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Effects of Mecamylamine on Spontaneous EEG and Performance in Smokers and Non-Smokers

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PICKWORTH, W. B., R. V. FANT, M. F. BUTSCHKY AND J. E. HENNINGFIELD. *Effects of mecamylamine on EEG and performance in smokers and non-smokers.* PHARMACOL BIOCHEM BEHAV **56**(2) 181–187, 1997.—In a previous study, mecamylamine, a centrally active nicotine antagonist, exacerbated EEG signs of tobacco abstinence in abstinent smokers. In the present study, the effects of mecamylamine were compared in non-smokers and nondeprived smokers. Mecamylamine (0, 5 and 10 mg, p.o.) was administered to six smokers and six non-smokers; eight of these subjects were also given a 20 mg dose. Before drug administration, resting EEG was similar in both groups. In both groups, mecamylamine caused dose-related decreases in alpha frequency and increases in delta frequency; beta frequency was increased by the 5 and 10 mg doses. The similarity of effects in smokers and non-smokers suggests a direct pharmacological action rather than precipitated nicotine withdrawal. Significant baseline differences existed between smokers and non-smokers in systolic blood pressure, pulse rate, skin temperature and pupil diameter. Response time slowed in both vigilance and distractibility tasks and delayed recall was impaired. Mecamylamine increased ratings of: "relaxed," "nodding," "sleepy" and "coasting." This small-sample study tentatively suggests that nicotinic cholinergic mechanisms modulate brain electrical activity and cognitive function in smokers and non-smokers. Disruption of these neural systems could mediate the symptoms of tobacco withdrawal and be involved in the pathophysiology of Alzheimer's disease. **Published by Elsevier Science Inc., 1997**

Mecamylamine EEG Performance Cognition Nicotine

MECAMYLAMINE is a ganglionic blocker that readily enters the brain and prevents the effects of exogenously administered nicotine such as: drug reinforcement (8), psychoactivity and discrimination (27,31) and regional brain metabolism (16). However, nicotine's effects are not prevented by the administration of hexamethonium and pentolinium, ganglionic blockers that do not enter the brain (16,31). Although mecamylamine functions in certain respects like a competitive antagonist, it does not occupy nicotine binding sites; rather it disrupts nicotine-induced effects by preventing the action of nicotine to increase cation channel ion transfer (review: 18).

Mecamylamine has proven useful in assessing the role of brain nicotine receptors in responses to nicotine (31). For example, mecamylamine reduced the discriminative effects of nicotine in animals (8) and humans (20,26). As expected of a pharmacologic antagonist, single doses of mecamylamine increased nicotine self-administration, whereas chronic administration tended to decrease nicotine self-administration (8). These data show that mecamylamine has many of the properties of a pharmacologic antagonist. One question of interest is whether or not mecamylamine administration to smokers might precipitate withdrawal symptoms. This possibility has not been systematically tested in previous human research; however, data from animal studies indicate that mecamylamine precipitates withdrawal symptoms in nicotine-dependent rats (17).

In a previous study at this laboratory (24), mecamylamine decreased the electroencephalographic (EEG) effects of nicotine chewing gum in tobacco-deprived smokers. It was also reported that mecamylamine exacerbated the EEG signs of tobacco withdrawal by further increasing EEG theta power and decreasing alpha frequency. Those EEG effects of meca-

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mylamine could have been caused by antagonism of residual nicotine present after overnight tobacco deprivation, or mecamylamine could have altered a tonic nicotinic/cholinergic system involved in the regulation of the spontaneous EEG. The purpose of the present study was to clarify those alternative explanations. If mecamylamine acted by antagonizing residual nicotine, one would expect EEG effects in smokers but not in non-smokers. On the other hand, if mecamylamine affects a tonic nicotinic neural system that regulates spontaneous EEG, one would expect effects in both smokers and nonsmokers, although the effects may not be equal because chronic nicotine administration increases the number of brain nicotine receptors (29).

The results of several studies have supported the importance of nicotinic/cholinergic mechanisms mediating arousal and attention in healthy subjects (3,35,37). Others have emphasized the role of nicotinic cholinergic function in the pathophysiology of Alzheimer's disease (11,21,22,28). The role of nicotinic cholinergic systems in cognitive function may be inferred from the effects of a nicotine antagonist. Another purpose of the study was to determine whether blockade of nicotinic receptors with mecamylamine disrupts cognitive performance.

METHODS

Subjects

Six non-smokers and six smokers participated in the study. Non-smokers (three men) were subjects who had never smoked more than five cigarettes in a day and had not smoked any cigarettes (or used other tobacco products) in the last five years. Their age averaged 31.3 yr (range: 22–42) and their weight averaged 70.8 kg (51.8–95.0).

The six smokers (three men) were current smokers who had smoked cigarettes for at least 2 yr. Their scores on the Fagerström Nicotine Tolerance Questionnaire (5) averaged 8.2 (7–9) indicating a high level of nicotine dependence. They smoked an average of 25.8 cigarettes a day (15–30). The FTC nicotine yield of their cigarettes averaged 1.1 mg. Their age averaged 35.7 yr (22–44) and their weight averaged 65.9 kg (52.7–74.1).

Before beginning the study, the subjects gave informed consent according to the guidelines of the Department of Health and Human Services and the local institutional review board. For their participation in the study, volunteers were paid approximately $400.

Procedure

Subjects were tested on four days (four subjects were tested on three test days, described below); study days were separated by at least 48 hr. Subjects reported to the laboratory in the morning. Before the session started, a urine sample was collected and analyzed for: phencyclidine, benzodiazepines, opiates, marijuana, barbiturates, cocaine and amphetamines by means of latex agglutination immunoassays (OnTrak, Roche Diagnostics, Nutley, NJ). Subjects in the smoking group were encouraged to smoke before arriving at the laboratory and were required to smoke a cigarette before the test session and at three times during the session (immediately before the drug administration, 90 and 150 min after drug). Cigarettes were smoked after the collection of physiologic measures and before collection of performance measures at the 90 and 150 min time points.

Drug Administration

Capsules containing placebo or mecamylamine (5, 10 and 20 mg) were administered with a large glass of water. Drug administration was double-blind and the treatment order was randomized with the restriction that the first three non-smokers were given the low dose before the higher doses. During the course of the study, administrative and medical safety concerns over the use of the 20 mg dose of mecamylamine resulted in deleting this dose from the protocol. Consequently the dose was withheld from three subjects in the nonsmoking group and one subject in the smoking group.

Dependent Measures

Physiologic measures. EEG recordings were collected from Fz, Pz, C3 and C4 (monopolar, linked ear reference) for 1 min with eyes closed at the following times: twice before drug, 30, 60, 90, 120 and 180 min after drug. The EEG was collected and analyzed with a Nicolet Pathfinder II (Nicolet Instruments, Madison, WI) as described elsewhere (25). The computer-controlled collection and analysis software continuously acquired 4 sec epochs from each of the four EEG electrodes. The EEG was digitized at 256 Hz and samples with artifacts were automatically rejected. The digitized EEG was converted to the frequency domain using a fast fourier transform. For each one-minute sample, the computer printed the power (μV^2) and peak frequency (resolution 0.25 Hz) in the following frequency bands: delta, 0.25–3.75 Hz; theta, 4–7 Hz; alpha, 7.25–14 Hz; and beta, 14.25–25 Hz.

Pupil diameter and response to a light flash were measured with a Pupilscreen (Fairville Medical Optics, Amersham Bucks, England).

Systolic and diastolic blood pressure and pulse rate were measured with an automated vital sign monitor (IVAC Corp., San Diego, CA).

Skin temperature was measured from the middle finger of the left hand by means of a thermister (Cole-Palmer, Chicago, IL).

Subjective measures. The Single Dose Questionnaire, SDQ,(6) which measures: general drug effect, drug identification, drug liking and drug symptoms was administered 30, 60, 90, 120 and 180 min after the drug. Seven visual analog scales were administered before and 30, 60, 90, 120 and 180 min after the drug. The visual analog scales measured: sleepiness, dry mouth, blurred vision, dizziness, nausea, abdominal cramps, and weakness on 100 mm lines anchored with the phrases "Not at all" and "Extremely."

Performance measures. An extended version (23) of the paired associate learning subtest of the Wechsler Memory Scale (36) was administered for immediate and delayed (30 min) recall before the drug and 90 min after drug. Eight pairs of words containing four easy associations (e.g., murder : crime) and four hard associations (e.g., music : teeth), were read to the subject. Then the first word of each pair was read to the subject who responded with the associated word. Incorrect responses were corrected and the list was repeated until perfect recall occurred or a maximum of six times. The list was repeated three times regardless of accuracy. Dependent variables were the number of correct responses in the first three trials (perfect score: 12 easy; 12 hard) and the number of correct responses at the delayed recall (perfect score: 4 easy; 4 hard).

The Gordon vigilance task (7) presents a series of digits (1/sec) for 6 min. Subjects were required to press a response

button whenever a "9" followed a "1." The task was administered before the capsules and 60, 90 and 180 min after the capsules. The 6-min Gordon distractibility task required the same response but the presentation included random digits at random intervals (distracters) in display windows on either side of the target window. For both the Gordon vigilance and distractibility tasks, the dependent variables were total correct responses (perfect score = 30), number of commission errors and response latency.

Statistical Analyses

The primary analyses were conducted on data from the 8 subjects (5 smokers, 3 non-smokers) who received all dose conditions (0, 5, 10 and 20 mg mecamylamine). Statistics and figures reported below are from these analyses. Skin temperature data from one non-smoker was not collected because of equipment failure. On each measure, data from each subject were converted to change-from-baseline scores. These data were then subjected to three-way analysis of variance (ANOVA) with smoking history (smoker vs non-smokers) as a between-groups factor and dose (4 levels) and time (5 levels) as within-subjects factors (38). Post hoc analyses were performed using Tukey's honestly significant difference test (38).

A secondary ANOVA was performed on data from all (n = 12) subjects that received the 0, 5, and 10 mg doses of mecamylamine. The within-subjects factors in these analyses were dose (3 levels), time (5 levels) and the between-groups factor, smoking history, (2 levels).

To assess differences in baseline values between smokers and non-smokers in the primary analysis, another three-way ANOVA was performed which included the baseline data. The mean square error terms of the history by time interaction tests of these ANOVAs were used in Tukey analyses to determine differences between the two groups at the baseline time point.

RESULTS

EEG Effects

Figure 1A shows mean change-from-baseline alpha frequencies at Pz for smokers and non-smokers as a function of mecamylamine dose. Mean baseline frequencies were 9.9, 10.0, 10.0, and 10.2 Hz among the smokers prior to administration of 0, 5, 10, and 20 mg mecamylamine, respectively, and were 9.9, 10.0, 10.1, and 10.3 Hz among the non-smokers. Differences in baseline values between smokers and non-smokers were not statistically significant. Mecamylamine produced significant effects on alpha frequency [dose: $F(3, 18) = 6.0$, $p < .005$]. Post hoc analyses revealed differences between the 0 mg condition and both the 10 and 20 mg conditions, as well as differences between the 5 mg and 20 mg conditions. The largest decrease from baseline (0.6 Hz) occurred following 20 mg mecamylamine at the 90 min time point. Dose-related changes in alpha frequency did not vary as a function of smoking history [dose-by-history interaction: $F(3, 18) = 0.3$, ns].

Figure 1B shows mean change-from-baseline beta frequencies at Pz for smokers and non-smokers as a function of mecamylamine dose. Mean baseline frequencies were 19.1, 18.4, 18.5, and 19.1 Hz among smokers prior to 0, 5, 10, and 20 mg mecamylamine administration, respectively, and were 18.9, 19.0, 18.9, and 21.5 Hz among non-smokers. Differences in baseline values were not statistically significant between smokers and non-smokers. There was a significant mecamylamine effect on beta frequency [dose: $F(3, 18) = 3.75$, $p < .05$]. Beta

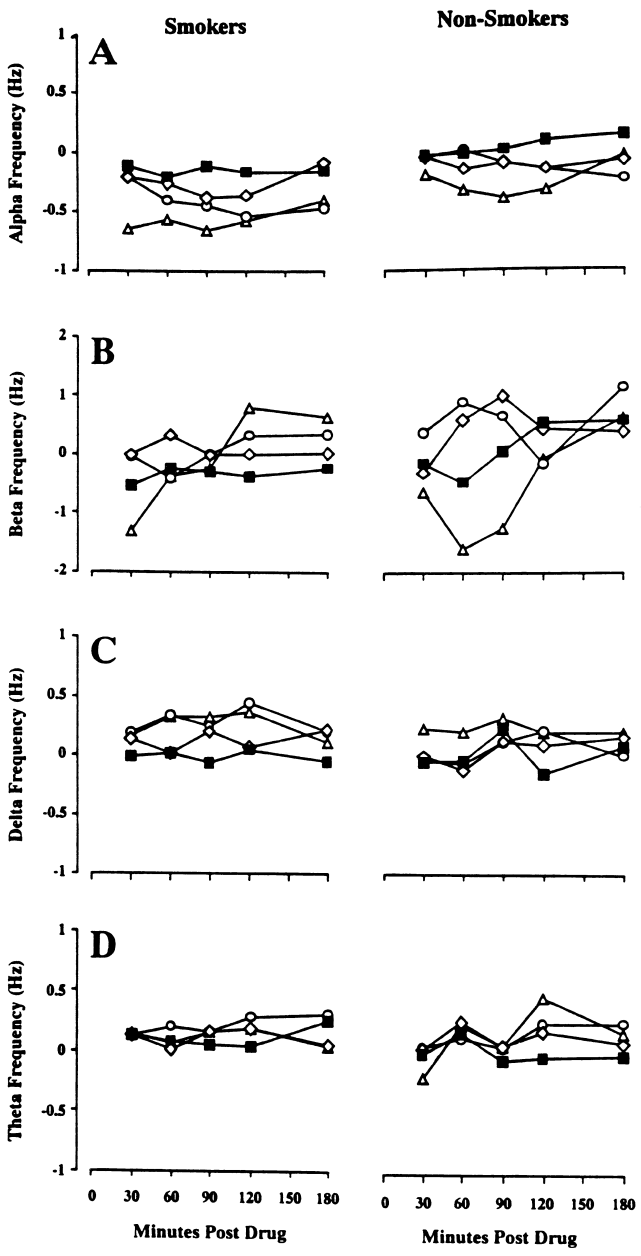

FIG. 1. Mean changes-from-baseline in EEG frequencies after placebo –■–; or mecamylamine (5 –◇–, 10 –○– and 20 –△– mg) to non-deprived smokers (n = 5) and non-smokers (n = 3). Data are from recordings at the Pz electrode.

frequency decreased slightly following administration of 0 and 20 mg mecamylamine (0.2 and 0.3 Hz, respectively), but increased following the 5 and 10 mg mecamylamine doses (0.4 and 0.6 Hz, respectively). Peak increases in beta frequency following the 10 mg mecamylamine dose (1.3 Hz) occurred 180 min after drug administration. Post hoc analyses revealed significant differences between the 10 and 20 mg conditions only. Dose-related changes in beta frequency did not vary as a function of smoking history [dose-by-history interaction: $F(3, 18) = 1.8$, ns].

Figure 1C shows mean change-from-baseline delta fre-

quencies at Pz for smokers and non-smokers as a function of mecamylamine dose. Baseline frequencies among non-smokers were 1.6, 1.5, 1.6, and 1.5 Hz prior to administration of 0, 5, 10, and 20 mg mecamylamine and were 1.6, 1.5, 1.5, and 1.7 Hz among non-smokers. Baseline differences between smokers and non-smokers were not statistically significant. Mecamylamine produced significant effects on delta frequency [dose: $F(3, 18) = 3.2$, $p < .05$]. Post hoc analyses revealed significant differences between the 0 and 20 mg mecamylamine doses. Peak increases in frequency (0.3 Hz) were seen 90 min after 20 mg mecamylamine administration. Dose-related changes in delta frequency did not vary as a function of smoking history [dose-by-history interaction: $F(3, 18) = 1.2$, ns].

Figure 1D shows mean change-from-baseline theta frequencies at Pz for smokers and non-smokers as a function of mecamylamine dose. Baseline frequencies among non-smokers were 6.2, 6.3, 6.3, and 6.3 Hz prior to administration of 0, 5, 10, and 20 mg mecamylamine, respectively, and were 5.9, 6.0, 5.9, and 6.0 Hz among non-smokers. Baseline differences between smokers and non-smokers were not statistically significant. No changes in theta frequency were observed as a function of dose [dose: $F(3, 18) = 0.9$, ns], nor was there a dose-by-history interaction [$F(3, 18) = 0.7$, ns].

Mecamylamine-induced changes in beta and delta frequencies were similar at all electrode recording sites. The changes in alpha frequency were only observed at the Pz electrode. In the interest of clarity, the results described above and in Figure 1 are the effects of mecamylamine at the Pz electrode. There were no significant effects of mecamylamine on alpha, beta, delta, or theta power at Pz. In addition, there were no interactions between history and dose on power in any frequency band.

Results from the secondary analyses in which data from all ($n = 12$) subjects who received the 0, 5, and 10 mg doses revealed a similar EEG response as in the primary analyses. Alpha frequency decreased significantly as a function of mecamylamine [dose: $F(2, 20) = 7.8, p < .05$]. Dose-related changes in alpha frequency did not vary as a function of smoking history [dose-by-history interaction: $F(2, 20) = 1.3$, ns]. Beta, delta, and theta frequencies did not significantly change due to mecamylamine administration. Power did not significantly change due to mecamylamine administration in any frequency band.

Cardiovascular Effects

Pulse rate (Figure 2A). Baseline pulse rates were significantly greater among smokers than among non-smokers; mean baseline pulse rates were 77.1 beats per minute (bpm) among smokers and 63.7 bpm among non-smokers. There were dose-related changes in pulse rate following mecamylamine administration [dose: $F(3, 18) = 2.6$, $p < .10$]. Pulse rate decreased 3.1 bpm following the 0 mg mecamylamine dose, but increased 2.1, 3.6, and 6.0 bpm following 5, 10, and 20 mg doses. These changes in pulse rate were not mediated by smoking history [dose-by-history interaction: $F(3, 18) = 1.05$, ns].

Systolic blood pressure (Figure 2B). Baseline systolic blood pressure was significantly greater in non-smokers than in smokers; mean baseline pressures were 118.4 mm Hg among smokers and 125.0 mm Hg among non-smokers. There was no significant effect of mecamylamine on systolic blood pressure [dose: $F(3, 18) = 0.5$, ns]. Systolic blood pressure changes were not related to smoking history [dose-by-history interaction: $F(3, 18) = 0.1$, ns].

Diastolic blood pressure (Figure 2C). Baseline diastolic

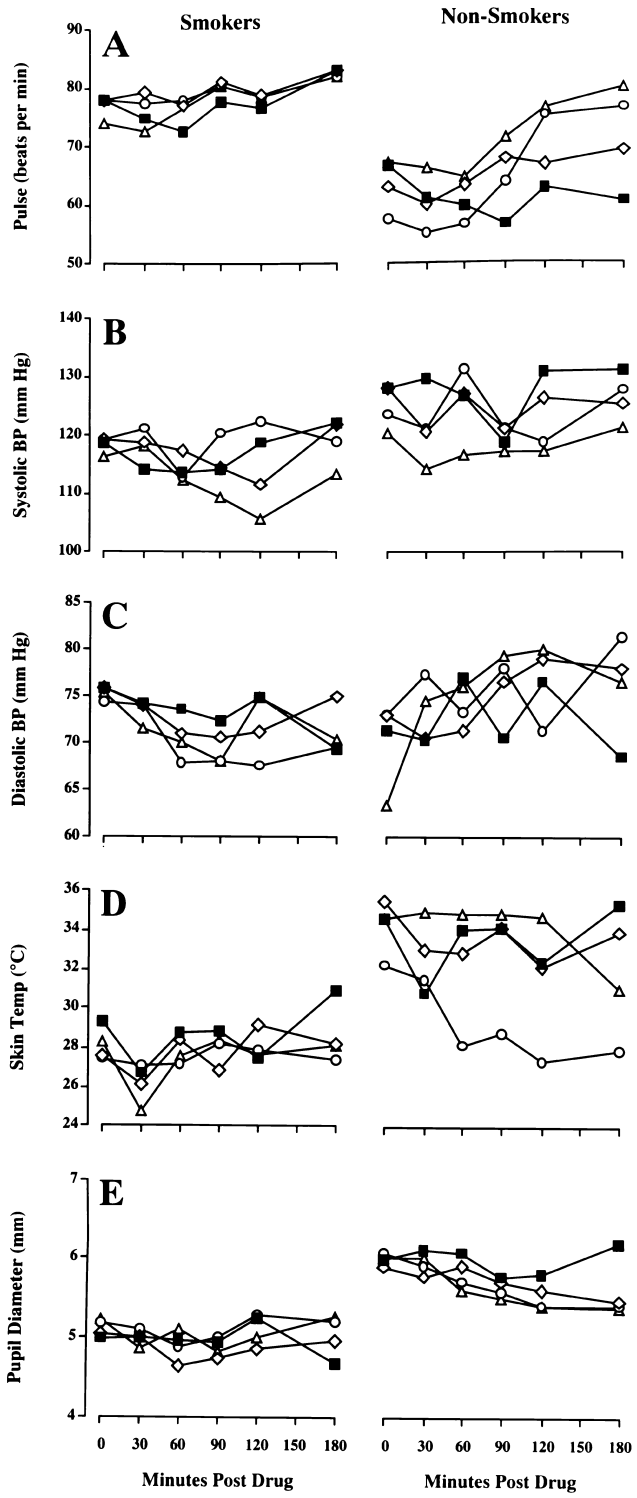

FIG. 2. Mean pulse rate (beats per minute), systolic and diastolic blood pressure (mm Hg), skin temperature (°C) and pupil diameter (mm) in non-deprived smokers ($n = 5$) and non-smokers ($n = 3$) after mecamylamine (5 –◇–, 10 –○– and 20 –△– mg) or placebo –■–.

blood pressure was not significantly different between smokers and non-smokers; mean baseline pressures were 75.4 mm Hg among smokers and 70.2 mm Hg among non-smokers. There was a small effect of mecamylamine on diastolic blood pressure [dose: $F(3, 18) = 2.9$, $p < .10$]. Mean diastolic pressure collapsed across time and smoking history decreased between 1.4 and 1.8 mm Hg following 0, 5, and 10 mg mecamylamine, but increased an average of 2.5 mm Hg following the 20 mg dose. This mecamylamine dose effect was related to smoking history. Mean diastolic blood pressure in smokers decreased slightly, between 3.0 and 4.9 mm Hg, following 0, 5, 10, and 20 mg mecamylamine, but increased 1.3, 2.1, 3.3, and 14.0 mm Hg, respectively, following these doses among non-smokers.

Skin Temperature (Figure 2D)

Baseline skin temperature was significantly greater among non-smokers than among smokers; mean baseline skin temperature was 28.2 °C among smokers and 33.4 °C in non-smokers. There were no dose-related changes in skin temperature following mecamylamine administration [dose: $F(3, 15) = 0.1$, ns] nor were mecamylamine effects mediated by smoking history [dose-by-history interaction: $F(3, 15) = 0.4$, ns].

Pupil Diameter (Figure 2E)

Baseline pupil diameter was significantly greater among non-smokers than among smokers; mean baseline diameters were 5.1 mm among smokers and 6.0 mm among non-smokers. There were no dose-related changes in pupil diameter [$F(3, 18) = 1.3$, ns] nor were mecamylamine effects mediated by smoking history [$F(3, 18) = 0.6$, ns].

Performance Effects

Gordon distraction and vigilance tasks. Neither number of correct responses nor number of errors of commission were affected by mecamylamine administration. Latency to respond on the vigilance task was significantly affected by mecamylamine [dose: $F(3, 18) = 5.9$, $p < .01$]. Response latencies decreased an average of 24 and 9 msec from baseline levels following placebo and 5 mg mecamylamine. However, latencies increased 23 and 29 msec following the 10 and 20 mg doses. Dose-related changes in latency to respond did not vary significantly as a function of smoking history [dose-by-history interaction: $F(3, 18) = 0.2$, ns]. Latency to respond on the distraction task was not significantly affected by mecamylamine [dose: $F(3, 18) = 2.35$, ns]. Latencies decreased from baseline levels in each drug condition but the latency decrease after placebo was obtunded by mecamylamine. Specifically, mean latency decreases from baseline were 39, 3, 7, and 9 msec following 0, 5, 10, and 20 mg mecamylamine, respectively.

Wechsler task. Immediate recall of easy and hard items was not affected by mecamylamine. However, delayed recall of easy items was affected by mecamylamine [dose: $F(3, 18) = 3.6$, $p < .05$]; mean changes from baseline were 0.1, 0.3, −0.4, and −0.1 following 0, 5, 10, and 20 mg mecamylamine, respectively. This effect was not related to smoking history [dose-by-history interaction: $F(3, 18) = 1.2$, ns]. Delayed recall of hard items was not affected by mecamylamine.

Subjective Effects

Data from the SDQ (6) indicated that subjects could detect mecamylamine, but there was little liking for it. For example, 80% of the subjects reported that they could not feel the placebo but 60% of the subjects reported feeling the 10 mg dose of mecamylamine. The results from the drug identification question of the SDQ (6) indicated that 100% of the time subjects reported that the placebo was a blank but 44% of the time subjects reported that the 20 mg dose was a blank. The identity of the 20 mg dose was most frequently reported as "unsure" although 20% of the time it was identified as Valium or a "downer." Subject liking for the 10 and 20 mg doses of mecamylamine was rated as "not at all" or "slightly" between 88 and 92% of the time, whereas after placebo and 5 mg mecamylamine 80 to 100% of the time subjects rated their liking as moderate or no effect. From the symptom checklist of the SDQ, subjects after mecamylamine endorsed adjectives such as "relaxed," "sleepy," "nodding," "coasting" or "spacy" about 64% of the time, whereas after placebo none of these symptoms were acknowledged. There were no significant mecamylamine-induced effects on measures of drug action indexed with visual analog scales.

DISCUSSION

The main finding of this small-sample study was that mecamylamine, a ganglionic blocker with activity at brain nicotinic receptors, caused similar EEG effects in both smokers and non-smokers. These results suggest that mecamylamine-sensitive nicotinic cholinergic systems mediate brain electrical activity in smokers and non-smokers. This conclusion is bolstered by subjective reports of lethargy and the cognitive slowing that accompanied mecamylamine administration in this study.

In previous studies overnight tobacco abstinence caused characteristic EEG changes including decreases in alpha frequency (14,33) and increases in theta power (9,33). These EEG changes were rapidly reversed by smoking or the administration of nicotine polacrilex (25). Mecamylamine exaggerated the EEG signs of tobacco withdrawal and prevented the nicotine polacrilex from reversing these EEG effects (24). The exaggeration could have been caused by mecamylamine antagonizing the EEG effects of nicotine still present after overnight deprivation or by a direct effect on tonically active nicotinic/cholinergic systems that ordinarily modulate brain electrical activity. These explanations were tested in the present study where the effects of mecamylamine in non-deprived smokers and non-smokers were compared.

Mecamylamine decreased alpha frequency, and increased delta and beta frequency with the changes in alpha and delta frequency being most evident after the 20 mg dose. In contrast, mecamylamine increased beta frequency at the 5 and 10 mg doses. In the secondary analyses, only the effect on alpha frequency was significant. None of the EEG effects in the present study were significantly associated with the smoking status of the subjects. This result tentatively suggests that in both smokers and non-smokers mecamylamine affects neural systems that regulate EEG frequency. However, the small sample of subjects dictates that the results of the present study be interpreted with caution.

There were no significant baseline EEG differences between the experimental groups suggesting that non-deprived smokers and non-smokers have similar resting EEG. These results differ from those of Brown (2) who reported an abundance of EEG beta activity in smokers compared to non-smokers. There are well documented EEG effects of acute nicotine administration in abstinent smokers (3, 13, 14). Kadoya et al. (12) reported that acute administration of nicotine caused EEG changes that were significantly related to the

plasma levels of nicotine. It may be the rate of change in plasma nicotine levels, not the plasma level per se, that determines the EEG effects of acute nicotine administration and differentiates smokers from non-smokers.

Mecamylamine did not increase theta power in the present study. Increased theta power is a typical EEG sign of nicotine abstinence in heavy smokers (9) and mecamylamine administration further increased theta power in overnight deprived smokers (24). These results indicate that mecamylamine does not precipitate all of the EEG signs of tobacco abstinence, but it may exaggerate the tobacco abstinence syndrome. The mechanism for the EEG changes after mecamylamine remain unclear, but the results of the present study indicate that in both smokers and non-smokers tonically active mecamylamine-sensitive neural systems may regulate the alpha frequency.

Smokers and non-smokers could be distinguished on the baseline values of cardiovascular and peripheral physiologic measures. For example, smokers had significantly faster pulse rates, lower systolic blood pressures, lower skin temperatures and smaller pupils than the non-smokers. The group differences in cardiovascular measures and in skin temperature have been reported elsewhere (15,34) but the difference in pupil size has not been previously reported. The mechanism for the miosis among smokers is unclear. It is possible that pharmacologic activity of cotinine, a major metabolite of nicotine (1) with activity at serotonergic receptors (4), may account for the smaller pupil size. In animals (32) and humans (19), serotonergic mechanisms have been implicated in the control of pupil size and the light reflex. Mecamylamine caused small, and occasionally statistically significant, increases in pulse rate, an effect reported in previous studies (22, 24). Mecamylamine-induced changes on diastolic blood pressure differed with the smoking history of the subject. In non-smokers, mecamylamine caused small increases in diastolic pressure, whereas the drug decreased diastolic pressure in smokers.

Mecamylamine slowed performance on the Gordon vigilance distractibility tasks. Newhouse et al. (22) reported that mecamylamine caused performance decrements in non-smokers on the learning component, but not the performance (retrieval) component of a repeated acquisition task. Furthermore, older subjects were more sensitive than younger subjects to the performance effects of mecamylamine. The subjects of the present study were closer in age (mean age = 33 years) to younger subjects in the Newhouse et al. study (mean age = 24) than to the older subjects (mean age = 63). Therefore, we expected the performance deficits to be small, if present at all. Newhouse et al. studied the effects of mecamylamine on non-smokers; in the present study, the effects of mecamylamine on performance occurred regardless of the smoking status of the subject. Mecamylamine did not cause significant changes in response accuracy. Response slowing without changes in accuracy is the pattern induced by tobacco deprivation on computer-delivered cognitive performance tests (30). In the present study, mecamylamine caused a small, but significant, decrease in delayed recall of the easy pair in the associative memory task. This result differs from the Newhouse et al. (22) report where mecamylamine did not affect retrieval in an acquisition test.

The data from the subjective questionnaires indicate that mecamylamine could be detected by the subjects, but they endorsed little drug liking. Subjects compared the drug to downers, Valium and alcohol and described its effects as "relaxed," "sleepy," "nodding" and "coasting." These effects were evident after the high dose in both smokers and non-smokers. These results agree with those of Stolerman et al. (31) who reported that mecamylamine increased ratings of tired, bored, difficulty concentrating and mental slowing. These are the same as some symptoms endorsed by subjects undergoing tobacco abstinence (10).

In conclusion, the data from the present study indicate that mecamylamine, a centrally active nicotine antagonist, decreased alpha frequency, slowed response time on a performance task and engendered subjective responses of mental slowing and lethargy. The presence of these effects in both non-smokers and non-deprived smokers suggests that mecamylamine is affecting neural systems that modulate the brain electrical activity, cognitive processes and subjective thought. These actions are hallmarks of the tobacco withdrawal syndrome suggesting that mecamylamine can precipitate some signs and symptoms of that syndrome. It has been argued that the cholinergic deficits of Alzheimer's disease are responsible for the cognitive failure (21). Furthermore, acute nicotine administration improved several measures of cognitive function in patients with Alzheimer's disease (11,28). The results of the present study imply that the pathological process may be modeled in healthy young subjects through the use of centrally acting nicotinic antagonists.

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