO: placebo; SRC: slow release caffeine. *Significant difference between SRC and PBO conditions, $P < 0.05$.

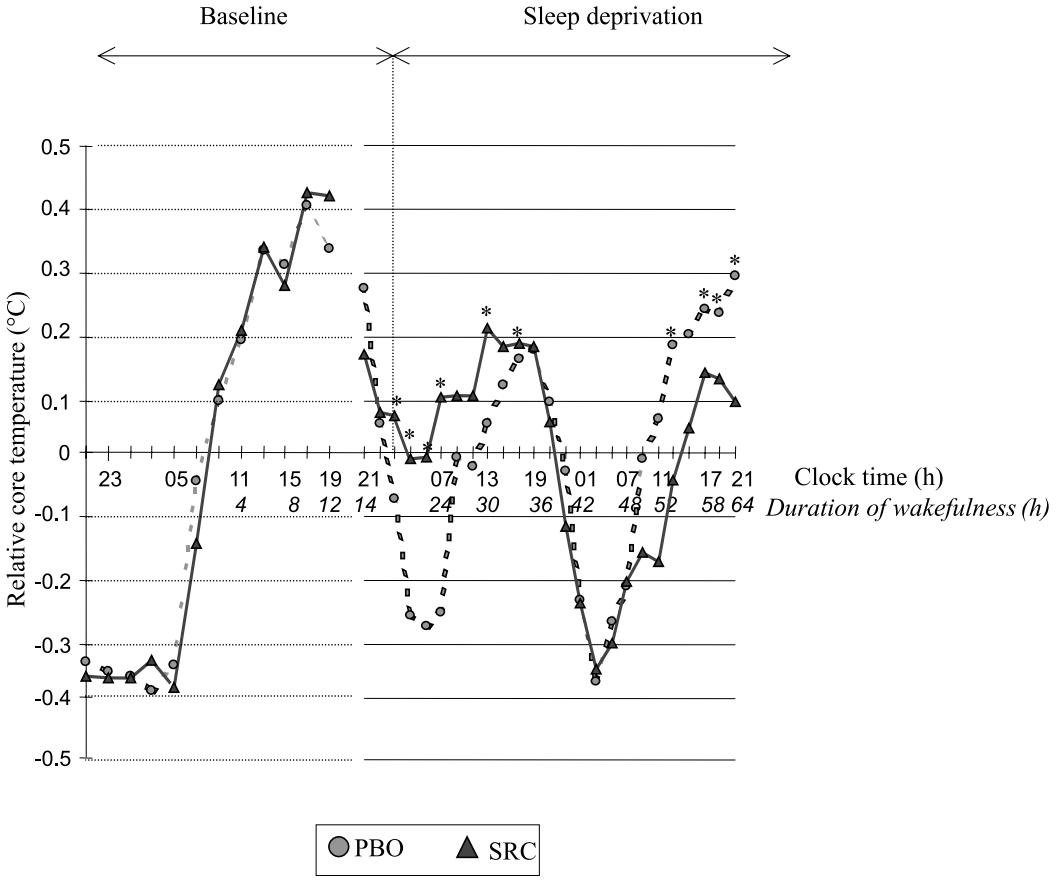

Figure 9. Evolution of relative core temperature (mean value ± SD) in baseline and SD conditions. PBO: placebo; SRC: slow release caffeine. *Significant difference between SRC and PBO conditions, $P < 0.05$.

dose given between 20:00 and 21:00 h, the alerting effects of SRC have shown to reverse the deleterious effect of SD for at least 24 h (Patat *et al*. 2000). On the other hand, fast absorption caffeine must be taken at larger or repeated doses to enhance performance with an efficiency lasting no more than 24 h (Bonnet *et al*. 1995; Walsh *et al*. 1990). Therefore, we designed our study to check the hypothesis that because of its longer effective half life, a 300-mg SRC given twice daily is efficient to alleviate the deleterious effect of a longer continuous wakefulness period (64-h) (Fig. 2). Our current study confirms that SRC has positive effects on vigilance and cognitive performance as soon as these parameters are

impaired. Moreover, it is important to point out that SRC does not induce any clinical or psychological impairment throughout continuous wakefulness period. The duration of SRC efficacy is variable and should be studied as a function of test.

Results of the placebo group confirm the already well-known effects of prolonged SD on wakefulness and performance (Lieberman 1992; Lorenzo *et al*. 1995). Indeed, since our subjects were non or very low consumers of caffeine on a regular basis, the decrease in performance and vigilance cannot be linked to negative effects of a caffeine withdrawal in the PBO subjects (Richardson *et al*. 1995). Compared with PBO, the repeated administration of SRC for a more or less prolonged SD period results in a longer sleep latency, more important motor activity, a feeling of being more awake and having clearer ideas, and a better level of cognitive performance.

The wakening effect is particularly interesting because, during 39 h of SD, the SRC group sleep latencies remain near the physiological mean values of a young normal population without SD (about 7 min) (as when they fall asleep in the PBO group). The study of microsleep shows that the SRC wakening effect is sufficiently potent to cancel the physiological nadir of wakefulness of the first night and reduce strongly the one of the second night of SD. From this point of view, SRC is superior to caffeine which has been shown to have shorter effects on vigilance, less than 6 h (Walsh *et al*. 1990) and only on the first night of sleep loss (Bonnet *et al*. 1995).

The wakening effect of SRC in our study is also confirmed by the slight number of failures of response and control losses during psychomotor tests with SRC compared with PBO. This fact which reflects a lower index of occurrence of microsleep during the task, is known as 'Walter Reed lapse hypothesis' (Williams *et al*. 1959), and can be considered as an indication that vigilance is maintained in spite of SD. This remark is confirmed objectively by the number of microsleep recorded after 23 h of SD.

All the tests implemented in this study were used by most of the authors to assess the impact of a psychotrope on wakening in man. The MSLT – which is widely used – gives a good index of the wakening effect of different doses of caffeine with or without SD (Bonnet and Arand 1992; Walsh *et al*. 1990; Zwyghuizen-Doorenbos *et al*. 1990) which explains the effect observed with SRC from the first measure after treatment administration.

Wrist actigraphy was validated by several authors as indirect index of wakening in study in wake–sleep activity research (Bonnet and Arand 1992; Brown *et al*. 1990; Caldwell *et al*. 1994; Lowden and Akerstedt 1999; Reid and Dawson 1999; Walsh *et al*. 1990; Zwyghuizen-Doorenbos *et al*. 1990).

There was no concordance between core temperature and motor activity values. The temporary increase in core temperature in SRC group could not be attributed to an increase in thermogenesis following supplementary motor activity. This result is consistent with sedentary experimental conditions. The effect of caffeine on melatonin secretion (Wright *et al*. 1997a) and consequently on temperature may be an interesting hypothesis but our experiment did not allow its verification.

Finally, the subjective aspects of alertness were also rapidly improved for subjects of SRC group. Subjects felt more awake than those of the PBO group from the first evaluation after the administration of treatment. This effect was potent till the forty fifth hour of SD.

The impact on psychomotor performance appeared much later, specifically after the twenty fourth hour of SD when a previous degradation of performance appeared (Lagarde *et al*. 2000; Linde 1995; Loke and Meliska 1984; Roach and Griffith 1987). The delayed effect of caffeine intake can be explained by the late degradation of psychomotor tests as shown by the results obtained in the PBO condition. As a matter of fact, caffeine acts as a stimulating substance when there is no SD (Hasenfratz and Bättig 1994; Kerr *et al*. 1991; Mumford *et al*. 1994) but is mainly particularly active when there is a previous degradation of performance. The interest of this new galenic form of caffeine is the delayed effect as a result of the slow release of the caffeine granules. Most of the previous studies carried out assessed the effect of caffeine 45–50 min after administration (Warburton 1995), 3 and 6 h after (Dawe *et al*. 1995), 1 h after (Linde 1995), 40 min and 3 h after treatment (Lieberman *et al*. 1987), i.e. relatively close to treatment administration, which corresponds to the plasmatic peak of caffeine.

The results obtained from the psychomotor tests confirm the efficacy of SRC to maintain a good level of performance despite the negative effects of SD (Tilley and Brown 1992). It should be noted that the action of caffeine is not limited to shorter response times but that it also has a positive action on the number of errors. As a matter of fact, caffeine seems to have a global action on information processing and divided attention management.

The effects of caffeine consumption on performance lead to much debated results. In normal conditions and according to the dose, caffeine may or may not improve recollection in memory tasks (Erikson *et al*. 1985; Roach and Griffith 1987), caffeine decreases performance for tasks requiring a fine motor co-ordination (Loke *et al*. 1985) and improves the choice reaction time as well as the results of a tracking task and the response time for a short-term memory task (Kerr *et al*. 1991). Caffeine also induces an increase in performance for visual vigilance task (Fine *et al*. 1994). However, the results are more constant in fatigue or SD conditions. Therefore, caffeine was tested to maintain performance during continuous operations with SD. Caffeine consumption (200 mg) at the beginning of a night work increases objective wakefulness over 8 h of work and maintains vigilance to baseline for the mathematical, logical reasoning and visual vigilance tests during the whole experiment (Walsh *et al*. 1990), whereas a degradation was observed for the PBO group. A 400 mg dose of caffeine results in a performance level peak for reasoning task, computation task and symbol substitution task during almost 6 h after the first administration in 52-h SD condition (Bonnet *et al*. 1995). During a 64.5- h SD, a 600-mg dose of caffeine taken after

49 h of wakefulness improves performance for reaction time, calculation, and logical reasoning tasks for 12 h after administration (Penatar *et al*. 1994). The facilitating effects found in caffeine could be related to the fact that caffeine fights against the degradations of performance caused by fatigue (Fagan *et al*. 1988). This hypothesis has been confirmed by Lorist *et al*. (1994): tired subjects showed a higher increase in performance (decrease in error rates) after caffeine administration than rested subjects.

All the results obtained in our study show essentially the prolonged effect of SRC on vigilance and performance data during prolonged SD, without major side effects, providing further evidence of the interest of SRC compared with repeated intakes of caffeine-containing beverages which would result in swings of efficacy associated with clinical disorders (see Fig. 1). Indeed, SRC did not induce any clinical or psychological impairment during all the continuous wakefulness period. These results contrast with those generally found with caffeine solution where the pharmacodynamical effects are limited in duration (Quinlan *et al*. 1997) and where doses higher than 400 mg induce severe side effects (Boulenger *et al*. 1984). This study corroborates the results of our previous study on SRC during a 30-h SD particularly with regard to the immediate awakening effect, observed 2 h after the administration. Yet, this stimulating and awakening effect run out on and after the thirty ninth hour of SD. The fourth administration is nearly inefficient: MSLT is still significantly greater in the SRC group but this seems clinically minor in relation to the overwhelming sleepiness at that time. In a repeated administration situation, the use of SRC must be limited and joined with prophylactic naps as demonstrated by numerous studies (Batéjat and Lagarde 1999; Bonnet and Arand 1994; Bonnet *et al*. 1995).

In conclusion, slow release caffeine (300 mg/dose given twice daily) exerts prolonged positive effects on vigilance and performance for a longer SD period than caffeine does. Therefore, for long work schedule in case of increase in workload and also as a treatment for fatigue in standard medical practice, slow release caffeine could be a possible alternative to other psychostimulants, which have a more restricted use, as amphetamines or eugregorics.

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