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Variations of Cyclic Alternating Pattern Rate and Homeostasis of Sleep Organization: A Controlled Study on the Effects of White Noise and Zolpidem

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TERZANO, M. G., L. PARRINO, G. FIORITI, A. FAROLFI, M. C. SPAGGIARI, S. ANELLI AND T. ARCELLONI. *Variations of Cyclic Alternating Pattern Rate and homeostasis of sleep organization: A controlled study on the effects of white noise and zolpidem.* PHARMACOL BIOCHEM BEHAV **29**(4)827–829, 1988.—The Cyclic Alternating Pattern (CAP) is a physiologic structure of normal non-REM (NREM) sleep, functionally correlated to long-lasting arousal instability. In 12 healthy volunteers, a continuous 45 dB (A) white noise induced no remarkable changes on the standard sleep parameters. However, compared to the baseline conditions, the acoustic perturbation determined a significant increase of the Cyclic Alternating Pattern Rate (CAPR), that measures the amount of CAP during sleep. Ten mg of zolpidem, a novel imidazopyridine hypnotic compound, did not modify the structure of unperturbed sleep, but induced a highly significant reduction of the increased values of CAP Rate due to white noise. The homeostatic function of CAP is stressed. CAPR appears to be a highly sensitive indicator of environmental modifications during sleep.

Cyclic Alternating Pattern Noise and sleep Zolpidem

THE Cyclic Alternating Pattern (CAP) is a physiologic component of normal non-REM (NREM) sleep [5]. This EEG periodic activity is organized in biphasic 40-sec cycles (Fig. 1), which are clustered in sequences and assume peculiar features within the 4 NREM stages. On the basis of their selective reactivity to the same arousing stimulus, the two phases of CAP correspond to levels of greater and lesser arousal, respectively. Therefore, whatever the sleep stage, CAP sequences are functionally related to long-lasting fluctuations in the level of arousal [5,6]. Actually, in the classic sleep histogram, CAP sequences are often chronologically linked to the major dynamic events of sleep such as falling asleep, arousals and stage changes [5,6]. Apart from CAP sequences, the remaining NREM sleep is characterized by prolonged background activities peculiar to the different stages and functionally related to a relative steady state of arousal [6]. This pattern is defined as non-CAP (NCAP). Therefore, in NREM sleep, CAP and NCAP correspond to two distinct functional states in the arousal control mechanisms.

CAP rate (CAPR) measures the percentage of CAP to Total Sleep Time (CAPR/TST), to total NREM sleep (CAPR/NREM), and to each NREM sleep stage [5,6]. As CAP sequences may occur either spontaneously or following subawakening arousal stimuli [6], a continuous 45 dB (A) white noise delivered to normal sleepers induces a significant increase of CAP rate, which is correlated with deterioration of sleep quality, in spite of lack of significant changes in the structural organization of sleep [7].

On the basis of these preliminary results, we supposed the increase of arousal instability, expressed by the rise of CAP rate and due to white noise, to be attenuated by the administration of an hypnotic drug. For this purpose, we used a new imidazopyridine compound, denominated zolpidem, that at low doses (10 mg), induces a physiologic sleep pattern [2].

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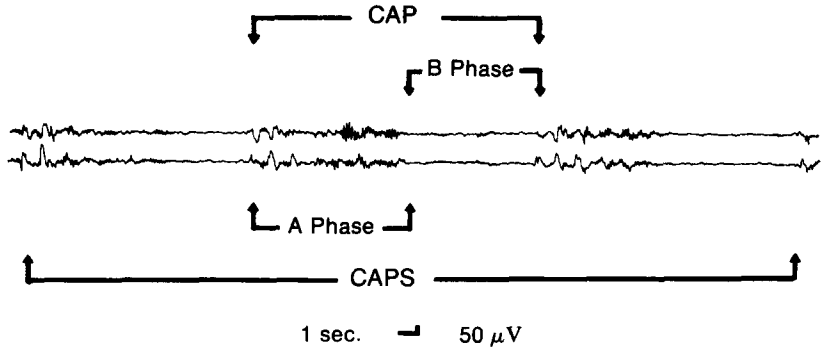

FIG. 1. Segment of a Cyclic Alternating Pattern sequence (CAPS) during stage 2 of sleep. Each cycle (CAP) is composed by a phase A (K-complexes associated with spindles and alpha-like activity) and by a phase B (background rhythms peculiar to the specific sleep stage).

METHOD

Twelve healthy young adults, 6 males and 6 females, 25.1±0.99 years old (range: 19–29 yr), with normal habits and no sleep complaints, were suitable for the trial and gave written consent to take part in it.

The subjects were polygraphically recorded (EEG, electrooculogram, electromyogram, electrocardiogram, mouth and nose respiration) at the Parma University sleep lab, where ambient sound pressure level never exceeded 27 dB (A) Leq. After an adaptation night, treatments were administered 4 times at 48 hour intervals, according to a completely randomized cross-over factorial design: (1) either 10 mg zolpidem or placebo; (2) presence or absence of acoustic perturbation, accomplished by a continuous 45 dB (A) white noise automatically delivered and controlled during the entire sleep recordings. Each subject received the treatments according to a latin square randomization for four possible sequences. Administration was double-blind as was blind the physician who analysed the polysomnograms. Drugs were administered 15 min before lights-out. Time in bed lasted 500 min.

Subjective assessment of sleep quality and daytime Multiple Sleep Latency Test (MSLT) were completed by all volunteers. The analysis of sleep recordings was performed according to standard criteria [4], whereas CAP and NCAP detection was carried out on the basis of the guidelines defined in previous papers by Terzano *et al.* [5,6].

The following sleep variables were scored: Total Sleep Time; Wake After Sleep Onset; Total Wake Time; Sleep Latency; total duration of stages 1, 2, 3, 4 and REM; Sleep Period Time; Wake After Final Awake. CAP rate, referred to the ratio CAP Time/Sleep Time, was calculated for Total Sleep Time (*CAPR/TST* = Total CAP Time/TST × 100) and for total NREM sleep (*CAPR/NREM* = Total CAP Time/Total NREM Sleep × 100).

Under the different experimental conditions, all variables were analysed both by a factorial mixed ANOVA test and by a Wilcoxon rank test for paired data.

RESULTS

When white noise was associated with placebo, subjects complained of impaired sleep quality, in spite of no significant changes in the conventional polysomnographic variables. However, CAP rates were significantly influenced by both perturbation and drug effects. Compared to the baseline values (CAPR/TST: 18.8% and CAPR/NREM: 24.9%), white noise induced an increase of more than 120% during the placebo nights (42% and 55.1%, respectively), and less than 60% during the zolpidem nights (29.5% and 38.1%, respectively). On the other hand, under unperturbed conditions, zolpidem was basically devoid of significant effects on the standard sleep parameters and on both CAPR/TST (19.6%) and CAPR/NREM (26%).

No remarkable changes emerged in the overall course of MSLT. All the recruited subjects completed the trial.

DISCUSSION

Although the level of white noise was well beyond the limits recommended by the World Health Organization for physiologic sleep [3], it did not induce disruptive effects on the architecture of Dement and Kleitman stages and cycles [1].

Since CAP sequences are functionally correlated to controlled oscillations of arousal, the selective enhancement of CAP rate could express the amount of "stress" exerted by the brain to preserve a consistent organization of sleep. The different behaviour of CAP rate and standard polygraphic variables could be explained by a hierarchic sensitivity of the structural components of sleep in response to the same perturbing event. On the basis of our present knowledge, no definite inferences can be made on the single threshold levels. However, pilot studies directed to graduate the effects of increasing sound pressure on sleep indicate that a progressive expansion of CAP rate generally precedes the appearance of major changes in the architecture of sleep. The highly significant increase of CAP rate, contrasting with the trivial variations of the conventional polygraphic variables, is strongly suggestive of an homeostatic role of CAP in the regulatory mechanisms of sleep [8].

As for the treatment factor, zolpidem did not affect sleep under unperturbed conditions, but it did show selective effects on CAP rate under acoustic perturbation. Therefore, at therapeutic doses, zolpidem did not modify the structure of normal sleep, but it was highly effective in helping the sleeping brain to counteract the prominent instability of arousal induced by a sustained disturbance.

Our model may supply an original framework for the study of situational insomnia that we reproduced at a subawakening level in order to assess the effects of a controlled perturbation on a preserved sleep structure. The latter condition, indeed, could explain the lack of significant modifications of daytime sleepiness.

In conclusion, CAP rate appears as a highly sensitive indicator of environmental manipulations, even when no major changes occur in the organization of sleep. In light of this peculiarity, the scoring of CAP may represent a useful tool for monitoring the effects of hypnotic drugs during sleep.

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