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A Nicotine Antagonist, Mecamylamine, Reduces Cue-Induced Cocaine Craving in Cocaine-Dependent Subjects

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We have previously shown that nicotine enhances cue-induced cocaine craving. In the present study, the effects of a nicotine antagonist, mecamylamine, on cue-induced cocaine craving were investigated. Twenty-three cocaine-dependent patients, all cigarette smokers, were randomly assigned to mecamylamine (2.5 mg tablet) or placebo in a single-dose, placebo-controlled, crossover, double-blind study. Craving and anxiety were measured before and after cocaine cues with visual analog scales for desire to use cocaine and mood. Skin conductance, skin temperature and heart rate were recorded before and during cocaine cues. Following exposure to cocaine cues, all patients reported an increase in cocaine craving and anxiety relative to the pre-cue measures. Cue exposure also produced an increase in skin conductance and decrease in skin temperature. The cue-induced increase in cocaine craving was reduced, while the cue-induced skin conductance and temperature responses were unaffected, by mecamylamine. These findings show that cue-induced cocaine craving is attenuated by mecamylamine. Further study on the use of mecamylamine in relapse prevention programs are suggested.

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KEY WORDS: *Cocaine; Craving; Mecamylamine; Nicotine; Addiction*

Over the past several years, numerous studies have demonstrated that environmental cues previously associated with cocaine use will consistently induce cocaine craving in cocaine-dependent subjects (Ehrman et al. 1992; O'Brien et al. 1990; Berger et al. 1996; Reid et al. 1998). This behavior is readily elicited in a clinical laboratory setting by means of a standardized cocaine cue procedure involving both visual/audio presentation and cocaine paraphernalia handling (Ehrman et al. 1992; Reid et al. 1998). The cocaine cue procedure appears to be contextually specific because opiate-related cues are less effective whereas cues specific to the subject's mode of cocaine use are most effective (Ehrman et al. 1992; O'Brien et al. 1990, 1992). Furthermore, cocaine cue reactivity persists inpatients who have not used cocaine for several months (Rohsenow et al. 1991; O'Brien et al. 1990). In recent years, this model has been used to investigate medications for their ability to reduce cue-induced cocaine craving, and consequently, it has been proposed as a screening mechanism for identifying potentially therapeutic compounds for the treatment of cocaine addiction (Berger et al. 1996; Robbins et al. 1992; Kranzler and Bauer 1992; Satel et al. 1995).

Studies investigating the pharmacological modulation of cue-induced cocaine craving have tested a wide variety of compounds. These include bromocriptine

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(Kranzler and Bauer 1992), amantadine (Robbins et al. 1992), haloperidol (Berger et al. 1996) and nicotine (Reid et al. 1998), as well as tryptophan depletion, which reduces serotonin levels (Satel et al. 1995). Most of these studies found either a reduction (haloperidol, tryptophan depletion) or no change (bromocriptine, amantadine) in self-reported cocaine craving and have led to the suggestion that dopamine may be involved in mediating cocaine craving (Berger et al. 1996; Wickelgren 1997). More recently, we found that nicotine produced an increase in cue-induced cocaine craving (Reid et al. 1998). This findings is consistent with previous investigations of cocaine–nicotine interactions. Thus, epidemiological studies have reported that cigarette smoking is significantly more prevalent in cocaine-dependent individuals (Budney et al. 1993; Sees and Clark 1991), that cocaine-dependent smokers reported an earlier age of onset and more frequent use of cocaine than cocaine-dependent nonsmokers (Budney et al. 1993) and that smoking is predictive of the abuse of psychoactive drugs such as cocaine (Henningfield et al. 1990; U.S. Department of Health and Human Services 1988). Indeed, anecdotal reports by patients claim that smoking mentholated cigarettes prolongs the cocaine high and can even substitute for cocaine during periods of abstinence (Sees and Clark 1991). Finally, animal studies have shown that subchronic pretreatment with nicotine increases the subsequent acquisition and rate of cocaine self-administration in rats (Horger et al. 1992). These studies indicate that nicotine could stimulate the use of cocaine and possibly increase the risk of relapse in cocaine-dependent individuals during rehabilitation. Moreover, this suggests that a nicotine antagonist could reduce cue-induced cocaine craving and, consequently, could be of therapeutic value in the treatment of cocaine addiction. Mecamylamine is a clinically available, centrally active nicotine antagonist with known therapeutic value in smoking cessation; it reduces relapse in cigarette smokers when combined with nicotine patch treatment (Rose et al. 1994). Therefore, in the present study, we have investigated the effects of mecamylamine on cue-induced cocaine craving in cocaine-dependent "crack" smokers.

METHODS

Participants

This human study was approved by an independent, University of California research council: Committee on Human Research. Individuals were recruited from the transition group at the Substance Abuse Treatment (SAT) clinic at the San Francisco Veterans Affairs Medical Center (SFVAMC), as well as by word of mouth at other outpatient treatment clinics in the San Francisco metropolitan area. Initial contact and recruitment were done over the phone, followed by a screening interview at the SFVAMC with a SAT trained psychology technician with experience in cocaine abuse diagnosis and treatment. Patients were included if they were: (1) males or nonpregnant/nursing females, (2) 18–65 years of age, (3) regular (10 cigarettes/day) cigarette smokers, (4) "crack" cocaine was their drug of choice, (5) had smoked "crack" cocaine within the last 3 months and (6) cocaine-dependent within the last 3 months according to DSM-IV criteria from the Structural Clinical Interview (SCID). Patient were excluded if they were: (1) currently abusing opiates or in a methadone maintenance program, (2) had undergone alcohol or drug detoxification within the last 30 days, (3) taking prescribed psychoactive medication, (4) taking prescribed antibiotics, (5) had coronary heart disease or high blood pressure, or (6) had previously suffered from a serious head injury (trauma) or stroke. The psychiatric status of all patients was initially evaluated by a Master's degree level SAT psychologist. Those with erratic behavior were interviewed by an SAT psychiatrist, and if they met criteria for an axis I psychiatric disorder (other than substance abuse), they were excluded from the study.

Following the screening interview, written informed consent was obtained, and all study participants underwent an intake assessment including a demographic questionnaire, the drug and alcohol sections of SCID for DSM-IV (First et al. 1996), the Addiction Severity Index (ASI) (McLellan et al. 1980), the Fagerström Nicotine Tolerance Questionnaire (Fagerström 1978) and the Profile of Mood States (POMS) (McNair et al. 1971), and test dates for two separate sessions (at least 72 h apart) were scheduled.

Descriptive data of the patient population derived from the screening interview, ASI, POMS, and Fagerström Nicotine Tolerance Questionnaire are shown in Table 1. All patients abused cocaine by smoking "crack" cocaine, 14 of them had used within the last 30 days, 10 were currently in the SAT outpatient program, and all were current cigarette smokers.

Study Design: Methodological Considerations

All patients were instructed to abstain from smoking from midnight before each test day. (Studies began at 9:30 A.M. and were completed by approximately 1:30 P.M.) Compliance was verified on each test day using a carbon monoxide (CO) breath monitor (15 PPM cut-off level). All patients were also instructed to abstain form cocaine use for at least 2 days before each test day, which was verified with qualitative urine screens for cocaine (300 ng/ml cut-off).

Mecamylamine (2.5 mg tablet, Merck) or placebo (lactose tablet) were administered in gelcaps in a double-blind, randomized, counterbalanced design. All patients served in all conditions resulting in a within-patient

Table 1. Subject Demographics and Drug Use History

	Frequency	Mean (SD)
Demographics		
Race		
African American	19	
Caucasian	4	
Gender		
Male	20	
Female	3	
Age		40.6 (5.1)
Income in last 30 days ($)		
Employment		82 (159)
All		833 (1854)
Years of education		13.2 (1.3)
Self reported drug and alcohol use		
Number of days of drug use in last 30 days		
Cocaine		8.8 (9.1)
Alcohol		5.1 (9.4)
Cannabis		2.4 (6.4)
Amphetamine		0 (0)
Number of days since last cocaine use		28.5
Money spent in last 30 days ($)		
Alcohol		10 (19)
Drugs		237 (430)
Years lifetime use		
Cocaine		12.3 (7.0)
Alcohol		15.1 (10.4)
Cannabis		11.8 (9.6)
Amphetamine		2.6 (5.5)
Nicotine use		
Cigarettes/day		15.6 (7.4)
Number of attempts to quit smoking		2.3 (1.8)
Addiction scores		
Fagerström Nicotine Tolerance Total		6.5 (2.0)
ASI Drug Composite		0.17 (0.13)
POMS Total Mood Disturbance		47.9 (47.5)

Lifetime drug use defined as Addiction Severity Index (ASI) criterion for 3 or more times a week for at least 1 month. Means and standard deviation (SD) are reported. The ASI (Drug) Composite scores were calculated using drug-related measures as described by McLellan and colleagues (1980), the Nicotine Tolerance (Total) scores were calculated using the sum of derived nicotine related measures as described by Fagerström (1978) and the Profile of Mood States (POMS) Total Mood Disturbance scores were calculated according to McNair and colleagues (1971).

study design. Randomization of treatment schedule by block (4×) permutation ensured that a roughly equal number of patients received mecamylamine or placebo on the first day of testing (to control for cue novelty effects). The dose of mecamylamine was chosen to minimize its peripheral side effects and because of its contribution to any possible tobacco withdrawal.

Study Design: Test Procedures

A time-line descriptive schemata of the procedures for Day 1 and Day 2 can be seen in Figure 1. Both days of testing took place in the SFVAMC Psychiatry Services Inpatient Unit clinical research laboratory. Upon the beginning of each test session, skin conductance, skin temperature and heart rate electrodes were attached to the patient's nonwriting hand. Both measurements were recorded continuously. For the first baseline psychological measurements, the patient was given the Within Sessions Rating Scale and the Mood Analog Scale immediately before cue presentation. Thereafter, each individual was shown a 5-min neutral cue videotape followed by the handling of neutral cues for 5 to 7 min. After completion of the video and handling of the neutral cues, the Within Sessions Rating Scale and the Mood Analog Scale were administered again. Once completed, the physiological recordings were stopped and the patient was administered mecamylamine (2.5 mg) or placebo. After a 2-h medication absorption period, a procedure similar to the neutral cue presentation was followed, except that patients were exposed to a 5-min videotape containing cues specific to crack cocaine and were instructed to handle cocaine and crack related

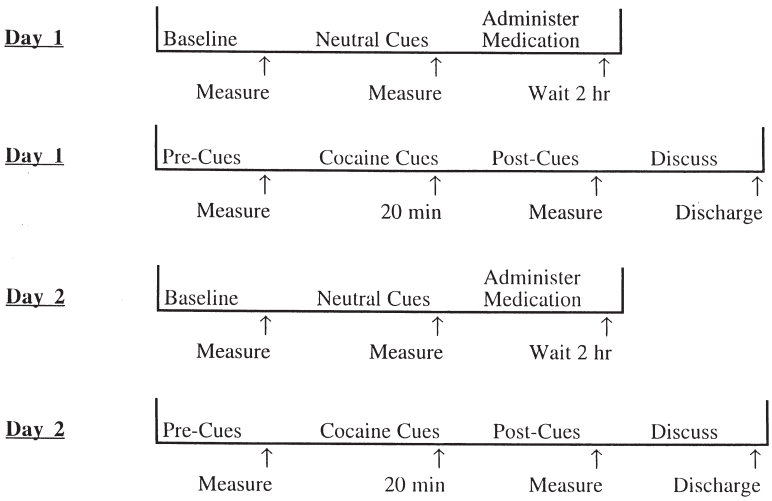

Figure 1. Cue-induced cocaine craving study design summary. Each test day lasted approximately 4 h (9:30 A.M.–1:30 P.M.). Test days 1 and 2 were at least 72 h apart.

paraphernalia for 5 to 7 min after viewing the videotape. As previously described, skin conductance, skin temperature and heart rate were recorded continuously, and the Within Sessions Rating Scale and the Mood Analog Scale were administered immediately before and after cocaine cue presentation.

On Day 2, all individuals were tested in a counterbalanced format: Patients who received mecamylamine on Day 1 received placebo and vice versa. The testing procedure was identical to that of Day 1, except the video contained a different cocaine-related scene. Following completion of Day 2, all patients were asked, in a double-blind setting, which day (Day 1 or Day 2) they felt the most cocaine craving. Patients were then paid for their study participation.

Subjective Measures

Drug craving was rated on a recent version of the Within Session Rating Scale developed by Childress and colleagues (Childress et al. 1986), whereas mood was measured using the Mood Analog Scale (Berger et al. 1996). The Within Session Rating Scale is a self-reported measure in which patients estimate the intensity of their current desire and likelihood to use cocaine, cocaine-like high, desire to use tobacco, tobacco withdrawal, and a variety of drug-related states on a 1- to 100-mm visual analog scale. The Mood Analog Scale contains 16 adjectives describing the patient's current feelings that are rated on a similar 1- to 100-mm visual analog scale. The anxiety related adjectives: "nervous," "anxious," and "irritated" were chosen for analysis based on previous studies of cue-induced cocaine craving (for more detail see Reid et al. 1998).

The primary outcome measures from the Within Session Rating Scale and Mood Analog Scale were cocaine craving, desire to use cocaine now, anxiety, and cocaine-like high. A secondary outcome measure from the Within Session Rating Scale, tobacco withdrawal, was used to test for effects of medication alone. Of these five measures, three (cocaine craving, anxiety, tobacco withdrawal) were derived by averaging more than one individual item and two (cocaine-like high, desire to use cocaine now) were derived from a single item on the visual analog scales. Of the indexed items, cocaine craving was obtained by averaging the scores of four cocaine craving questions, anxiety was obtained by averaging the scores of three anxiety-related questions, and tobacco withdrawal was obtained by averaging the scores of two smoking-related questions. One of the individual items, desire to use cocaine now, was analyzed to assure comparability with previous research (Robbins et al. 1992; Kranzler and Bauer 1992; Satel et al. 1995; Berger et al. 1996).

Physiological Measures

Skin conductance (μMHOS), skin temperature (C°) and heart rate (bpm) were recorded at a 2 Hz frequency using fingertip electrodes connected to a laptop PC via a RS232 beltpack/interface unit (ProComp, Thought Technology, Montreal, Canada). Skin conductance was recorded using Ag-Ag/Cl paste electrodes, skin temperature was recorded using an electric thermister, and heart rate was recorded using a photoelectric pulse sensor (for more detail see Reid et al. 1998).

Cocaine Cues

The 5-min cocaine cue video tape contained scenes performed by actors simulating the purchase and smoking of "crack" cocaine, which were interspliced with video clips of actual crack smoking (provided by Childress and colleagues). In the subsequent 5 to 7 min, patients handled cocaine and crack paraphernalia, including various crack pipes, screens, lighters, and a benzocaine-

derived white crystalline powder designed to simulate crack "rocks," and were asked to smell a recently used pipe for any scent of crack residue (reapplied every month using pseudo-cocaine); patients were then instructed to prepare a pipe of their choice for smoking crack (mock ritual).

Neutral Cues

The 5-min neutral cue video tape consisted of images of pine cones and seashells. In the subsequent 5 to 7 min, patients handled shells, rocks, and a pine cone, were asked to smell a fragrant spice (nutmeg), and were instructed to make 2 to 3 patterns on the desk top with the items.

Data Analysis

Mean levels of the subjective outcome measures were compared for statistical significance using a 2 (pre-cue, post-cue)-by-2 (mecamylamine, placebo) repeated measures ANOVA model. All of these models were analyzed after initially testing for cue reactivity order effects and, except for anxiety (drug × time interaction: $F(1,21) = 4.90$, $p = .038$), none were found. Because the neutral cue presentation, the effects of medication alone, and cocaine cue presentation addressed separate research questions their data were analyzed separately. Baseline and cue-induced levels of skin conductance, skin temperature, and heart rate were analyzed using using a 2 (mecamylamine, placebo) × 3 (baseline, video viewing, paraphernalia handling) × 10 (time points/stimulus phase) repeated measures ANOVA model. Each time point was calculated as the mean of a 30 s recording period. As a secondary analysis, correlation coefficients were estimated to measure the relationship between cue-induced cocaine craving and (1) cue-induced anxiety, (2) the number of days since last cocaine use, (3) current enrollment in a cocaine abuse rehabilitation program, (4) ASI Drug Composite, (5) Fagerström Nicotine Tolerance, and (6) POMS Total Mood Disturbance (TMD) scores. Proportion of patients correctly guessing which medication was received was tested for difference from a chance level of 50%.

RESULTS

Subjective Measures: Control Tests

Neutral cues were tested on all patients before receiving medication. Comparison of pre- and postneutral cue Within Session Rating Scales and Mood Analog Scales revealed no significant changes in cocaine craving, desire to use cocaine now, cocaine-like high, anxiety and tobacco withdrawal over time (time effect), though the overall levels of craving were higher on the first day of testing (day effect: $F(1,13) = 14.22$, $p = .002$). The effects of medication alone were tested by comparing baseline with precocaine cue Within Session Rating Scales and Mood Analog Scales; the analyses are presented in Table 2. An overall decrease in cocaine craving, desire to use cocaine now and anxiety, was found across time (time effect), but this did not differ by drug condition (time × drug effect). In contrast, no overall changes in cocaine-like high or tobacco withdrawal were found across time (time effect), though comparison between mecamylamine and placebo conditions revealed a moderate drug-induced drop in tobacco withdrawal (time × drug effect). The mean values and standard deviation for each of the outcome measures at the baseline and precocaine cue time points of the protocol, showing the effects of mecamylamine or placebo, are shown in Figure 2a–e.

Each patient was also asked to guess whether he/she had received mecamylamine or placebo on each testing day (part of the Within Sessions Rating Scale). Tests of proportion using a McNemar's chi-squared statistic on precocaine cue answers revealed that they were unable to detect which medication they had received on Day 1 (chi-squared = 0.000, $df = 1$, $p = 1.000$) or Day 2 (chi-squared = 1.333, $df = 1$, $p = .248$).

Subjective Measures: Cue-Induced Cocaine Craving Tests

The effects of mecamylamine on cue-induced changes in subjective measures were tested by comparing pre- and postcocaine cue scores from the Within Sessions

Table 2. ANOVA *F* and *p* Value for Drug, Time, and Drug × Time Effects of Baseline to Precocaine Cue Changes on Subjective Outcome Measures

	Factor	*F*	*d.f.*	*p*
Cocaine craving	Drug	0.07	1,22	.807
	Time	21.3	1,22	.001
	Drug × Time	0.25	1,22	.621
Desire to use cocaine now	Drug	0.04	1,22	.836
	Time	7.13	1,22	.014
	Drug × Time	0.65	1,22	.428
Anxiety	Drug	0.07	1,22	.794
	Time	5.18	1,22	.033
	Drug × Time	0.02	1,22	.893
Cocaine-like high	Drug	0.00	1,22	.962
	Time	0.26	1,22	.612
	Drug × Time	0.18	1,22	.677
Tobacco withdrawal	Drug	1.72	1,22	.203
	Time	2.85	1,22	.105
	Drug × Time	6.33	1,22	.020

Statistical analyses of the change in each subjective outcome measure during the medication treatment phase of testing (baseline to pre-cue testing).

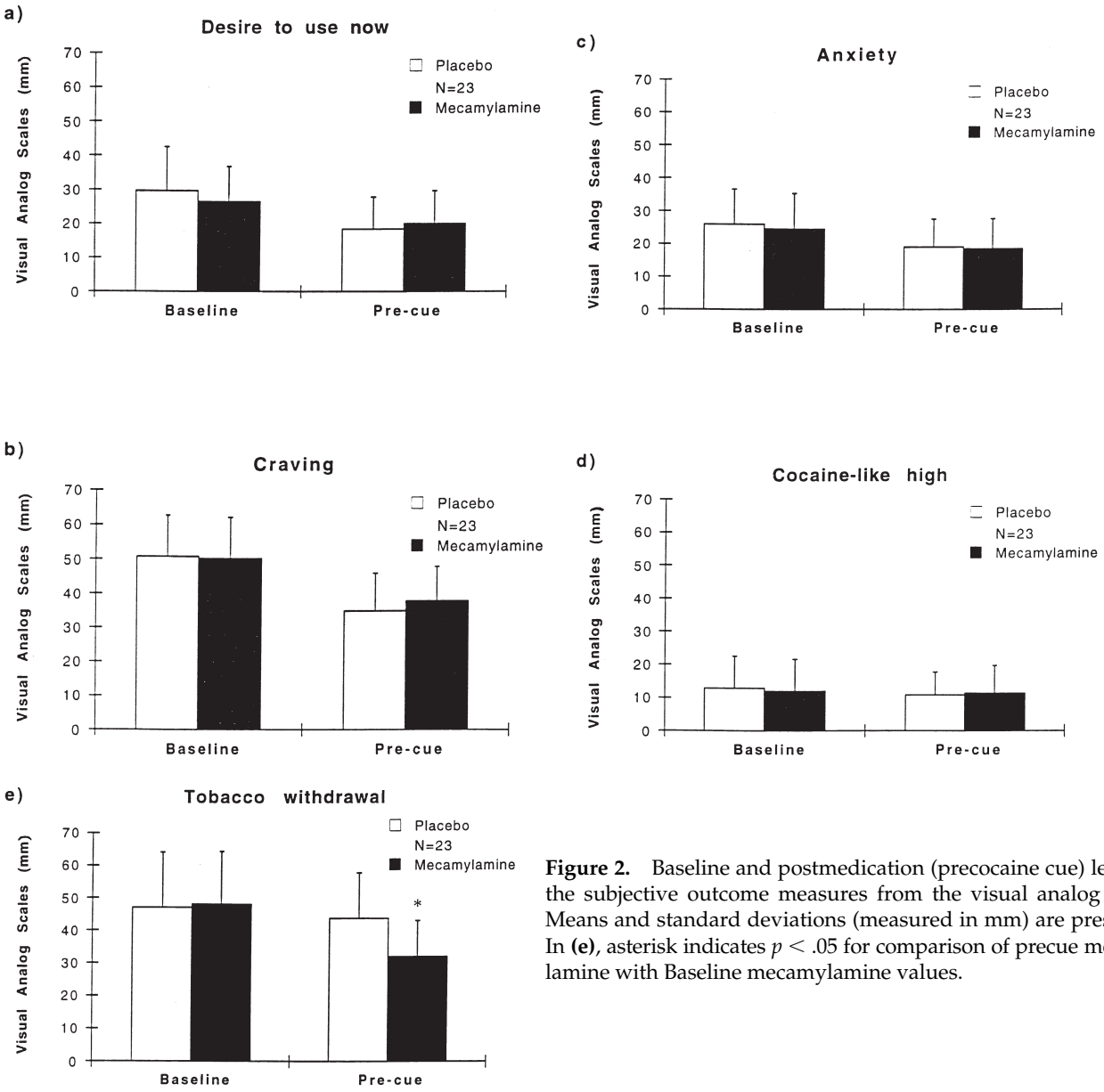

Figure 2. Baseline and postmedication (precocaine cue) levels of the subjective outcome measures from the visual analog scales. Means and standard deviations (measured in mm) are presented. In **(e)**, asterisk indicates $p < .05$ for comparison of precue mecamylamine with Baseline mecamylamine values.

Rating Scales and the Mood Rating Scales; the analyses are presented in Table 3. Consistent with our previous studies (Berger et al. 1996; Reid et al. 1998), exposure to cocaine-related cues resulted in a significant increase in all primary outcome measures during both mecamylamine and placebo conditions (time effect). Comparison of the increase in each measure across condition (time × drug effect) revealed that cue-induced cocaine craving and desire to use cocaine now were significantly lower during the mecamylamine condition. Cue-induced anxiety and cocaine-like high were unaffected by mecamylamine treatment (time × drug effect). The mean values and standard deviation for the cocaine cue-induced change in each of the primary outcome measures, during mecamylamine and placebo conditions, are shown in Figure 3. Kendall Tau correlations revealed a negative relationship between cue-induced cocaine craving and the number of days since last cocaine use during the placebo ($\tau = -0.417$, $p = .048$) but not the mecamylamine ($\tau = 0.114$, $p = .604$) condition. All other correlation analyses between cue-induced cocaine craving and cue-induced anxiety, cocaine abuse treatment status, ASI, Fagerström Nicotine Tolerance, or POMS TMD scores did not reveal any significant association during either condition. Following completion of the last day of testing (Day 2), patients were asked during which day (Day 1 or Day 2) they felt the highest level of cocaine craving following cue exposure. A majority of the subjects (77%) reported that they felt more craving during the placebo than mecamylamine condi-

Table 3. ANOVA *F* and *p* Values for Drug, Time, and Drug × Time Effects of Pre- to Postcocaine Cue Changes on Subjective Outcome Measures

	Factor	*F*	*d.f.*	*p*
Cocaine craving	Drug	0.51	1,22	.444
	Time	33.9	1,22	.001
	Drug × Time	4.73	1,22	.041
Desire to use cocaine now	Drug	2.25	1,22	.148
	Time	39.2	1,22	.001
	Drug × Time	6.30	1,22	.020
Anxiety	Drug	0.97	1,22	.336
	Time	7.04	1,22	.015
	Drug × Time	1.55	1,22	.227
Cocaine-like high	Drug	0.13	1,22	.727
	Time	32.6	1,22	.001
	Drug × Time	0.95	1,22	.340

Statistical analyses of the change in each of the primary subjective outcome measures following exposure to cocaine cues (pre- to post-cocaine cue testing).

tion, which was significantly different ($p < .05$) from a chance level of 50% in a binomial test of proportion.

Physiological Measures

Skin conductance, skin temperature, and heart rate recordings were successfully obtained in 16 of 23 patients studied. The mean recordings of skin conductance and skin temperature are shown (Figure 4a,b) however, due to considerable variability in the heart rate recordings these data are presented as mean values for each phase of cue presentation (Table 4). Statistical analysis of the physiological recordings are presented in Tables 5 and 6. Baseline measures of skin conductance, skin temperature and heart rate were stable before cue exposure (time effect) and, though it appeared that mecamylamine produced moderate reduction in baseline conductance and increase in baseline temperature, did not differ by drug condition (drug effect) (Table 5). Following exposure to cocaine cues there was a significant increase in skin conductance and decrease in skin temperature but no change in heart rate over time (time effect) in which each phase of cue presentation (baseline, video, handling) elicited an incrementally greater response (phase effect). However, comparison of the cue-induced changes in skin conductance, skin temperature, and heart rate revealed no significant differences between mecamylamine and placebo conditions (drug × time, drug × phase, and drug × time × phase effects) (Table 6).

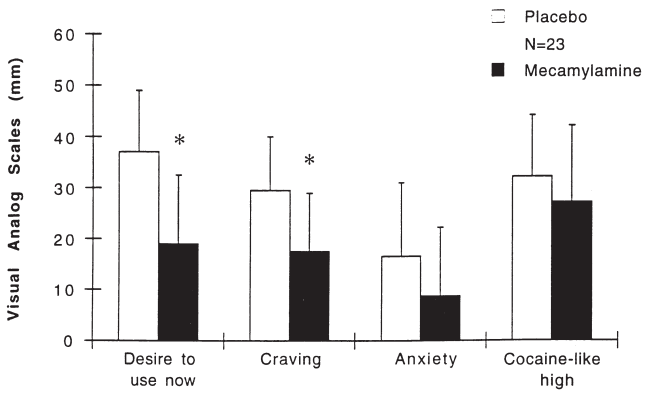

Figure 3. Cue-induced changes (pre- to postcocaine cue testing) in the primary outcome subjective measures from the visual analog scales measured in mm. Means and standard deviations are presented; asterisks indicate $p < .05$ for comparison of mecamylamine with placebo.

DISCUSSION

The main finding from this study is that treatment with a nicotine antagonist, mecamylamine, reduces cue-induced cocaine craving in cocaine-dependent subjects. In addition, mecamylamine also produced a moderate reduction in tobacco withdrawal before cocaine cue testing. Precocaine cue levels of cocaine craving, however, were not affected by mecamylamine. These findings extend our previous work on the effects of transdermal nicotine patches (Reid et al. 1998) by further demonstrating the ability of nicotinergic drugs to modulate conditioned cocaine craving. Indeed, the opposing effects of a nicotinic agonist and antagonist indicate the involvement of a specific receptor site in the CNS.

All patients were instructed to abstain from smoking cigarettes for 12 to 14 hr before being tested, which might result in a moderate level of distress and tobacco withdrawal before cocaine cue testing. In addition, the administration of a nicotinic antagonist might possibly exacerbate this condition, based on previous studies showing that mecamylamine produces an increase in the rate of smoking and self-administered nicotine dose level (Nemeth-Coslett et al. 1986; Rose et al. 1989). However, although mecamylamine may reduce the level of satisfaction obtained from cigarette smoking (Rose et al. 1994), it is not clear that mecamylamine will induce withdrawal symptoms per se (Eissenberg et al. 1996) or even attenuate the withdrawal-alleviating effects of subsequent smoking (Rose et al. 1994). We found that mecamylamine treatment actually reduced the levels of self-reported tobacco withdrawal, even though patients were unable to detect when they received active medication. All other subjective measures, including anxiety, had similar baseline levels and were unaffected by mecamylamine treatment. The drop in tobacco withdrawal may be reflective of the low dose of mecamylamine used in this study because others have reported

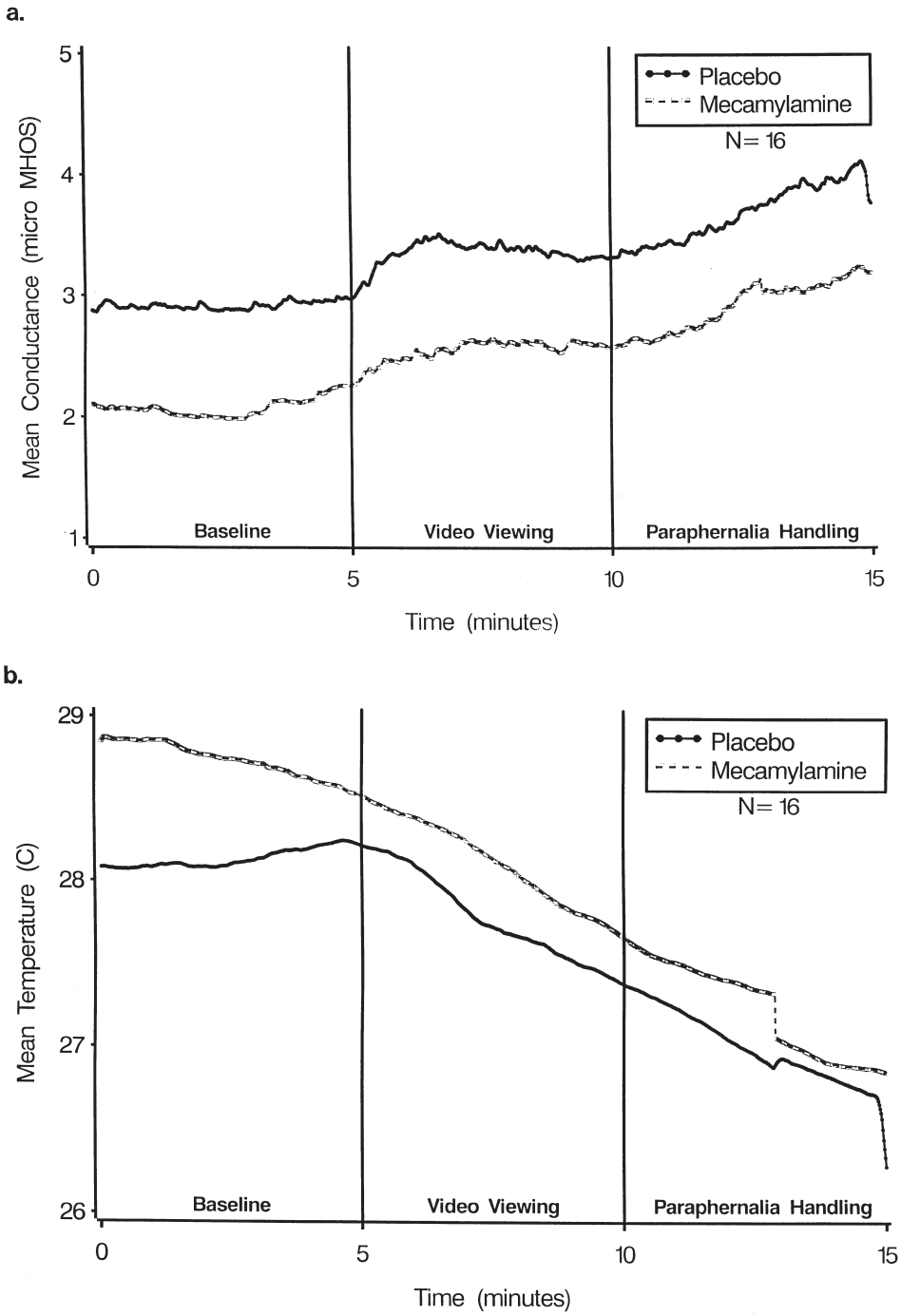

Figure 4. Physiological measures of **(a)** skin conductance and **(b)** skin temperature on each test day. The means across all patients (n = 16) were calculated at each recording time. In **(a)**, the units of skin conductance are expressed as μMHOS [conductance (MHO) is inverse of the resistance (OHM)] and in **(b)**, the units of skin temperature are expressed in °C.

that low doses (2.5–10 mg) of mecamylamine produce a decrease in the desire to smoke (Rose et al. 1989). Previous studies on smoking cessation found that co-administration of mecamylamine (2.5–5 mg/kg/day) with nicotine transdermal patches improved the rate of abstinence in smokers, and it was suggested that mecamylamine reduced cigarette craving whereas nicotine attenuated withdrawal symptoms (Rose et al. 1994). Our findings on baseline levels of tobacco-related withdrawal are consistent with this hypothesis.

Though the overall ratings of cocaine craving tended to be higher on the first day of testing these, as well as the other subjective measures, were unaffected by neutral cues. This lack of neutral cue effects is consistent with previous cue reactivity studies (Ehrman et al. 1992). The reduction in cocaine craving from Day 1 to Day 2 might be attributed to patient habituation to the testing procedure and is consistent with previous studies reporting a decline in baseline levels of desire for cocaine and cocaine-like euphoria from Session 1 to Ses-

Table 4. Heart Rate Levels (bpm) During Cocaine Cue Presentation ($n = 16$)

	Placebo	Mecamylamine
Baseline	70.6 (12.0)	72.7 (10.1)
Video viewing	70.2 (15.8)	70.9 (11.9)
Paraphernalia handling	69.8 (16.2)	71.0 (11.4)

Heart rate levels during baseline, video viewing, and paraphernalia handling phases of cocaine cue presentation. Mean and standard deviation (SD) of beats per minute (bpm) are reported.

sion 2 (Kranzler and Bauer 1992; Robbins et al. 1992). Though a reduction in baseline cocaine craving between days could arguably influence the outcome of the cue-induced cocaine craving tests, statistical analysis revealed no order effects on this and the other subjective measures (except for anxiety).

Cue-induced increases in cocaine craving and desire to use cocaine now were significantly reduced by mecamylamine. The increase in each of these measures was reduced by approximately 50% during the active day. The concordance between these two craving related measures indicates the robust effect of mecamylamine and further supports our contention that the individual cocaine craving related questions in the Within Sessions Visual Analog Scale are highly correlated (see also Reid et al. 1998; Berger et al. 1996). In addition, a significant majority of patients reported more craving on the placebo day when asked to compare both days of testing. Although the measures for cocaine craving were found to be reduced, cue-induced cocaine-like high was not altered by mecamylamine treatment. This is an important distinction and suggests that these related cocaine-conditioned responses are not similarly regulated. Similar findings were obtained in our previous study on nicotine—modulation of the craving but not cocaine-like high responses (Reid et al. 1998). Together, these findings support the suggestion that nicotinergic compounds selectively modulate craving responses in cocaine-dependent patients. In contrast, the ability of haloperidol to reduce both cue-induced cocaine craving, anxiety, and cocaine-like high (Berger et al. 1996) suggests that dopaminergic compounds produce a more generalized effect on cocaine-conditioned responses. Consistent with this latter suggestion, Robbins and colleagues (1992) found that amantadine enhanced the arousal response—increases in heart rate and skin resistance—to cocaine cues. It must be acknowledged, however, that the selective cocaine craving modulatory effects of nicotine and mecamylamine in our studies may have been influenced by the fact that all subjects were also cigarette smokers.

Correlation analyses found a significant, negative correlation between cue-induced cocaine craving and the number of days since last cocaine use during the placebo condition. This indicates that the cocaine craving response was stronger in patients who had abused cocaine more recently, and may be reflective of the current users (versus individuals in rehabilitation programs) in our subject population. Although it would be speculative to draw any conclusions from this finding, our previous study also found a correlation between cue-induced cocaine craving and the number of days since last cocaine use, but this was a positive correlation and occurred during the nicotine condition (Reid et al.

Table 5. ANOVA F and p Values for Drug, Time, and Drug × Time Effects During Baseline Skin Conductance, Skin Temperature, and Heart Rate Recording

	Factor	*F*	*d.f.*	*p*
Conductance	Drug	2.88	1,15	.110
	Time	1.00	9,135	.445
	Drug × Time	0.12	9,135	.999
Temperature	Drug	0.11	1,15	.745
	Time	0.99	9,135	.452
	Drug × Time	0.43	9,135	.915
Heart rate	Drug	0.13	1,15	.719
	Time	1.11	9,135	.361
	Drug × Time	0.55	9,135	.836

Statistical analyses of baseline skin conductance, skin temperature and heart rate before cocaine cue exposure.

Table 6. ANOVA F and p Values for Drug, Time, and Phase (Including Factor Interaction) Effects on Skin Conductance, Skin Temperature, and Heart Rate Before and During Cocaine Cue Exposure

	Factor	*F*	*d.f.*	*p*
Conductance	Drug	2.12	1,15	.166
	Time	3.96	9,135	.001
	Phase	5.89	2,30	.007
	Drug × Time	0.23	9,135	.989
	Drug × Phase	0.02	2,30	.985
	Time × Phase	5.76	18,270	.001
	Drug × Time × Phase	0.25	18,270	.999
Temperature	Drug	0.20	1,15	.660
	Time	20.4	9,135	.001
	Phase	22.1	2,30	.001
	Drug × Time	0.10	9,135	.999
	Drug × Phase	0.33	2,30	.719
	Time × Phase	4.30	18,270	.001
	Drug × Time × Phase	0.46	18,270	.973
Heart Rate	Drug	0.03	1,15	.875
	Time	0.52	9,135	.861
	Phase	0.61	2,30	.550
	Drug × Time	0.20	9,135	.918
	Drug × Phase	0.36	2,30	.702
	Time × Phase	0.38	18,270	.991
	Drug × Time × Phase	0.51	18,270	.952

Statistical analyses of the change in skin conductance, skin temperature and heart rate following exposure to cocaine cues (baseline, video viewing and paraphernalia handling time points).

1998). Therefore, it is suggested that the duration of cocaine abstinence before testing could significantly influence cue-induced cocaine craving, and, consequently, future cocaine cue reactivity studies should take this into account.

Cue-induced anxiety was not significantly affected by mecamylamine treatment, although a moderate decrease was seen. Our previous study indicated that nicotine increases cue-induced anxiety (Reid et al. 1998) and, though caution should be taken when comparing data from different studies, the levels of anxiety seen during mecamylamine were less than 50% of those seen during nicotine. This difference supports the suggestion that nicotinergic drugs do in fact modulate cue-induced anxiety. However, it cannot be ruled out that the anxiety measures were affected by other factors besides drug or cocaine cue exposure, and it is quite possible that nicotinergic drugs could have different effects in cocaine-dependent, nonsmokers.

Cocaine cues produced a significant increase in skin conductance and decrease in skin temperature, whereas heart rate remained unchanged. Similar to ours and other earlier studies (O'Brien et al. 1990; Reid et al. 1998), the changes in conductance and temperature were greatest at the end of the cue exposure protocol, during the paraphernalia handling phase. Previous studies have found similar skin conductance and temperature results; however, they also reported a significant increase in heart rate following exposure to cocaine cues (Ehrman et al. 1992; Kranzler and Bauer 1992; Robbins et al. 1992). This discrepancy is likely be due to the high variability of heart rate recordings obtained from the fingertip photoelectric pulse sensors used in the present study. Comparisons based on drug condition did not reveal any significant effects of mecamylamine on basal or cue-induced changes in skin conductance or temperature. However, visual analysis suggested a minor increase in baseline skin temperature and decrease in baseline skin conductance following mecamylamine. This difference would be consistent with the peripheral, hypotensive and ganglionic blocking effects of mecamylamine (see Eissenberg et al. 1996). Furthermore, such drug effects could attenuate the dynamics of skin temperature and conductance responses to cocaine cue exposure.

The present finding that mecamylamine reduces cue-induced cocaine craving in cocaine-dependent patients suggests that mecamylamine might be a useful tool in relapse prevention programs. It should be noted, however, that these studies were limited to cocaine-dependent subjects who are also cigarette smokers. In terms of addiction treatment, it is already known that mecamylamine is of therapeutic value in smoking cessation (Rose et al. 1994). The ability of low doses to reduce the desire to smoke and the satisfaction derived from smoking (Nemeth-Coslett et al. 1986; Rose et al. 1994) suggests that it is an effective anti-craving agent. The findings that smokers spontaneously decrease their smoking habits when receiving mecamylamine, even before they begin the smoking cessation treatment (Rose et al. 1994), suggests that it may also induce a form of reward extinction. Our findings with cue-induced cocaine craving indicate that these effects might also apply to cocaine addiction processes. Further studies on the psychopharmacological effects of mecamylamine in cocaine-dependent subjects, including treatment trials for cocaine addiction, are needed to address these questions.

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