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Electroencephalographic Effects of Nicotine Chewing Gum in Humans

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PICKWORTH, W. B., R. I. HERNING AND J. E. HENNINGFIELD. *Electroencephalographic effects of nicotine chewing gum in humans.* PHARMACOL BIOCHEM BEHAV **25**(4) 879–882, 1986.—The electroencephalographic (EEG) and subjective effects of nicotine chewing gum (0, 2 and 4 mg) were compared in three tobacco deprived (12 hr) heavy smokers. EEG responses were recorded from F_7, F_8, T_5, and T_6 positions before and after the subjects chewed nicotine gum (chew rate = 1 per 2 sec) for 10 min and subsequently analyzed by a computer-based data acquisition and analysis system. Analysis of the chewed gum indicated that the subjects extracted approximately 50 percent of the available nicotine. The nicotine gum increased EEG frequencies in the alpha (7.25–14 Hz) and beta (14.25–25 Hz) bands and decreased theta (4–7 Hz) power. The EEG effects were most evident in the resting subject; the effects of the gum were similar but weaker when the EEG was aroused by a mental arithmetic task. Nicotine gum had EEG stimulant effects like those of inhaled tobacco smoke which were most apparent in the relaxed subject. In spite of this similarity, the subjects did not identify the effects of the gum as being identical to those of cigarettes.

Electroencephalogram Nicotine Nicotine gum

NICOTINE administration in the form of smoked tobacco has been shown to increase EEG alpha frequency [23] and decrease alpha and theta power [9] in the nicotine deprived smoker. Similarly intravenous nicotine transiently decreased alpha power [15]. Another form of nicotine, nicotine polacrilex (chewing gum) is now available (by prescription in the United States and elsewhere) for the treatment of tobacco dependence (American Hospital Formulary Service, 1985). The nicotine gum is prescribed as a substitute for tobacco and is hypothesized to block the pharmacologic aspects of withdrawal while the behavioral components of tobacco dependence are treated [7]. The treatment is statistically efficacious; however, most studies reveal that fewer than half of the patients treated with nicotine gum are able to maintain tobacco abstinence at one year follow-up suggesting that the gum is an imperfect substitute. Since the self reported effects of nicotine gum differ from those of smoked nicotine [7,17], it is plausible that the EEG changes induced by nicotine gum differ from those induced by smoked tobacco. The main purpose of this study was to describe the EEG activity following nicotine gum in nicotine deprived normal volunteers.

METHOD

Subjects

Three adult (mean age = 34, range = 24–50 years) male subjects with histories of smoking cigarettes for at least seven years were tested during their stay on a residential research unit. The subjects smoked an average of 22 cigarettes per day (range = 16–30) and had mean Fagerstrom Tolerance Questionnaire scores of 8 (range = 7–9) [5].

Procedure

Subjects abstained from caffeinated beverages and tobacco products for 12 hr prior to the EEG recording sessions. Abstinence from tobacco was confirmed by breath carbon monoxide testing. The CO levels obtained immediately prior to the tests averaged 11.9 ppm (range = 7–20 ppm). All recording sessions were completed in the afternoon while the subject was comfortably seated in a reclining chair in an electrically shielded sound attenuated recording chamber. EEG recordings were derived from: C_z–T_6, C_z–T_5, C_z–F_7 and C_z–F_8. Grass silver cup electrodes with impedences below 10 k ohms were used. The recording period consisted of a three-minute EEG recording while the subject relaxed with his eyes closed and another three-minute recording while the subjects performed a mental arithmetic (sequential subtraction) task. After the recording periods, the subject chewed a single piece of chewing gum containing 0, 2 or 4 mg of nicotine. They were visually monitored while they chewed for 10 minutes at a chew rate of 1 chew per 2 seconds for a total of 300 chews. A prerecorded tone indicated the chew times. The chewed gum was collected, frozen and subsequently analyzed for nicotine content. The subjects completed the Addiction Research Center (ARC) single dose questionnaire at the conclusion of the gum chewing [12]. The test contains scales for the subjects to report if they were given a drug, to identify the drug, to indicate the symptoms ("sensations") that were produced, and to rate their magnitude of liking the drug. The EEG recording periods were repeated immediately after the subject completed the questionnaire about 3 min after chewing the gum. The studies were conducted according to a double blind latin

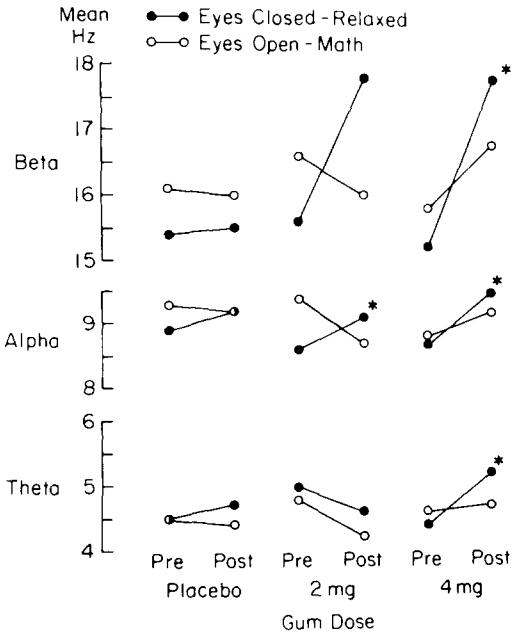

FIG. 1. Mean (n=3) peak EEG frequency in leads C_z–T_5 and C_z–T_6 for theta (4–7 Hz), alpha (7.25–14 Hz) and beta (14.25–25 Hz) bands before and after nicotine 2 and 4 mg or placebo gum. *Significant difference from pregum value ($p<0.05$, paired t-test).

square design whereby each subject was tested three times, once at each dose level.

Instrumentation

Power spectral analysis of the EEG data was accomplished on-line by a Nicolet Pathfinder II. The algorithm identified the peak frequency and power in one minute artifact free samples in each of the usually defined frequency bands: theta, 4–7 Hz; alpha, 7.25–14 Hz and beta, 14.25–25 Hz. The peak frequency and power for each minute of the three minute sessions were obtained. The before and after gum sessions were compared by means of paired t-tests.

RESULTS

Analysis of the nicotine context of the chewed gum indicated a mean of 0.85 mg (SD=±0.48) or 43 percent of nicotine was extracted from the 2 mg gum, and 2.08 mg (SD=±0.29) or 52 percent of the available nicotine from the 4 mg gum. Figure 1 shows the peak frequency of EEG in the various bands during sessions with the eyes closed (closed circle) and eyes open-math task (open circle). During the eyes closed-relaxed EEG recording session, the 4 mg nicotine gum significantly ($p<0.05$, paired t-test) increased peak frequencies in the beta, alpha and theta bands. The 2 mg gum had significant effects only on the alpha frequency; the placebo gum did not significantly change EEG frequency in any of the frequency bands. During the session in which the subjects concentrated on a math task with open eyes, no significant EEG frequency changes occurred as a result of nicotine administration.

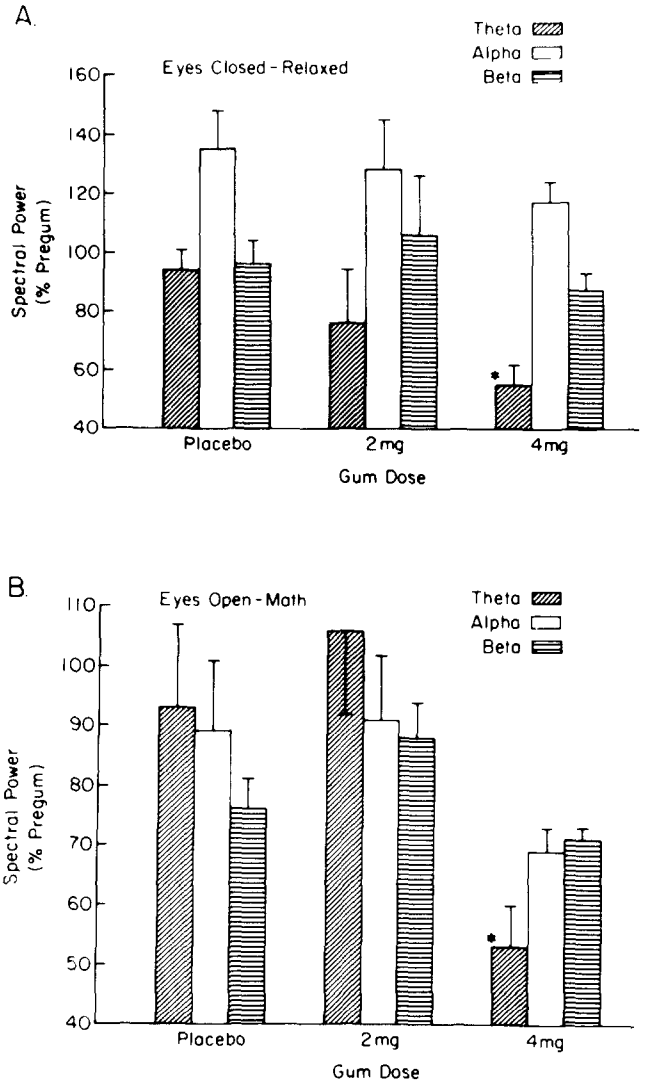

FIG. 2. Mean (n=3) spectral power in leads C_z–T_5 and C_z–T_6 after nicotine 2 and 4 mg or placebo gum. Power is shown as percent (±SEM) of pregum values while subjects relaxed with eyes closed (A) or during a math task with eyes open (B). *Indicates significant difference from placebo gum and ($p<0.05$, paired t-test).

The spectral power of the posterior electrodes in the theta band but not in other frequency bands was significantly reduced by the 4 mg nicotine gum (Fig. 2 A and B). The reduction occurred whether the subjects were tested with eyes closed or in the eyes open-math task. Spectral power derived at the anterior electrodes were similar, i.e., theta power significantly decreased after the administration of 4 mg gum in both recording situations. The ratio of alpha and theta power in the left and right hemispheres were compared before and after the gum doses. No consistent or significant nicotine-induced alterations in the ratios were observed.

On the ARC single dose questionaire two of the three subjects reported having been given a drug after the placebo and both doses of the nicotine gum. The 2 mg dose was identified as tobacco by 2 of the 3 subjects; none of the

subjects identified the 4 mg dose as tobacco. Scores on the liking scale were not changed by the administration of the nicotine gum.

DISCUSSION

The EEG effects of the nicotine delivered by chewing gum in this study are similar to those produced by nicotine delivered from inhaled tobacco smoke. Cigarette smoking reversed the EEG alpha slowing which occurred during a 24 hr deprivation period [23]. Consistent with these findings, in our study, the 2 and 4 mg nicotine gum significantly increased alpha frequency in the resting subjects following a 12 hr deprivation. The increased alpha frequency we observed is also similar to that observed by others [13]. Other studies had shown that nicotine deprivation in smokers produced increased theta [9,23] which was reversed by cigarettes. We consistently found that nicotine gum (4 mg) significantly reduced theta power in relaxed subjects or during a math task. The 4 mg gum also caused a nonsignificant reduction in alpha power in both recording conditions.

We also found gum delivered nicotine increased the beta frequency in the resting subject. The observed increase in beta frequency has not been reported after cigarette delivered nicotine. Smokers have greater abundance of beta activity than nonsmokers; however, the frequency of the beta activity in the comparison groups was not different [2]. The effect of nicotine administration on the beta activity during deprivation in smokers was not studied. In another study [23] a nonsignificant increase in beta power occurred during deprivation which was reversed when smoking was resumed. It is interesting to note that administration of cocaine also increases beta frequency [1,10], since intravenous nicotine injections are frequently identified as cocaine by experienced subjects [8].

The EEG effects of the nicotine gum depended on the recording situation and the behavior (or task) required of the subject. The effects of nicotine administration on EEG were most pronounced when the subject was instructed to relax with his eyes closed. When the subject was instructed to perform the math task with his eyes open nicotine's stimulant-like effects were less pronounced. Specifically, the increases in theta, alpha and beta frequencies was attenuated during the eyes open math task condition. Theta power was significantly decreased by the 4 mg dose in both the relaxed and the math task situation, after the 2 mg dose a nonsignificant decrease was evident only in the relaxed subject. Smoked tobacco increased dominant alpha frequency in subjects with eyes closed [14]. However, others [9] found nonsignificant effects of tobacco in subjects performing a math task with open eyes. These results and those of the present study are consistent with hypotheses that nicotine has cortical stimulating effects in the relaxed subject [3,4].

The results of recent behavioral and evoked response studies suggest that nicotine improved performance and concentration. For example, cigarette smoking increased speed and accuracy in a concentration demanding rapid processing task [24]. Nicotine gum reversed the deprivation-induced performance decrements and response slowing during a series of cognitive tasks [22]. In deprived smokers, the P300 latency—a measure of stimulus evaluation time—was increased by the imposition of background noise; this effect is prevented by gum delivered nicotine [11]. These and other studies [3] suggest that nicotine improves stimulus processing and causes concomitant electrocortical changes in evoked potentials and spontaneous EEG.

When the subjects chewed the gum according to the scheduled procedure of this study they extracted about one half the available nicotine. The extraction percentage of nicotine from the gum we observed is similar to that previously reported [6]. Previous reports indicate that nicotine plasma levels comparable to those seen obtained after ad lib smoking can be maintained by 4 mg but not 2 mg nicotine gum [21]. A single 4 mg dose of gum produces plasma levels of nicotine comparable to the levels after the smoking of a single cigarette [16]. Although we did not measure plasma levels of nicotine, sufficient nicotine was absorbed from the gum to cause EEG effects like those of inhaled tobacco smoke. However, our subjects did not identify the effects of the gum as being identical to those of tobacco. Subjects in other studies failed to identify the gum's effects as being identical to tobacco [7,17]. The subjects' failure may be related to the speed of nicotine absorption [20], which is notably slower after the gum compared to cigarettes [19] or to differences in chemosensory cues [18]. Taken together, the present findings suggest that despite self reported differences between gum and tobacco smoke delivered nicotine, the effects on the EEG responses are orderly and similar.

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