



Mecamylamine moderates cue-induced emotional responses in smokers

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Abstract

The nicotinic antagonist, mecamylamine, has been shown to reduce cue-elicited cocaine craving and to aid in smoking cessation. In a within-subjects design, 16 dependent smokers received mecamylamine (10 mg) or placebo capsules on two different days. Subjects imagined smoking urge and non-urge scenarios after smoking their usual brand vs. denicotinized cigarettes. Smoking usual-brand cigarettes produced greater positive effects and mecamylamine blocked heart rate (HR) boost and cigarette sensory impact. Mecamylamine also resulted in greater craving and less calmness, regardless of cigarette smoked. Urge script imagination in the mecamylamine+denicotinized condition resulted in calmness similar to usual-brand conditions and higher than the placebo+denicotinized condition. A similar trend was observed for negative affect. These results suggest that mecamylamine can moderate smoking cue-induced emotional responses in smokers.

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1. Introduction

Although other factors have been identified (e.g., sensory factors), it is widely accepted that nicotine is the primary psychoactive substance in tobacco and that the effect of nicotine is

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the chief reason for tobacco dependence. Among numerous mechanisms that have been identified (see Watkins, Koob, & Markou, 2000 for review), the activation and desensitization of nicotinic receptors (nAChRs) in the mesolimbic dopamine reward system likely account in large part for the positive and negative reinforcing effects of nicotine (Corrigall, Coen, & Adamson, 1994; Dani, Ji, & Zhou, 2001; Hart & Ksir, 1996; Reavill, 1990).

An accumulating body of evidence, however, suggests that nAChR systems play a role in the self-administration of nonnicotine drugs of abuse. In animals, nicotine has been found to enhance the acquisition of self-administration of cocaine (Horger, Giles, & Schenk, 1992), while nicotinic antagonists have been shown to both inhibit (mecamylamine; Levin et al., 2000) and increase (Dh β E; Corrigall et al., 1994) cocaine self-administration. Furthermore, nicotine has been shown to increase alcohol self-administration in rats (Lê, Wang, Harding, Juztsch, & Shaham, 2003) and nicotinic antagonists have been shown to attenuate the positive effects of alcohol in humans (Blomqvist, Hernandez-Avila, Van Kirk, Rose, & Kranzler, 2002; Chi & de Wit, 2003).

In addition to nicotinic mediation of drug self-administration, recent evidence suggests nAChRs may also regulate the acquisition of and responses to conditioned reward cues. Olausson, Jentsch, and Taylor (2003) observed chronic nicotine administration to potentiate learning the relationship between conditioned cues (tone+light) and unconditioned water reward in rats. Furthermore, they observed acute nicotine and mecamylamine (a nicotinic agonist) to potentiate and attenuate, respectively, responding with conditioned reinforcement in rats (Olausson, Jentsch, & Taylor, 2004). Consistent with these findings, Zachariou et al. (2001) observed attenuation and potentiation of cocaine-related place preference by mecamylamine and nicotine, respectively in mice. In humans, nAChR stimulation and blockade have been shown to alter cue-elicited drug craving. In two separate placebo-controlled studies, Reid, Mickalian, Delucchi, and Berger (1999) and Reid, Mickalian, Delucchi, Hall, and Berger (1998) exposed cocaine addicts who were also nicotine dependent to cocaine cues following acute nicotine (44 mg) or mecamylamine (2.5 mg) administration and found that nicotine enhanced while mecamylamine reduced cue-elicited cocaine craving.

Evidence suggests that conditioned drug cues play an important role in the maintenance of nicotine self-administration (Balfour, Wright, Benwell, & Birrell, 2000; Caggiula et al., 2001; Rose, Behm, Westman, & Johnson, 2000). However, assessing the role of nAChRs on conditioned cue responding in nicotine dependence is complicated by the fact that smokers are dependent on a nicotinic agonist—namely nicotine. Thus, the effects of nicotine administration on reactivity to nicotine cues may be due to any number of factors including (1) withdrawal alleviation by nicotine, (2) the positive, reinforcing effects of nicotine, or (3) an effect of nicotine on nonspecific processes underlying conditioned reinforcement. Likewise, while mecamylamine has been shown to increase tobacco smoke self-administration (Nemeth-Coslett, Henningfield, O'Keefe, & Griffiths, 1986; Rose, Behm, & Westman, 2001) and reduce the positive, reinforcing effects of smoking (Rose et al., 1994), these effects are presumed to be caused by blockade of withdrawal alleviation by nicotine and the blockade of the positive reinforcing effects of nicotine rather than blockade of nonspecific processes underlying conditioned reinforcement.

The aim of the present study was to assess the effects of nicotine and mecamylamine on cue-elicited craving, mood, and physiology in overnight nicotine abstinent dependent smokers. Using a within-subject design, subjects were administered placebo or mecamylamine in two separate sessions. During each session, subjects smoked both denicotinized and their usual brand of cigarettes and completed ratings of smoking characteristics and effects. Craving was induced using a validated and reliable script-driven imagery paradigm (Drobes & Tiffany, 1997) in which subjects heard and then imagined scenarios describing smoking-related (urge) and everyday (non-urge) situations. Physiology (heart rate, skin conductance (SC)) was measured during, and self-report craving and mood were measured after script-driven imagery.

2. Methods

2.1. Participants

One hundred and thirty-three individuals inquired about participating in the study and of these, thirty-three were scheduled for initial screening sessions. Screening sessions were conducted for 22 subjects and disqualifications were made for illicit drug use ($n=2$), EKG abnormality ($n=1$), and extremely high cholesterol level ($n=1$). Eighteen subjects met all study criteria and were scheduled to participate in the full study. Of these 18, 1 subject subsequently decided not to participate and 1 subject completed the first but not the second experimental session due to scheduling conflicts, leaving 16 subjects who completed all aspects of the study.

2.2. Script-driven imagery

Six scripts describing smoking (urge) and six describing everyday (non-urge) situations were modified from or modeled after Drobes and Tiffany (1997). Urge scripts described situations in which active smokers might have urges to smoke, but, for one reason or another, are either unable to (e.g., cigarettes not available) or dissuaded from (e.g., nonsmoking friend in car) smoking. Non-urge scripts described everyday situations not necessarily associated with smoking (e.g., grocery shopping, raking leaves). All scenarios were emotionally neutral and matched for length.

Scripts were presented to participants in the following way. Before each script presentation, subjects were instructed to close their eyes and relax while baseline physiological measures were recorded for 30 s. Subjects then heard the script presented over headphones. Then, a tone signaled the beginning of the imagination period. Previously, subjects had been instructed that, during this period, they should imagine the situation as vividly as possible, attempting to recreate in their mind the sights, sounds, and even smells associated with the situation. Following the imagination period, participants completed a modified version of the Script Imagination Rating Form (SIRF; see below) based on how they felt during the imagination period.

2.3. Mecamylamine administration

Mecamylamine hydrochloride (Inversine) was purchased from Merck (Westpoint, PA). The Duke Medical Center Pharmacy prepared 5 mg mecamylamine and placebo (lactose) capsules.

2.4. Cigarettes

During the experiment, participants smoked both their usual brand of cigarettes and ‘denicotinized’ cigarettes. Denicotinized cigarettes were manufactured and provided by Philip Morris. These cigarettes deliver tar at levels similar to nicotine-containing cigarettes (9 mg FTC) but nicotine at less than 0.1 mg. [Rose, Behm, Westman, and Coleman \(1999\)](#) validated that smoking these cigarettes results in negligible plasma nicotine and heart rate (HR) increases in deprived smokers. For menthol cigarette smokers, denicotinized cigarettes were mentholated prior to the experiment by placing them in an airtight humidor with menthol crystals overnight. All cigarettes were disguised to reduce brand-specific cues.

2.5. Procedure

Each potential subject completed a screening session, in which an Institutional Review Board-approved informed consent form was reviewed and signed. Health and smoking history, vitals including EKG, mood reports, and biological samples were obtained. Subjects underwent an evaluation by the study physician, and, blood chemistry, pregnancy status, and drug testing results were reviewed. Eligible subjects were invited to return for laboratory sessions.

Qualified subjects completed two identical 4-h experimental sessions. Subjects were required to be abstinent overnight prior to the experimental session that began between 7:30 and 9:30 A.M. At the beginning of each session, expired CO level was measured and two 5-mg mecamylamine or placebo capsules were consumed. During the next half hour subjects completed questionnaires, physiological sensors were attached, and they received instructions regarding experimental procedures. Subjects then completed practice urge and non-urge versions of the script-driven imagery task. In order to partially alleviate craving ([Brauer et al., 2001](#); [Rose et al., 2000](#)) and thus avoid self-report ceiling effects, subjects smoked denicotinized cigarettes at 0.5 (1st cigarette) and 1.5 h (2nd cigarette) and read quietly. At 2.5 (3rd cigarette) and 3.5 h (4th cigarette), participants smoked either a denicotinized or usual-brand cigarette. Following smoking the 3rd and 4th cigarette, subjects filled out questionnaires and completed urge and non-urge versions of the script driven imagery task. At the end of the session, expired CO was measured.

All participants imagined urge and non-urge scripts under all four conditions: mecamylamine+usual-brand cigarette, mecamylamine+denicotinized cigarette, placebo+usual-brand cigarette, and placebo+denicotinized cigarette. However, the order in which participants underwent the various conditions was randomly assigned. Half the participants took mecamylamine on the first session, half took the placebo capsule. Half the participants

smoked a usual-brand and denicotinized cigarette as their 3rd and 4th cigarette, respectively, while half-smoked cigarettes in the opposite order. Half the subjects always imagined urge scripts first while the other half always imagined non-urge scripts first. Each participant heard and imagined all 12 scripts (6 urge; 6 non-urge).

2.6. *Dependent measures*

2.6.1. *Smoking sensory ratings*

The Cigarette Sensory Scale (CSS; Westman, Levin, & Rose, 1992) measures perceptions of cigarette puffs with nine items on a 7-point likert scale (1=not at all to 7=extremely). Responses to items on the CSS administered after each cigarette were used to form the following scales: Puff Satisfaction (liking, satisfying), Similarity (similarity to own brand), Respiratory Tract Impact (strength in the back of mouth and throat, windpipe, chest), Sensory Impact (strength on tongue, in nose), and Nicotine Strength (high nicotine).

2.6.2. *Smoking withdrawal symptoms*

After smoking each cigarette, subjects completed a nine-item short version of the Shiffman-Jarvik withdrawal questionnaire (SWQ; Shiffman & Jarvik, 1976). The SWQ uses a 7-point likert scale (1=not at all to 7=extremely) to measure: Craving (urge to smoke, miss a cigarette, crave cigarettes), Arousal (wide awake, concentrate), Calmness (calm), Negative Affect (tense, irritable), and Hunger (hungry).

2.6.3. *Script imagination ratings*

The Script Imagination Rating Form (SIRF) combines items from the SWQ with two additional items: 'How vividly did you imagine the scene?', and 'How much did it remind you of a personal experience?'. After the imagination period of each script-driven imagery task, subjects were instructed to complete the form according to 'how they felt while they imagined the situation'.

2.7. *Physiological measures*

Pulse was recorded from a BIOPAC photoelectric pulse plethysmograph transducer attached to the nondominant index finger. Pulse peak detection was conducted online and signal was converted to continuous heart rate (HR).

Skin conductance (SC) was recorded from two BIOPAC Ag/AgCl electrodes filled with isotonic gel and attached to the ring and middle fingers of the nondominant hand. Signal was amplified at 10 $\mu\text{mho/V}$ (0–100 μmho range) and bandpass filtered online (1.0 to 0.05 Hz).

All signals were digitized at 250 Hz, passed to a PC-based BIOPAC MP100 data acquisition workstation, and saved to disk. Mean HR and mean, area, and maximum SC during each script-driven imagery task were quantified for three discrete periods: (1) the

middle 20-s of the 30-s baseline, (2) the 50-s scenario presentation, and (3) the middle 20-s of the 30-s imagination period.

2.8. Data analysis

CSS and SWQ scales were submitted to a mixed 2(Capsule: mecamylamine, placebo) \times 2 (Cigarette: usual brand, denicotinized) \times 2 (Capsule Order: mecamylamine first, placebo first) \times 2 (Cigarette Order: usual brand first, denicotinized first) repeated-measures analysis of variance (ANOVA) using SPSS 11.5 (SPSS, 2002). The within-subjects variable Script (urge, non-urge) was added in analyses of SIRF scales. Script (urge, non-urge) and Period (baseline, script, imagination) were added in the analyses of physiological variables. Greenhouse–Geisser correction was only applied to analysis of physiological variables as the *df* numerator only exceeded 1.00 for those measures.

Between-subjects factors were included in analyses in order to model variance accounted for by these variables. However, because effects including these variables had small cell sizes, these effects are only described when they are theoretically interesting or when they accounted for a large proportion of variance.

3. Results

3.1. Participants

Participant characteristics are presented in [Table 1](#).

3.2. Abstinence verification and smoke delivery

Expired CO values were not available for one subject due to equipment failure. CO levels following overnight abstinence (Mean=9.06 ppm, S.D.=4.83) were significantly lower than at screening (Mean=20.93 ppm, S.D.=9.65) [$F(2,26)=19.91, p<0.001$] and increased significantly over the course of the laboratory session (Mean=20.17 ppm, S.D.=5.86) [$F(1,11)=69.18, p<0.001$]. Mecamylamine administration did not alter CO levels.

3.3. Blind

Subjects were able to identify at a rate better than chance which capsule they were administered at Visit 1 [$X^2(1, N=16)=7.27, p<0.05$], but experimenters were not [$p>0.05$]. Subjects and experimenters were able to accurately identify the administered capsule at Visit 2 [$X^2(1, N=16)=7.27, p<0.01$] and [$X^2(1, N=16)=9.00, p<0.01$], respectively. Experimenters were aware of which cigarette subjects smoked first (denicotinized or usual brand) and subjects were able to easily discriminate these differences at Visit 1 [$X^2(1, N=16)=4.27, p<0.05$] and Visit 2 [$X^2(1, N=16)=12.44, p<0.001$].

Table 1
Participant characteristics

	<i>N</i>	Percent (%)
Gender		
Female	10	62.5
Male	6	
Race		
Caucasian	11	68.7
African–American	4	25.0
Hispanic	1	6.3
Cigarette size		
King	11	68.7
Other	5	31.3
Mentholated		
Yes	4	25.0
No	12	75.0
Cigarette type		
Light	6	37.5
Ultralight	5	31.3
Medium	2	12.5
Regular	3	18.8
	Mean	S.D.
Age	37.06	10.00
FTC nicotine	0.869	0.305
FTND	5.69	1.54
Baseline CO	20.93	9.65

3.4. Cigarette smoking

Compared to denicotinized cigarettes, subjects rated their usual brand of cigarettes significantly more satisfying [$F(1,12)=46.12, p<0.001$], higher in nicotine [$F(1,12)=13.36, p<0.01$], producing greater sensory [$F(1,12)=8.61, p<0.05$], and respiratory tract impact [$F(1,12)=12.63, p<0.01$], and more similar to their own brand (which it was) [$F(1,12)=33.86, p<0.001$]. Furthermore, following smoking their usual brand, subjects reported a greater decrease in craving [$F(1,12)=7.55, p<0.05$] and negative affect [$F(1,12)=5.70, p<0.05$].

As shown in Fig. 1, regardless of cigarette smoked, mecamylamine resulted in greater craving for cigarettes, [$F(1,12)=5.35, p<0.05$], lower calmness [$F(1,12)=5.98, p<0.05$], and higher negative affect [$F(1,12)=5.00, p<0.05$] following smoking.

As can be seen in Fig. 2, Cigarette interacted with Capsule on sensory impact [$F(1,12)=8.68, p<0.05$] and respiratory tract impact [$F(1,12)=6.17, p<0.05$]. Pairwise comparisons indicated that in the placebo capsule condition, usual-brand cigarettes were rated as having significantly greater sensory impact ($p<0.001$) and respiratory tract impact ($p=0.001$) than smoking a denicotinized cigarette. A tendency for

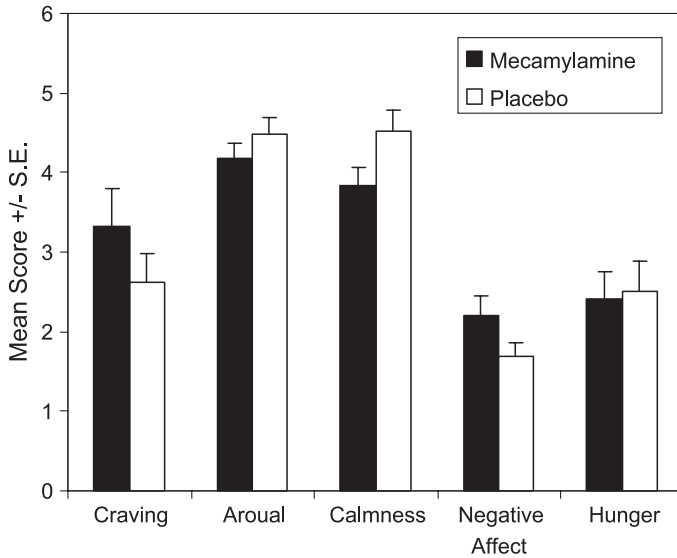


Fig. 1. Following smoking, mecamylamine (10 mg) resulted in higher craving [$p < 0.05$], lower calmness [$p < 0.05$], and higher negative affect [$p < 0.05$] as measured by a short version of the Shiffman-Jarvik withdrawal questionnaire.

mecamylamine to attenuate the sensory impact of usual-brand cigarettes was observed ($p = .058$).

3.5. Script imagination—subjective responses

While imagining urge scenarios, subjects reported feeling significantly lower calmness [$F(1,12) = 34.12$, $p < 0.001$], greater craving [$F(1,12) = 33.19$, $p < 0.001$], and greater negative affect [$F(1,12) = 14.50$, $p < 0.01$], compared to imagining non-urge scenarios.

As can be seen in Fig. 3, Script, Capsule, and Cigarette interacted for calmness [$F(1,12) = 5.34$, $p < 0.05$]. This interaction was largely due to a significant Script \times Cigarette interaction during the placebo session [$F(1,15) = 4.60$, $p < 0.05$]. Post hoc analyses of this interaction indicated significantly lower ($p < 0.001$) calmness during the urge imagination period in the denicotinized condition.

In order to better understand this potentially important interaction, self-report calmness during the urge script imagination period was evaluated. Calmness scores were higher ($p < 0.05$) in the mecamylamine+denicotinized cigarette condition than the placebo capsule+denicotinized cigarette condition. Thus, during exposure to drug cues, mecamylamine attenuated the decrease in calmness associated with smoking denicotinized cigarettes.

A similar, although marginally significant Script \times Capsule \times Cigarette interaction was observed for negative affect [$F(1,12) = 4.69$, $p = 0.051$]. Consistent with the findings for calmness, the highest negative affect scores were observed when participants imagined urge scripts after smoking denicotinized cigarettes on the placebo day.

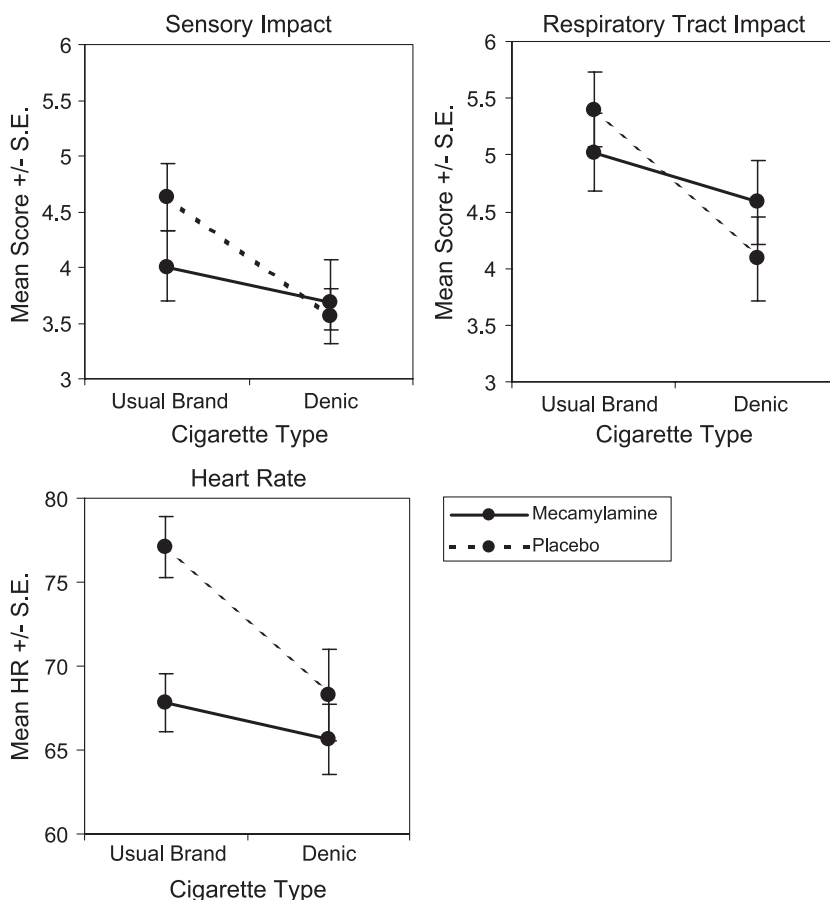


Fig. 2. Significant interactions of mecamlamine vs. placebo and smoking usual-brand vs. denicotinized cigarettes on heart rate (bottom), sensory impact (top left), and respiratory impact (top right) in dependent smokers. The heart rate boost typically associated with nicotine delivery was significantly [$p < 0.05$] attenuated by mecamlamine. In the placebo capsule condition, usual-brand cigarettes were rated significantly greater in sensory impact [$p < 0.001$] and respiratory tract impact [$p < 0.01$] than smoking denicotinized cigarettes. There was a trend for the sensory impact associated with usual-brand smoking to be attenuated by mecamlamine [$p = 0.058$].

3.6. Script imagination—physiological responses

Significantly higher mean HR was observed in the placebo compared to mecamlamine condition [$F(1,12) = 8.76$, $p < 0.05$], and following smoking usual brand compared to denicotinized cigarettes [$F(1,12) = 43.18$, $p < 0.001$]. Furthermore, as can be seen in Fig. 2, Capsule interacted with Cigarette [$F(1,12) = 38.54$, $p < 0.001$]. Mean HR following smoking usual-brand cigarettes in the placebo capsule session (Mean = 77.08 BPM, S.D. = 10.44) was significantly greater than smoking under all other conditions (all p values < 0.002 : usual-brand+mecamlamine (Mean = 67.81 BPM, S.D. = 6.96), denicotinized+mecamlamine (Mean = 65.65 BPM, S.D. = 6.58), and denicotinized+placebo (Mean = 68.28 BPM,

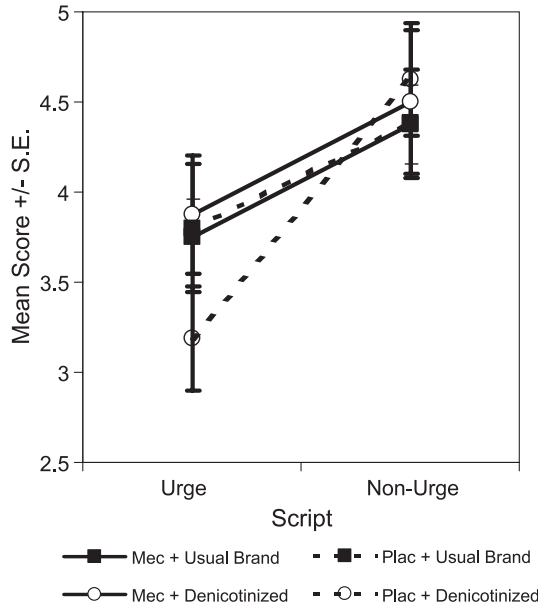


Fig. 3. The effects of mecamlamine and smoking usual-brand vs. denicotinized cigarettes on self-report ratings of calmness while imagining urge and non-urge situations. A significant Script \times Capsule \times Cigarette interaction was observed for calmness, [$F(1,12)=5.34, p<0.05$].

S.D.=8.67). This finding suggests that mecamlamine antagonizes the boost in HR usually associated with nicotine administration. No effects of Script or Period were observed.

Skin conductance area and maximum were higher following smoking usual brand as compared to denicotinized cigarettes [$F(1,12)=16.78, p<0.01$] and [$F(1,12)=17.39, p<0.01$], respectively. Furthermore, mean skin conductance level increased significantly [$F(2,22)=20.68, p<0.001$] from baseline (Mean=0.10, S.D.=0.03) to script presentation (Mean=0.11, S.D.=0.02) and from script presentation to imagination (Mean=0.12, S.D.=0.01). Skin conductance measures were unaffected by mecamlamine or script type.

4. Discussion

In the present study, mecamlamine was shown to decrease the reinforcing effects of cigarette smoking while also blocking cue-elicited reductions in calmness.

Subjects smoked their usual-brand and denicotinized cigarettes following administration of mecamlamine or a placebo capsule. As in a previous study (Rose et al., 1994), mecamlamine blocked some aspects of smoking nicotine-containing cigarettes including rated sensory and respiratory tract impact and HR increases. Interestingly, other effects of mecamlamine on smoking ratings were unaffected by the type of cigarette smoked—across usual-brand and denicotinized cigarettes, mecamlamine resulted in greater craving, lower calmness, and higher negative affect.

Following smoking cigarettes, subjects were asked to listen to and imagine scripts describing situations in which they might have an urge to smoke and everyday situations not associated with smoking. As in previous studies (Drobes & Tiffany, 1997), the urge scripts resulted in significant increases in craving for cigarettes and negative affect, and lower positive affect. While we did not observe main effects of cigarette type, cigarette type and capsule interacted to affect cue-elicited emotional responses. Self-reports of cue-elicited calmness were lowest when subjects smoked a denicotinized cigarette on the placebo day. This effect was moderated by mecamylamine, which, in combination with denicotinized cigarettes, produced calmness levels equivalent to smoking usual-brand cigarettes on the placebo day (i.e., smokers' preferred state). Although the effect of mecamylamine on cue-induced mood was relatively modest, it is consistent with previous reports suggesting this nicotinic antagonist may block cue-elicited drug craving in humans (Reid et al., 1999) and other conditioned drug responses in animals (Zachariou et al., 2001).

The findings that mecamylamine enhanced cue-elicited emotional responses while diminishing smoking-induced emotional enhancement suggests that nicotinic antagonism works in complex ways to alter mood and craving in smokers. As smoking withdrawal would presumably lead to both greater enjoyment of smoking a cigarette and greater cue-induced negative affect, it may be that mecamylamine moderates the effects of nicotine withdrawal. Additional studies assessing the effects of nicotinic antagonism on cue-reactivity in deprived and nondeprived smokers should help elucidate these issues.

The current study is limited by several factors. First, while efforts were made to minimize expectancy effects, our efforts to double- and single-blind mecamylamine and cigarette conditions, respectively, were largely ineffective. This may have been due, in large part, to our sample's sensitivity to the combined peripheral and central effects of nicotinic agonists and antagonists—sensitivities that would presumably also affect treatment using these same compounds. Second, we only tested two levels of cigarette-delivered nicotine (0 vs. usual-brand mg) and two levels of mecamylamine (0 vs. 10 mg). Thus, the effects of nicotine delivered in the absence of smoking and of other mecamylamine levels remain unknown. Finally, all subjects smoked during the session. Thus, we were unable to assess the effects of mecamylamine on drug cue reactivity in smoking and nicotine-deprived smokers.

At the dose tested, mecamylamine moderately enhanced cue-induced mood in minimally deprived cigarette smokers. In contrast with another study (Reid et al., 1999), cue-induced craving was unaltered under the same conditions. The results of this study, while they should be extended and replicated, suggest that mecamylamine may enhance emotional responses to drug cues in smokers.

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