EFFECT OF CAFFEINE ON SLEEP: EEG STUDY IN LATE MIDDLE AGE PEOPLE

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1 The effect of caffeine alkaloid base (300 mg) on whole night sleep was investigated by electrophysiological techniques in six late middle age subjects (mean age 56 years), comparison being made with decaffeinated coffee and with no drink prior to sleep, using each condition five times in a balanced order on non-consecutive nights.

2 After caffeine the mean total sleep time decreased on average by 2 h, the mean sleep latency increased to 66 minutes. The number of awakenings increased and the mean total intervening wakefulness was more than doubled after caffeine.

3 In the first 3 h of sleep a decreased amount of stage 3 + 4 was observed, accompanied by an increased amount of stage 2 and of intervening wakefulness, without a significant change in the amount of rapid eye movement sleep.

4 The change in sleep pattern observed suggests an increased capability for arousal and decreased ability to develop or sustain deeper stages of non-rapid eye movement sleep after caffeine.

Introduction

Caffeine, 3,5,7-trimethylxanthine, is a stimulant of the central nervous system (CNS) (Ritchie, 1968) daily consumed by a large population in the form of coffee, tea or cola drinks. Although insomnia has been included as one major symptom of both acute and chronic caffeine intoxication there are few quantified studies of sleep after moderate doses.

Subjective reports of sleep and mood after caffeine reveal big inter- and intra-individual variability of reaction (Goldstein, Warren & Kaiser, 1965; Goldstein, Kaiser & Whitby, 1969). Earlier electroencephalographic (EEG) sleep studies failed to show significant changes after caffeine admini-stered to young people (Gresham, Webb & Williams, 1963; Hartmann, 1968). Nevertheless an increased number of body movements during the night after caffeine has been repeatedly found (Mullin, Kleitman & Copperman, 1933; Schaff, Schwertz & Marbach, 1962; Schwertz & Marbach, 1965; Stradomsky, 1970). Disturbed sleep in the first 3 h after caffeine was reported by Müller-Limmroth (1972) using EEG recording.

The present study examines electro-physiological variables during sleep after caffeine administered to late middle age people: it is sometimes claimed that a decreased tolerance to caffeine accompanies normal ageing.

Methods

Subjects

Six normal volunteers aged 50-63 years (mean 56), two males and four females, were used. Three were rather energetic, self-confident personalities, the other three more sensitive, and anxiety prone. One reported taking diazepam for several weeks four months before the experiment because of restlessness and irritability. No subject was accustomed to sleeping pills, four were non-smokers, while the remaining two smoked ten and thirty cigarettes a day, respectively. Alcohol and all drugs were prohibited throughout the study.

Three subjects considered themselves to be good sleepers, three complained of difficulty in falling asleep and of frequent awakenings. The mean number of hours spent in bed was 7.5 h, with a range between 6 and 9 hours.

Habits of caffeine intake

The subjects regularly took coffee and tea. Three were drinking about as much coffee as tea, two more coffee than tea, one subject tea only. All were asked to maintain their usual habits.

The mean number of cups of coffee for the whole group was 2.7 ± 2.0, and cups of tea, 3.3 ± 3.0 per day. Most caffeine intake was in the

morning or the lunch hour. After 15.00 h, on average 0.7 cups of coffee were taken and 1.7 cups of tea. After 21.00 h only 0.5 cups of coffee were taken and 0.5 cups of tea. Two subjects were used to having their last coffee or tea at 21.00-21.30 h, four subjects as late as 23.00-24.00 hours. In a structured interview before the experiment no subject was found who believed that coffee or tea at bedtime would impair his sleep.

The usual caffeine per day was calculated from the amounts of coffee powder and tea each subject brought as an example of his intake and varied between 150 and 440 mg/day, with a mean at 291.3 mg. Body weight varied between 45.9 and 85.4 kg, and the daily intake of caffeine between 2.8 and 7.5 mg/kg, mean 4.5 mg/kg.

Experimental procedure

In each subject whole night sleep was recorded on 15 non-consecutive nights, so allowing recovery sleep at home in case of disturbed sleep on experimental nights. On 5 nights no drink was given prior to sleep, on 5 nights decaffeinated coffee, on 5 nights decaffeinated coffee containing added caffeine alkaloid base (300 mg). The three experimental conditions were balanced for each subject as well as for the whole group. Preliminary experiments had been conducted showing that the two drinks could not be discriminated by taste. Caffeine (300 mg) represented on average a dose of caffeine (4.7 mg/kg). Thus the subjects were given on caffeine nights a dose of caffeine equal on average to their usual whole day caffeine intake.

Decaffeinated coffee was made from 'Decaf' (1.5 g) mixed with hot water (150 ml). No milk was allowed, and only one teaspoonful of sugar. It was drunk at 22.15 h, with lights out at 22.30 h, and recording until 07.30 hours. The subjects urinated before retiring.

Subjective evaluation of mood and anxiety level in the day preceding sleep was recorded by means of self-rating analogue scales (Oswald, Lewis, Dunleavy, Brezinova & Briggs, 1971), and sleep quality and level of morning vigilance were rated by a similar method.

On all nights silver electrodes placed above and below each outer canthus provided two channels of bipolar eye movement recording, a pair of parieto-occipital electrodes provided one channel of the EEG, and a pair of submental electrodes monitored muscle tone. The paper speed was 15 mm/second. The records were scored blind according to international criteria (Rechtschaffen & Kales, 1968).

For statistical evaluation the first 3 nights (one under each condition) were omitted as adaptation nights. The means of the remaining 4 nights under each condition were computed for various sleep variables and the differences among all three conditions tested by a non-parametric test, namely, Friedman's two way analysis of variance (Siegel, 1956). Further, the means for the caffeine condition were expressed as percentages of the individual's baseline (= no drink) values. Possible relations of the caffeine reaction to other factors, such as age, were examined using the Mann-Whitney U test (Siegel, 1956).

Results

Whole night measures

The main results are presented in the Table 1 and Figure 1.

The duration of total sleep under baseline conditions averaged 475 min and did not differ substantially from that after decaffeinated coffee 467 minutes. After caffeine the average total duration of sleep was only 350 min, or 2 h less than baseline ($P < 0.01$). Only one subject completed an average of 7 h of sleep after caffeine, while one subject averaged only 4 h 25 minutes.

Sleep onset latency averaged 18 min baseline,

Table 1   Effect of caffeine (300 mg) on whole night sleep, mean ± s.d. for six subjects, 4 nights each condition

		Condition			
Sleep variable	No drink	Decaffeinated coffee	Caffeine	x_r^2	P
Total sleep time (min)	475 ± 22	467 ± 31	350 ± 59	9.33	0.01
Sleep onset latency (min)	18 ± 13	21 ± 11	66 ± 39	9.33	0.01
Awake + stage 1 (min)	64 ± 28	66 ± 26	140 ± 69	7.00	0.05
Shifts to awake	7 ± 3	7 ± 3	11 ± 5	9.33	0.01
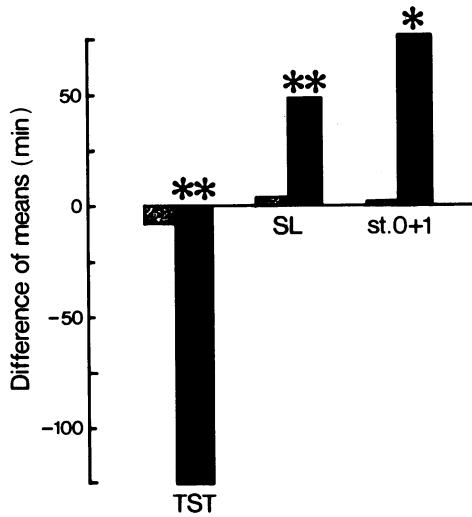
Fig. 1 Effect of caffeine on whole night sleep. The means across 4 nights under each condition in six subjects are shown for total sleep time (TST), sleep onset latency (SL), and amount of intervening wakefulness and drowsiness (st. 0 + 1). The mean values for decaffeinated coffee and caffeine are expressed as their difference from the baseline condition: o = no drink; (stippled columns) de-caffeinated coffee; (solid columns) decaffeinated coffee with caffeine (300 mg). Difference statistically significant. ** $P < 0.01$; * $P < 0.05$ (see also Table 1).
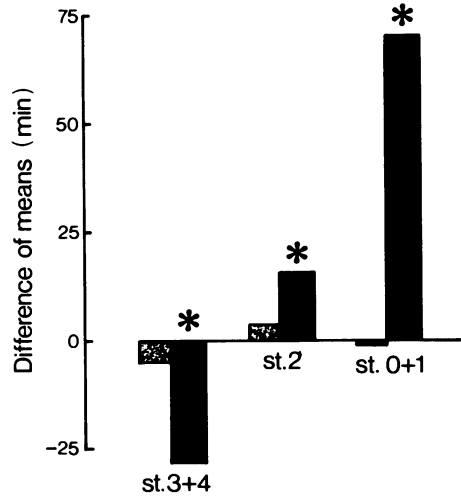
Fig. 2 First 3 h of sleep after caffeine. The means across 4 nights under each condition in six subjects are shown for intervening wakefulness and drowsiness (st. 0 + 1), light NREM sleep (st. 2) and the amount of slow wave sleep (st. 3 + 4). The mean values for decaffeinated coffee and caffeine are expressed as their difference from the baseline condition, o = no drink; (stippled columns) decaffeinated coffee; (solid columns) decaffeinated coffee with caffeine (300 mg). Difference statistically significant, * $P < 0.05$.

21 min on decaffeinated coffee, but 66 min after caffeine ($P < 0.01$).

The amount of wakefulness and drowsiness, i.e. the minutes of time awake and of stage 1 accumulated after sleep onset, averaged 64 min baseline, 66 min on decaffeinated coffee, and 140 min after caffeine ($P < 0.05$). The average number of awakenings also increased on caffeine: seven with baseline; seven with decaffeinated coffee; eleven after caffeine ($P < 0.01$).

The absolute amounts of stage 3 + 4 (slow wave sleep) and of rapid eye movement (REM) sleep were significantly smaller on caffeine nights,

consistent with the overall decrease in sleep time. The relative values, i.e. the amount of stage 3 + 4 and stage REM expressed as a percentage of the total sleep time, did not change significantly, although a trend to a decrease after caffeine was found.

First 3 h of sleep

As the half-life of caffeine is 3.5 h (Cornish & Christman, 1957), a particular evaluation was made of the first 3 h of sleep (Table 2, Figure 2).

A decrease in the amount of stage 3 + 4 was

Table 2 Effect of caffeine (300 mg) on first 3 h of sleep, mean ± s.d. for six subjects

		Condition			
Sleep variable	*No drink*	*Decaffeinated coffee*	*Caffeine*	χ^2_r	*P*
Awake + stage 1 (min)	15 ± 6	14 ± 8	85 ± 82	7.0	0.05
Stage 2 (min)	84 ± 14	88 ± 16	100 ± 14	6.33	0.05
Stage 3 + 4 (min)	66 ± 12	61 ± 19	38 ± 16	6.33	0.05
Stage REM (min)	22 ± 4	22 ± 5	25 ± 5	4.08	NS

found on caffeine nights. The average values were 66 min baseline, 61 min decaffeinated coffee, and 38 min after caffeine ($P < 0.05$).

The amount of stage 2 was increased after caffeine from 84 min and 88 min to 100 min ($P < 0.05$), as well as the amount of intervening wakefulness from 15 and 14 min to 85 min ($P < 0.05$).

The amount of stage REM was not changed significantly, though there was a tendency to increased values after caffeine (22 ± 5 min baseline, 22 ± 5 min decaffeinated coffee, 25 ± 5 min after caffeine).

Later hours of sleep

Comparisons of the later part of the night were less sure owing to the variations in total sleep. It was possible to compute the amount of intervening wakefulness, after the first 3 h of sleep but before a second 3 h of sleep were completed, in five subjects, omitting one subject who had 4.4 h of mean total sleep. The amount of intervening wakefulness in the second 3 h of sleep was significantly greater after caffeine, and this was so despite the fact that the sixth hour was not always completed, the mean durations being 14 ± 4 min baseline, 17 ± 12 min decaffeinated coffee, 47 ± 20 min after caffeine ($\chi_r^2 = 8.6, P < 0.02$).

Individual differences in reaction to caffeine

The big variability in reaction was expressed in the significantly bigger variance seen after caffeine in comparison with the other two in several sleep variables (e.g. sleep onset latency, $F = 9.0$ and 12.5). In one subject, the increase in sleep onset latency was excessive, averaging 131 min, but the succeeding sleep was less disturbed by intervening wakefulness than in other subjects. Another subject was able to get off to sleep on average within 14 min after caffeine, but the amount of intervening wakefulness substantially increased, especially in the late night. There was no sign of tolerance to the drug.

Self-rating scales

There were no significant differences among the three conditions as to the level of mood and anxiety prior to sleep. A significant decrease ($\chi_r^2 = 9.00, P < 0.02$) in sleep quality was reported after caffeine (Figure 3). The quality of sleep after caffeine was on average rated worse by 35% than that on either of the other conditions. There was a non-significant tendency to a decreased level of morning vigilance after caffeine nights.
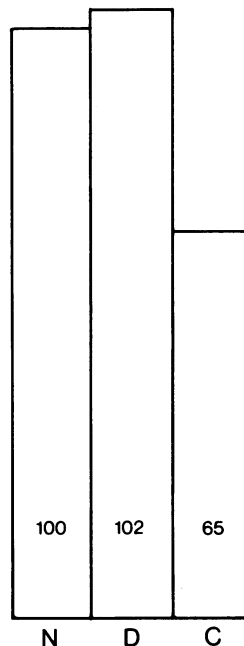
Fig. 3 Self-rated sleep quality after caffeine. The means across 4 nights under each condition in six subjects are shown. The values for decaffeinated coffee (D) and caffeine (300 mg; C) are expressed as percentages of the baseline condition, no drink (N). Sleep quality after caffeine was significantly impaired when compared with baseline and decaffeinated coffee ($P < 0.02$).

Possible sources of individual's differences in the reaction to caffeine

The only significant relation was found in respect of age. The three subjects between 50 and 55 years (mean 53) had a mean baseline total sleep time of 474 min and only 397 min after caffeine, a decrease of 77 minutes. The three subjects between 56 and 63 years (mean 59) averaged 477 min baseline and 304 min after caffeine, a much larger decrease of 173 min ($U = 0$, $P < 0.05$). The older three also had a greater increase in sleep onset latency.

Decaffeinated coffee

There were no significant differences between the baseline and the decaffeinated coffee findings.

Discussion

Caffeine, in a dose corresponding to two to three cups of coffee taken at bedtime, caused a

considerable sleep disturbance in a group of late middle age subjects. No tolerance was observed. Similar findings were reported by Goldstein et al. (1965) who used self-reports by young subjects of sleep onset latency and soundness of sleep after caffeine and decaffeinated coffee. Even subjects with high daily caffeine intake were not tolerant of the sleep disturbing effects.

The big variability in the reaction to caffeine, found in studies using self-report, was confirmed in this experiment using physiological measures.

Caffeine has been found to be completely absorbed within 1 h after ingestion and its plasma level tends to decline thereafter, with a half-life of 3.5 h (Cornish & Christman, 1957) and this is consistent with the time course of the observed changes in sleep.

The main feature of the reaction to caffeine was increased wakefulness, consistent with the conventional view of caffeine as a central stimulant (Ritchie, 1968). The decrease in the amount of stage 3 + 4 in the first 3 h of sleep, also found by Müller-Limmroth (1972), could be partly explained by frequent interruptions of sleep by awakening. Nevertheless, as the amount of stage 2 increased after caffeine, it seems that also when a manifest arousal did not occur, the development of deeper stages of non-rapid eye movement (NREM) sleep was impaired.

The increased arousal did not disturb the usual development of stage REM in the first 3 h, nor was the percentage of REM sleep in the total sleep time changed, a result consistent with that of Gresham et al. (1963) and that of Müller-Limmroth (1972). This distinguishes caffeine from another CNS stimulant, namely amphetamine. Although both amphetamine and caffeine have similar small effects on the waking EEG, speeding the EEG spectrum slightly (Gibbs & Gibbs, 1958), and both induce similar well pronounced arousal disturbances of sleep, amphetamine is a powerful suppressor of REM sleep (Oswald, 1970). Thus different mechanisms of cortical activation might be expected in the two drugs.

The central stimulant action of amphetamine has been attributed to its interference with central noradrenergic and dopaminergic mechanisms (Fuxe & Ungerstedt, 1970). Caffeine has been shown to have some similar effects, releasing norepinephrine in the CNS of the rat (Berkowitz, Tarner & Spector, 1970) and increasing turnover of norepinephrine and dopamine in the brain of mice (Waldeck, 1971).

The reaction to caffeine in the subjects reported here was considerably stronger than that obtained in experiments with younger subjects (Gresham, et al., 1963: Hartmann, 1968). It is therefore interesting that signs of increased catecholamine turnover have been reported in older people. Bowers & Gerbode (1968) found metabolites of biogenic amines to be present in higher concentrations in the cerebrospinal fluid of elderly patients, and Robinson, Nies, Davis, Bunney, Davis, Colburn, Bourne, Shaw & Coppen (1972) reported the level of monoamine oxidase in human brain, platelets and plasma to increase with age. Thus it is conceivable that the already altered metabolism of brain catecholamines in older people is related to their greater sensitivity to caffeine.

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