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Acute effects of nicotine and mecamylamine on tobacco withdrawal symptoms, cigarette reward and ad lib smoking

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Abstract

Separate and combined effects of nicotine and the nicotinic antagonist mecamylamine were studied in 32 healthy volunteer smokers after overnight abstinence from smoking. Subjects participated in three sessions (3 h each), during which they wore skin patches delivering either 0 mg/24 h, 21 mg/24 h or 42 mg/24 h nicotine. Thirty-two subjects were randomly assigned to two groups receiving oral mecamylamine hydrochloride (10 mg) vs. placebo capsules. Two and one-half hours after drug administration, subjects were allowed to smoke ad lib, rating the cigarettes for rewarding and aversive effects. Transdermal nicotine produced a dose-related reduction in the subjective rewarding qualities of smoking. Nicotine also reduced craving for cigarettes and this effect was attenuated, but not eliminated, by mecamylamine. Mecamylamine blocked the discriminability of high vs. low nicotine puffs of smoke, and increased nicotine intake substantially during the ad lib smoking period. Some of the psychophysiological effects of each drug (elevation in blood pressure from nicotine, sedation and decreased blood pressure from mecamylamine) were offset by the other drug. The results supported the hypothesis that nicotine replacement can alleviate tobacco withdrawal symptoms even in the presence of an antagonist such as mecamylamine. Mecamylamine did not precipitate withdrawal beyond the level associated with overnight cigarette deprivation, suggesting its effects were primarily due to offsetting the action of concurrently administered nicotine as opposed to blocking endogenous cholinergic transmission.

Keywords: Nicotine; Mecamylamine; Cigarette smoking; Craving; Addiction

The use of nicotine replacement therapy (NRT) for smoking cessation has become widely accepted in recent years; currently, modes of NRT include nicotine chewing gum, patch, inhaler and nasal spray (Hajek et al., 1999). However, long-term success rates are typically only 10–20% when these products are used in the absence of intensive behavioral support (Fiore et al., 1996; Hajek et al., 1999). These findings have prompted the exploration of alternative pharmacologic treatments, one of which is nicotinic blockade therapy (Stolerman, 1986). Mecamylamine is a noncompetitive antagonist at nicotinic receptors, blocking the open conformation of ion channels gated by nicotine (Lindstrom et al., 1995; Varanda et al., 1985). In rodent models, mecamylamine blocks nicotine discrimination (Stolerman et al., 1999) and can shift preference to higher doses of nicotine in an oral self-administration paradigm (Glick et al., 1999); however, it has also been shown to produce extinction of intravenous nicotine self-administration behavior (Corrigall and Coen, 1989; Watkins et al., 1999). In human studies, mecamylamine also attenuates the discriminability of nicotine (Perkins et al., 1999) and produces short-term increases in smoking behavior (Pomerleau et al., 1987; Rose et al., 1988; Stolerman et al., 1973); these findings have been interpreted as compensatory behavior in which smokers attempt to maintain nicotinic stimulation in the face of mecamylamine blockade. However, in a previous smoking cessation trial, we have reported that following a transient increase in smoking behavior in the first few days, a subsequent reduction in ad lib smoking occurs over the

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next 4 weeks. Moreover, long-term smoking abstinence increased substantially when mecamylamine was added to nicotine patch treatment (Rose et al., 1994b, 1998).

One question raised by these studies is to what extent nicotine replacement can exert therapeutic benefits such as relief of craving or other tobacco withdrawal symptoms in the presence of a noncompetitive antagonist such as mecamylamine. We hypothesized that nicotine administration would reduce symptoms of tobacco withdrawal after acute administration of mecamylamine at a typical behaviorally active dose used in human laboratory studies (10 mg), which produced similar plasma levels as the 5-mg b.i.d. dosing used in the previous clinical trials (Rose et al., 1998). Although high doses of a noncompetitive antagonist would be predicted to prevent nicotine from relieving craving, we expected that the 10-mg dose would allow for a demonstrable, if attenuated, effect of nicotine replacement. To assess whether a dose–response relationship for nicotine could be detected in the presence of mecamylamine, both standard (21 mg/24 h) and high doses (42 mg/24 h) of nicotine were administered via skin patches in the presence or absence of mecamylamine.

A second question addressed by the study was whether mecamylamine would induce withdrawal symptoms beyond that produced by nicotine deprivation (i.e., overnight abstinence from smoking). It might be predicted that mecamylamine, through blockade of endogenous nicotinic cholinergic activation, could induce a further increase in withdrawal symptoms. On the other hand, to the extent that withdrawal symptoms depend on missing the effects of nicotine, then mecamylamine would not be expected to intensify withdrawal symptoms in the absence of nicotine replacement. Eissenberg et al. (1996), for example, previously reported that mecamylamine did not precipitate withdrawal symptoms in smokers.

In addition to addressing the above questions, the following study also served to assess the tolerability of higher than usual doses of nicotine skin patch therapy (42 mg/24 h) in combination with mecamylamine. The study was intended to help guide the commercial development of a combined nicotine/mecamylamine skin patch by Sano (Miramar, FL), which licensed patent rights to this treatment method from the first author.

1. Methods

1.1. Design

The study sought to evaluate the acute interactive effects of transdermal nicotine and oral mecamylamine, in overnight smoking-deprived volunteers. Thirty-two subjects were randomly assigned to two groups receiving either 10-mg mecamylamine hydrochloride or placebo capsules at the beginning of each session. At this time, subjects received nicotine skin patches delivering either 0, 21 or 42 mg/24 h (one dose for each of three experimental sessions). Inasmuch as subjects were asked to smoke after 2 1/2 h of wearing the skin patches, when nicotine concentrations were expected to reach nearly peak concentrations, nicotine patch doses were presented in ascending order across days to minimize the possibility of nicotine overdose; anyone not tolerating the 21-mg patches would have been excluded from the 42-mg dose condition. Subjective reports of smoking withdrawal symptoms were collected every 30 min during the 2 1/2 h after capsules and patches were administered. Ratings of the rewarding effects of cigarettes were collected after the ad lib smoking period.

1.2. Participants

Healthy volunteers were recruited from the community by newspaper advertisements. To facilitate subject recruitment, prospective volunteers were offered two incentives; monetary payment of $10/h for each experimental session, and after completion of the present study, smoking cessation treatment including a free 6-week course of nicotine skin patch treatment (in which all participants chose to enroll). Subjects were 18–55 years of age, and smoked at least 20 cigarettes/day of a brand delivering at least 0.7-mg nicotine (by FTC method). Subjects' expired CO concentrations (measured in the afternoon) were at least 20 ppm (confirming inhalation). Subjects were healthy based on physical examination, ECG, serum chemistries, CBC and urinalysis, and were excluded if they had been diagnosed with coronary artery disease, cardiac rhythm disorder or any serious medical condition, current psychiatric disease (aside from nicotine dependence), glaucoma; impaired renal function; history of skin allergy; active skin condition (psoriasis) within the last 5 years, prostatic hypertrophy, hypertension (systolic >140 mm Hg, diastolic >90 mm Hg) or hypotension (systolic <90 mm Hg), or if pregnant or nursing.

1.3. Methods of nicotine delivery

Nicoderm skin patches were used, which deliver nicotine more rapidly than the other types of nicotine patches available; peak plasma nicotine concentrations are achieved within approximately 4 h after patch application (Gorsline, 1993). Identical placebo patches were employed, with subjects wearing two placebo patches in the 0-mg nicotine condition, one active + one placebo patch in the 21-mg condition, and two active patches in the 42-mg nicotine condition.

1.4. Smoking apparatus

A two-barreled smoke-mixing device developed in previous research (Herskovic et al., 1986; Rose et al., 1983, 1984, 1985) was used to assess subjects' ability to discriminate nicotine as well as to measure their preferred nicotine concentration in smoke 2 1/2h h after drug admin-

istration. By turning a knob, the nicotine delivery could be selectively varied by changing the relative proportion of high vs. low nicotine smoke obtained from the two barrels of the device. The low nicotine smoke was obtained from cigarettes delivering 0.7-mg nicotine by FTC standardized smoking procedures. The high nicotine cigarettes were created by injecting 20 μl of a 30% aqueous solution of nicotine base (Kodak) axially approximately 1 cm into the cigarette filter. The nicotine delivery of these cigarettes was approximately 1.5 mg. Distilled water was injected into the low nicotine cigarettes as a control. The position of high vs. low nicotine cigarettes in the smoke mixer (left vs. right barrel) was counterbalanced across subjects, but was held constant across sessions for a given subject to prevent confusion. To assess nicotine discrimination and preference, subjects were first instructed to take a puff each of 50%, 0% and 100% smoke from the left barrel of the smoke mixer, rating the perceived strength on a seven-point rating scale. Next, they freely adjusted the dial setting, smoking ad lib until the cigarettes were completed.

1.4.1. Mecamylamine administration

Mecamylamine hydrochloride (Inversine) was purchased from Merck, (West Point, PA) and capsules containing 10-mg mecamylamine hydrochloride or placebo (lactose) capsules were prepared by the Duke Medical Center Pharmacy.

1.5. Procedure

After a screening physical exam, subjects came to the laboratory on three occasions after overnight abstinence from smoking. Compliance with the smoking abstinence requirement was assessed at the beginning of the session by expired air CO measurement (and subsequently by nicotine analysis in the placebo patch condition). Baseline measures of smoking withdrawal symptoms and cardiovascular measures were collected (see details below). Next, two skin patches were applied to the upper body, which delivered nicotine at a total rate of either 0 mg/h, 21 mg/24 h or 42 mg/24 h. A capsule containing mecamylamine hydrochloride (or placebo) was also swallowed at this time. Dependent measures were assessed every 30 min for the next 2 1/2 h, at which time patches were removed. A sample of venous blood was then collected for nicotine and mecamylamine analysis. Next, subjects were allowed to puff ad lib from the smoke-mixing device described above; one cigarette was placed in each barrel of the device, and subjects were allowed up to 15 min to smoke these two cigarettes only. After subjects were done smoking, a second blood sample was collected and a final assessment of subjective and cardiovascular measures was conducted.

1.6. Dependent measures

The following dependent measures were assessed during each session.

1.6.1. Plasma drug concentrations

Samples of venous blood (10 cc) were collected before and after the smoking period. The samples were centrifuged, packed on dry ice and shipped from Durham, NC to the Clinical Pharmacology Laboratory at the University of California, San Francisco, for assay of nicotine and mecamylamine concentrations.

1.6.2. Smoking withdrawal symptom questionnaire

We used a modified Shiffman-Jarvik (1976) questionnaire, which we have employed previously in several laboratory studies. It has been sensitive in detecting effects of cigarette deprivation and pharmacologic treatments (e.g., Westman et al., 1993). The items comprise six subscales: *craving* (craved a cigarette, would have liked a cigarette, thought of cigarettes, missed a cigarette, had urges to smoke and, scored oppositely, would have refused a cigarette); *negative affect* (tense, irritable, and scored oppositely, calm, content); *arousal* (wide awake, able to concentrate, unusually sleepy); *somatic symptoms* (fluttery feelings in chest, heart beat faster than usual, hands shake, headache, cough, mouth sores, sore throat, heartburn, chest tightness, nausea, bad taste in mouth, upset stomach, dizziness), *appetite* (hungrier than usual, craved sweets, craved salty foods); and *habit* (missed something to do with the hands, missed having something in the mouth).

1.6.3. Cigarette evaluation questionnaire

This questionnaire, developed previously (Westman et al., 1992), was administered immediately after smoking in order to measure the subjective rewarding and aversive effects of smoking; items assessed *satisfaction*: (“Was it satisfying?”, “Was there a good taste?”); *psychological reward*: (“Did it calm you down?”, “Did it make you feel more awake?”, “Did it reduce your hunger for food?”, “Did it make you feel less irritable?”); *nausea/dizziness*: (“Did you feel nauseated?”, “Did you feel dizzy?”); *craving relief* (“Did it immediately reduce your craving for cigarettes?”); and *enjoyment of airway sensations* (“Did you enjoy the sensations in your throat and chest?”).

1.6.4. Anticipated cigarette evaluation questionnaire

This questionnaire, administered immediately prior to smoking, included the same items as the previous cigarette rating questionnaire, but asked subjects to rate the degree to which they expected to experience the rewarding and/or aversive effects during subsequent cigarette smoking.

1.6.5. Sensory questionnaire

To obtain detailed information about the sensory properties of cigarette smoke and nicotine, we administered a questionnaire used in several previous studies, which included items assessing: *estimated nicotine delivery*, *similarity to usual brand*, and perceived *strength* on the tongue, nose, back of mouth and throat, windpipe and chest.

All items of these questionnaires were rated on seven-point scales ranging from 1 (“not at all”) to 7 (“extremely”).

A side-effects questionnaire was also completed during the session, assessing presence or absence of blurred vision, dizziness when standing, weakness, abdominal pains, constipation or trouble urinating, lightheadedness, nausea, shortness of breath, palpitations, and headache. A questionnaire was also administered at succeeding sessions to assess side effects that may have occurred after leaving the laboratory the afternoon or evening of the prior session.

1.6.6. Smoking behavior

Ad lib smoking was assessed by measuring: (1) pre-post smoking plasma nicotine boost. The skin patches were removed 2 1/2 h after application, immediately prior to the smoking period; nicotine levels from the patch were assumed to be stable over the smoking period, inasmuch as the apparent half-life of nicotine following transdermal administration is 3–4 h (due to continued absorption from the skin (Gorsline, 1993)). Thus, the increase in plasma nicotine following smoking was taken as a measure of ad lib nicotine intake; (2) expired air CO concentrations were measured using a handheld CO monitor (Vitalograph, Lenexa, KS). Expired air CO concentrations were calculated by subtracting the background (ambient) CO from the peak CO reading; (3) the number of puffs taken from each cigarette was also counted by the research technician; and (4) nicotine preference, as reflected in the dial settings of the smoke mixing device.

1.6.7. Cardiovascular measures

Heart rate and blood pressure were measured at each time point, as well as the orthostatic change in blood pressure 1 min after rising from a seated to a standing position. Also, an EKG with rhythm strip was taken at the beginning of the session, after 2 1/2 h patch wearing, and again after smoking; the EKG record was examined for rhythm, QRS, S–T and T wave abnormalities to assess potential arrhythmia or cardiac ischemia.

1.7. Statistical analyses

Data analysis was performed using SUPERANOVA and STATVIEW (SAS Institute, Cary, NC). For each parametric variable (including questionnaire scales assessing smoking withdrawal symptoms, ratings of smoking satisfaction and reward), a multivariate approach to repeated measures analysis ANOVA was used, which is generally appropriate regardless of the correlation pattern among repeated measurements (Maxwell and Delaney, 1990). For each dependent measure, an analysis was first conducted using data from the 2 (mecamylamine vs. placebo) × 3 (0, 21 or 42 mg nicotine patch) × time (0, 30, 60, 90, 120, 150 min) design. Any significant interactions between factors were followed up with an analysis of simple effects (e.g., a three-way interaction between nicotine dose, mecamylamine and time would be followed up with analyses of each of the three component factors). Additionally, planned orthogonal contrasts compared the active patch dose conditions (21 and 42 mg) with placebo, and the 21-mg with the 42-mg condition. In the event of significant nicotine dose–effects (or Nicotine dose × Time interactions), the same analyses were repeated for the subjects in the mecamylamine condition, to determine whether mecamylamine produced less than a complete blockade of nicotine effects. In these analyses, we focused on the 150-min post-drug time point, when mecamylamine levels were measured and it was verified that effective levels of mecamylamine had been achieved.

One subject (in the no-mecamylamine group) experienced nausea with emesis in the 42-mg nicotine skin patch session, and his data were excluded from all statistical analyses.

2. Results

2.1. Subject characteristics

Table 1 shows characteristics of the subject sample, including age, gender, and information about cigarette smoking.

2.2. Assessment of compliance with overnight smoking abstinence

Expired air CO levels at the beginning of the sessions were generally low in all three nicotine dose conditions; the mean values were 12.8 ppm (S.D. = 4.24), 12.4 ppm (S.D. = 4.41) and 12.9 ppm (S.D. = 4.60) in the 0-, 21- and 42-mg patch conditions, respectively. Baseline plasma nicotine levels in the 0-mg patch condition (measured in blood samples collected at 2 1/2 h), which would have indicated recent smoking, averaged 1.7 ng/ml (S.D. = 1.79), also consistent with overnight abstinence.

Table 1
Subject characteristics, including age, gender, daily cigarette consumption, nicotine delivery of preferred brand (FTC rating), duration of smoking, expired air CO concentration assessed at screening physical exam, and Fagerstrom Test for Nicotine Dependence (FTND) score

Subject characteristics	Mecamylamine (N = 16)		No mecamylamine (N = 16)	
	Mean	S.D.	Mean	S.D.
Age	40.0	9.42	41.7	7.88
Gender	7M 9F		10M 6F	
Cigarettes/day	26.2	5.67	24.8	6.36
FTC nicotine	0.91	0.151	1.06	0.162
Years smoked	22.4	9.50	24.4	8.16
Screening CO	26.0	10.06	32.2	14.17
FTND	6.2	1.72	6.3	1.85

2.3. Smoking withdrawal symptoms

2.3.1. Craving

There was a significant Nicotine dose × Time interaction ($P = .02$), with increasing doses of nicotine reducing craving over the 2 1/2 h after patch application (see Fig. 1). Follow-up contrasts at each time point indicated that nicotine reduced craving relative to placebo at all time points (P's $< .01$) and that craving in the 42-mg patch condition was significantly lower than in the 21-mg patch condition from the 60-min point on ($P = .0005$ at 60 min, $P = .02$ at 90 min, $P = .003$ at 120 min and $P = .04$ at 150 min). The effect of nicotine dose was still significant even when the analysis was restricted to subjects in the mecamylamine condition ($P = .009$ for placebo vs. active patch comparison at 150 min). However, mecamylamine tended to offset the craving reduction produced by the nicotine skin patches, and there was a significant Mecamylamine × Time interaction within the two active nicotine patch conditions ($P = .049$). This interaction reflected a trend for mecamylamine to increase craving beginning at 90 min, with craving significantly higher at the 120-min time point ($P = .04$). The Mecamylamine × Time interaction was not significant in the placebo patch condition ($P = .6$).

2.3.2. Arousal

Subjective arousal showed a three-way interaction of Nicotine dose × Mecamylamine × Time ($P = .046$). As shown in Fig. 1, mecamylamine decreased arousal over time, but this effect was partially offset by concurrent nicotine administration. The three-way interaction reflects the fact that in the mecamylamine condition only, the Nicotine dose × Time interaction was highly significant ($P = .008$). Follow-up contrasts between placebo and active patch doses revealed that nicotine increased arousal at 60 min ($P = .01$), 90 min ($P = .0001$), 120 min ($P = .003$) and 150 min ($P = .0002$).

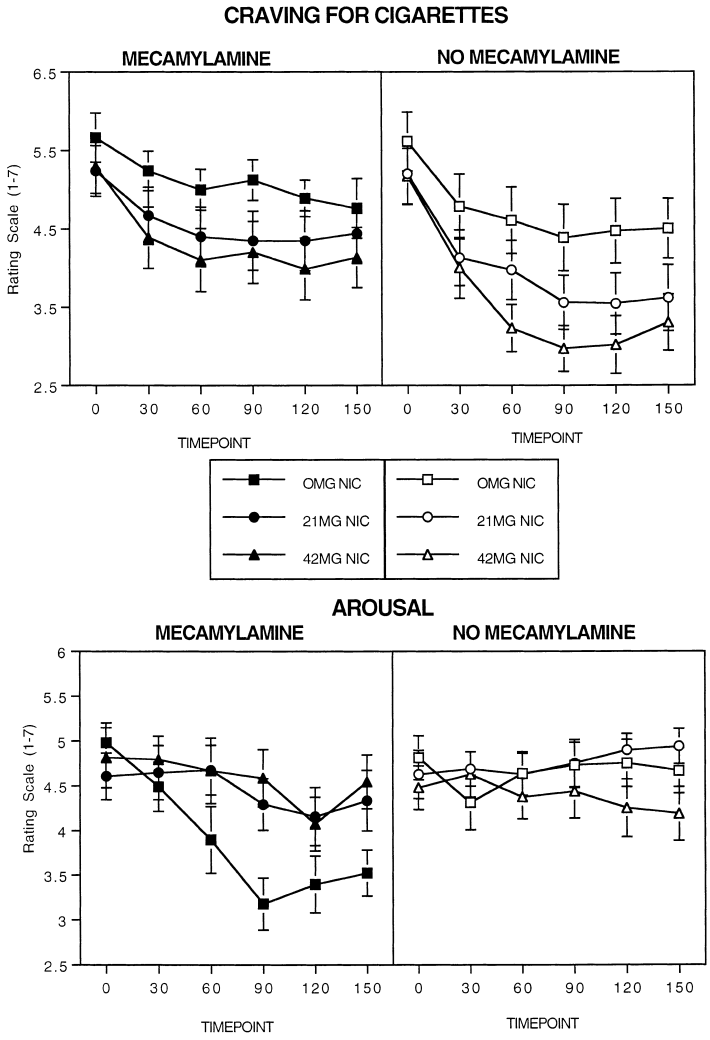

Fig. 1. Craving for cigarettes (mean ± S.E.M.) and subjective arousal at different times during the session as a function of nicotine patch dose and mecamylamine condition.

2.3.3. Appetite

Appetite ratings were extremely low throughout the session (mean of 1.2 on the 1–7 rating scale) and showed no relationship to drug condition.

2.3.4. Negative affect

There was a significant Nicotine dose × Time interaction (P=.01). However, this likely did not represent a pharmacologic effect of nicotine, because there was a baseline difference between the patch conditions at time 0, with negative affect higher on the placebo patch day (P=.0001). None of the subsequent time points showed a difference between patch conditions.

2.3.5. Habit withdrawal

Habit withdrawal symptoms showed no significant effects of either nicotine or mecamylamine administration.

2.3.6. Somatic symptoms

Overall, there were few somatic symptoms reported and no significant differences between conditions.

2.3.7. Anticipated reaction to smoking

Before smoking, subjects' reported anticipated reaction was significantly related to transdermal nicotine dose (Fig. 2, left panels). Anticipated smoking satisfaction as well as anticipated psychological reward from smoking were significantly reduced by nicotine dose; not only were the placebo vs. active patch contrasts significant (P's=.0001), but the 21-mg dose differed from the 42-mg nicotine condition (P's=.03). The placebo vs. active patch comparisons remained significant for the subjects in the mecamylamine condition (P=.05 and P=.03, respectively). Anticipated enjoyment of respiratory tract sensations showed a difference between placebo and

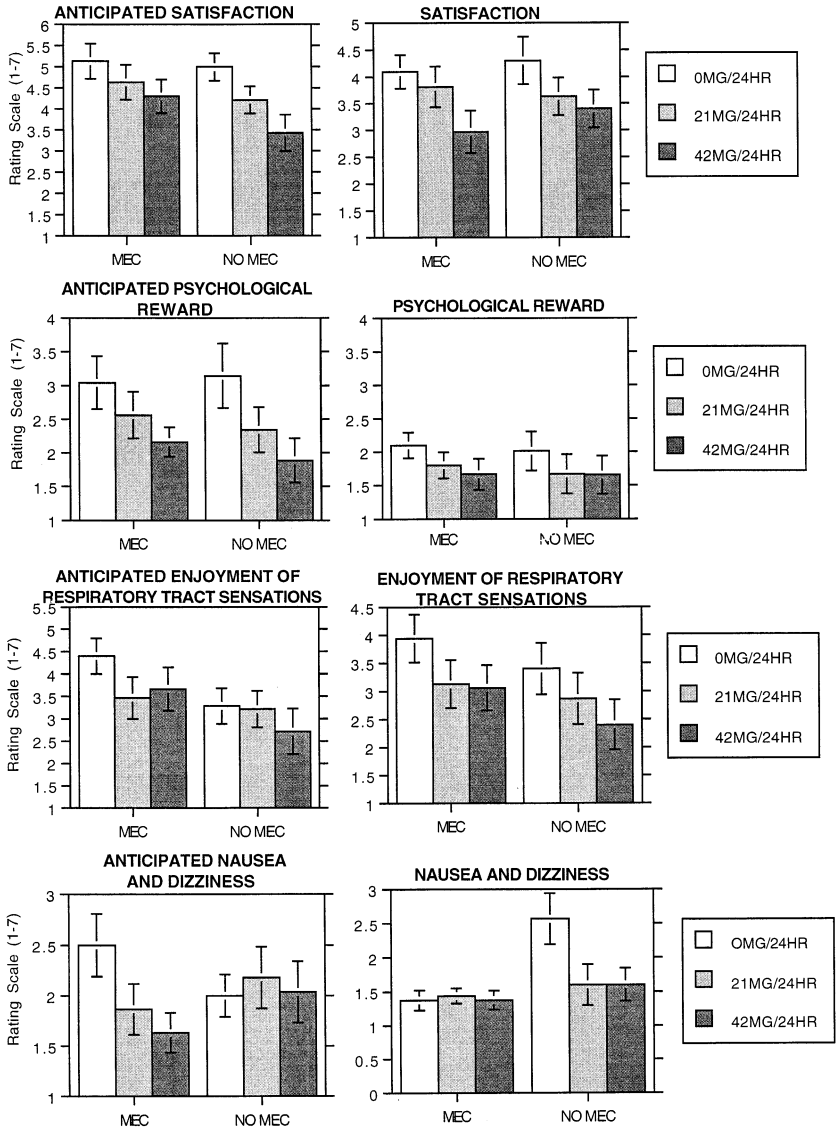

Fig. 2. Mean ratings (±S.E.M.) of anticipated (left panels) and obtained (right panels) smoking reward (mean±S.E.M.) as a function of nicotine patch dose and mecamylamine condition.

active patch conditions ($P=.03$ overall; $P=.07$ for the mecamylamine subjects).

None of the anticipated reactions to smoking were significantly affected by mecamylamine.

2.3.8. Cigarette evaluation scale

Fig. 2 (right panels) also depicts the ratings of cigarette smoke presented at the end of the session. For satisfaction, psychological reward, craving reduction, and enjoyment of respiratory tract sensations the two nicotine patch conditions were significantly lower than placebo ($P=.0006$, $P=.0006$, $P=.02$, $P=.0001$, respectively). For satisfaction, the 42-mg nicotine patch condition also differed from the 21-mg condition ($P=.03$). These effects remained significant in the mecamylamine group. Nausea/dizziness ratings showed a Nicotine dose × Mecamylamine interaction ($P=.004$). Follow-up analyses of simple effects showed that mecamylamine attenuated the aversive aspects of smoking in the placebo patch condition ($P=.009$), in which ratings of nausea/dizziness were higher than in the active patch conditions.

2.3.9. Sensory ratings

Ratings of estimated nicotine delivery showed a significant Nicotine dose × Mecamylamine interaction ($P=.04$), reflecting the fact that mecamylamine reduced ratings the most in the placebo patch condition. Regional airway sensations showed effects of nicotine patch dose and of mecamylamine; nicotine reduced the intensity of sensations in the tongue ($P=.0001$; $P=.02$ for the mecamylamine group) and back of mouth and throat ($P=.03$), but increased sensations

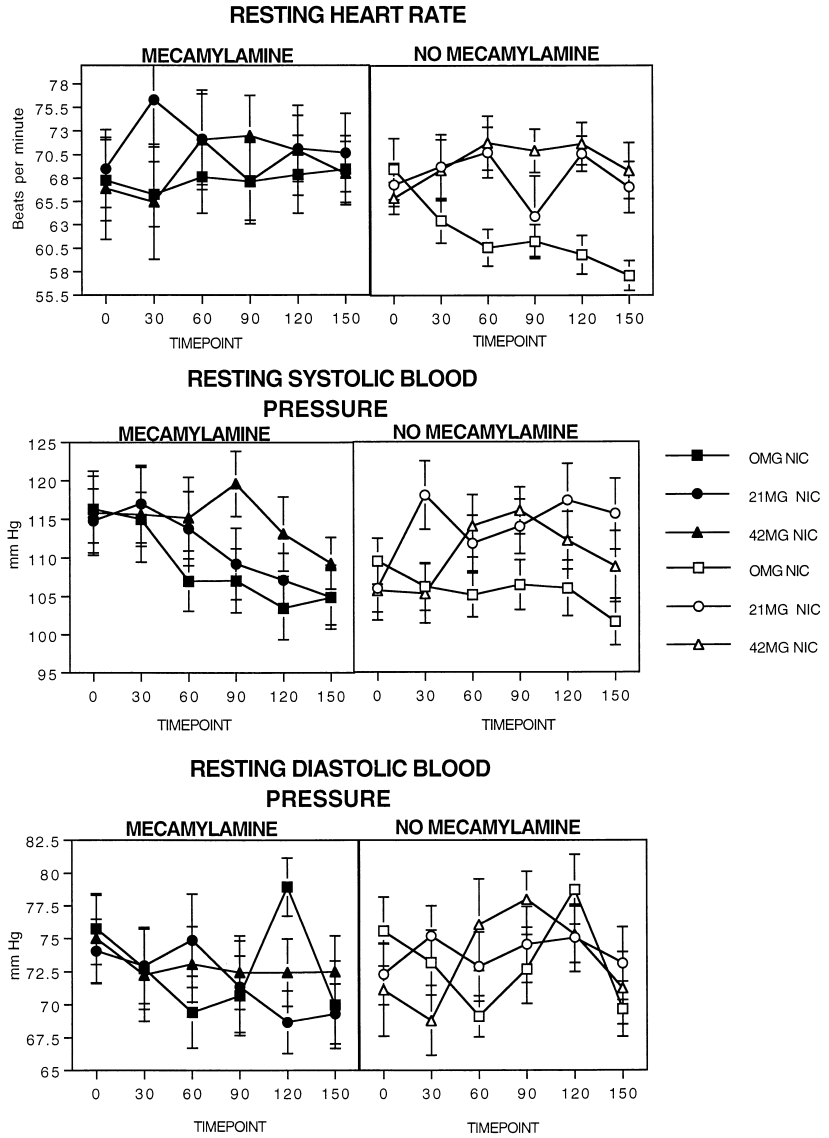

Fig. 3. Mean (±S.E.M.) heart rate, systolic and diastolic blood pressure at different times during the session, as a function of nicotine patch dose and mecamylamine condition.

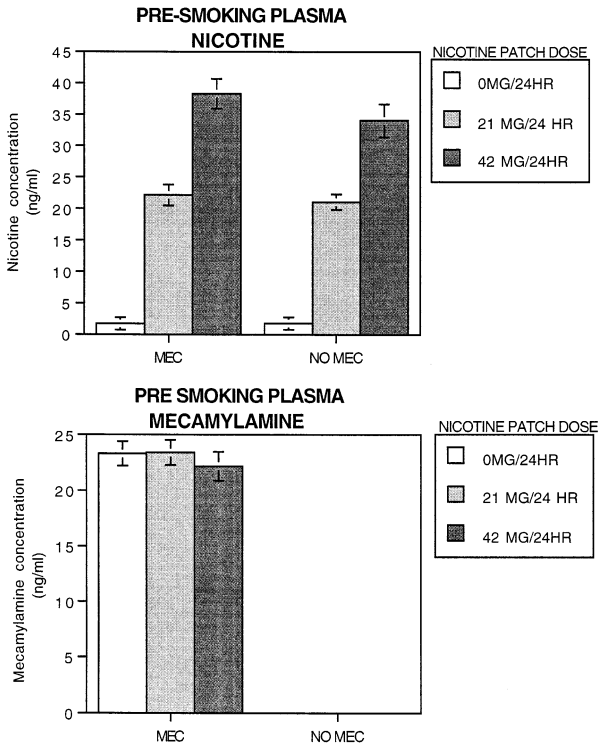

Fig. 4. Mean (±S.E.M.) plasma nicotine and mecamylamine levels 2 1/2 h after drug administration, prior to ad lib smoking in the different experimental conditions.

in the nose ($P=.03$). Mecamylamine significantly attenuated strength ratings for the windpipe region ($P=.03$).

2.3.10. Cardiovascular measures

For heart rate, there was a significant interaction of Nicotine dose × Mecamylamine ($P=.01$); see Fig. 3. In the no-mecamylamine condition, nicotine sustained a higher resting heart rate over time (Nicotine dose × Time interaction, $P=.0002$) with heart rate higher in the active vs. placebo patch conditions from 30 min on (P's $<.01$).

Resting systolic blood pressure (Fig. 3) showed a Nicotine dose × Time interaction ($P=.0001$), with a significant increase in the nicotine conditions from 30 min on (P's $<.05$). Moreover, blood pressure in the 42-mg condition was higher than in the 21-mg patch condition at the 30 min ($P=.0003$) and 90 min ($P=.001$) time points. The blood pressure effect of nicotine remained significant in the mecamylamine group from 60 to 120 min (P's $<.01$). In addition, there was a Mecamylamine × Time interaction ($P=.0001$), with mecamylamine tending to reduce systolic blood pressure over time, significantly at 120 min ($P=.02$), and 150 min ($P=.02$) in the 21-mg patch condition. Thus, nicotine and mecamylamine had opposing effects on systolic blood pressure.

Diastolic blood pressure (Fig. 3) also showed a Nicotine dose × Time interaction ($P=.0001$), with nicotine increasing blood pressure over time, significantly at 60 and 120 min (P's $<.001$ overall and for mecamylamine group). The 42-mg patch produced a further increase in blood pressure, which was significant at 30 min ($P=.02$). Mecamylamine also produced a reduction in diastolic blood pressure over time (Mecamylamine × Time interaction, $P=.04$).

The orthostatic change in systolic blood pressure showed no significant effects of nicotine dose or mecamylamine.

The EKG measures showed no clinically significant abnormalities associated with drug condition. One subject receiving mecamylamine, a 24-year-old male, possibly had three blocked premature atrial contractions (in the 21-mg and 42-mg patch conditions) that could not be confirmed due to lack of multiple EKG leads for comparison.

2.3.11. Nicotine and mecamylamine plasma measures

Prior to smoking, there was, as predicted, a significant nicotine dose-related increase in plasma nicotine concentrations ($P=.0001$), as shown in Fig. 4. There was no effect of mecamylamine on nicotine levels, and in fact plasma nicotine values were nearly identical in mecamylamine and no-mecamylamine conditions.

Mecamylamine concentrations (Fig. 4) were essentially zero after placebo capsule administration, and were significantly increased in the mecamylamine condition ($P=.0001$). There was no difference in mecamylamine concentrations among the three nicotine patch dose conditions, or between the pre- and post-smoking time points.

2.3.12. Ad lib smoke intake

The nicotine boost after smoking was affected by experimental condition, with a significant interaction of Nicotine dose × Mecamylamine ($P=.003$); as shown in Fig. 5, subjects in the mecamylamine condition took in substantially more nicotine in the 0-mg and 42-mg patch conditions ($P=.03$ and $P=.002$, respectively).

The boost in expired air CO (reflecting inhalation) showed an effect of nicotine dose, with the boost being lower in the active nicotine patch conditions relative to placebo ($P=.0002$). CO boosts averaged 4.1 ppm (S.D. = 2.08) in the placebo patch condition, 3.1 ppm (S.D. = 2.51) in the 21-mg patch condition and 2.5 ppm

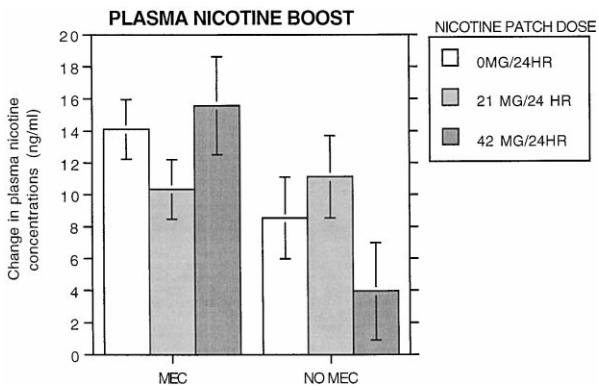

Fig. 5. Mean (±S.E.M.) plasma nicotine boost after ad lib smoking in the different experimental conditions.

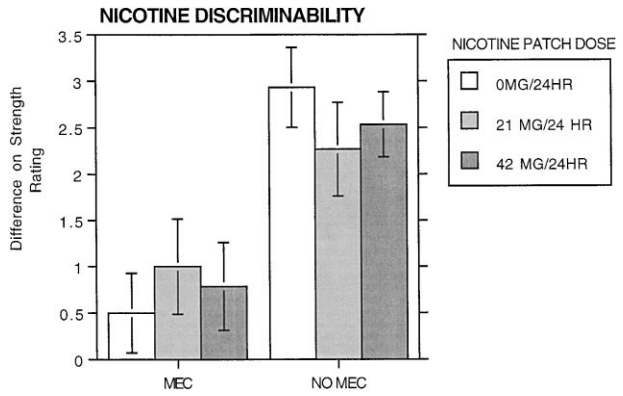

Fig. 6. Mean (±S.E.M.) nicotine discrimination, as assessed by the rated strength of high vs. low nicotine puffs of smoke, in the different experimental conditions.

(S.D. = 1.93) in the 42-mg patch condition. This effect of patch dose remained significant in the mecamylamine group ($P = .02$).

There were no significant effects of mecamylamine on CO boost, nicotine preference (as assessed by the smoke mixing device) or number of puffs taken. However, there were trends for nicotine preference and CO boost to be higher in the mecamylamine condition (preference for the high-nicotine cigarette was 49% (S.D. = 25.2) vs. 42% (S.D. = 28.2); mean CO boost was 3.5 ppm (S.D. = 1.84) vs. 3.0 ppm (S.D. = 2.62).

2.3.13. Nicotine discrimination

The difference in strength ratings between high and low nicotine puffs (puffs 2 and 3 from the smoke-mixing device) was substantial in the no-mecamylamine condition, but was greatly attenuated by mecamylamine ($P = .001$), as shown in Fig. 6. In contrast, patch nicotine dose had no apparent effect on the discriminability of high and low nicotine puffs.

2.3.14. Side effects questionnaire

With the exception of the one subject who experienced emesis, few adverse side effects were reported, and these were generally mild. The number of subjects reporting "moderate" or higher ratings of symptoms was as follows: blurred vision (1), dizziness (1), dry mouth (3), lightheadedness (2) and headache (1).

3. Discussion

The present study addressed several issues relating to the acute effects of nicotine and mecamylamine. The main finding was that nicotine replacement, using transdermal patches, produced a significant reduction in craving for cigarettes even after mecamylamine administration. In addition, nicotine reversed the sedative effect of mecamylamine as indexed by reduced arousal (Fig. 1). For this measure, the 42-mg nicotine patch dose was no more effective than the 21-mg dose, possibly reflecting a ceiling imposed by the noncompetitive blockade with mecamylamine.

Transdermal nicotine also reduced satisfaction and other indices of cigarette reward when subjects were allowed to smoke. It is possible that this reduction resulted from reduced nicotine intake, which was revealed by the lower plasma nicotine boosts in the nicotine vs. placebo patch conditions. However, the fact that ratings of anticipated smoking reward were also significantly attenuated by nicotine patches suggests that the effect was not solely dependent on changes in smoke intake. The attenuation of reward from smoking, produced by nicotine replacement, was unaffected by mecamylamine. One potential explanation for this result is that nicotine acts at multiple nicotinic receptor subtypes, which show different sensitivity to mecamylamine blockade. Thus, nicotine may reduce craving for cigarettes by a mechanism involving a subtype of receptor sensitive to mecamylamine blockade, but reduce smoking reward by stimulating other receptors less sensitive to mecamylamine. Alternatively, transdermal nicotine may reduce the rewarding effects of smoking by desensitizing (rather than activating) nicotinic receptors, an action that may be unaffected by mecamylamine.

While not completely blocking the effects of nicotine, the dose of mecamylamine was adequate to attenuate some of the effects of the nicotine, whether delivered via the patch or cigarette smoke. Mecamylamine attenuated some of the sensory effects of cigarette smoking, particularly the sensations in the windpipe. This was likely due to the action of mecamylamine on peripheral nicotinic receptors that mediate the sensory effects of nicotine (Jarvik and Assil, 1988; Rose et al., 1999). In addition, the blood pressure effects of nicotine were offset by mecamylamine. Moreover, mecamylamine virtually eliminated subjects' ability to discriminate between high and low nicotine puffs of smoke, based on rated strength.

However, surprisingly, no effect of mecamylamine was detected on smoking satisfaction ratings, in contrast to some other studies, which have reported that mecamylamine reduces smoking satisfaction (Rose et al., 1994a, 1998). The plasma mecamylamine levels in this study were as high as those measured in one of these previous studies. Possibly, the between-subject comparison of the present study lacked sufficient statistical power to detect an effect. Alternatively, initial ratings of smoking satisfaction may depend on mechanisms distinct from those involved in nicotine discrimination or withdrawal symptoms.

The present study found no evidence that mecamylamine precipitated craving for cigarettes beyond that produced by the absence of nicotine, even though mecamylamine did partially offset the craving relief provided by concurrent nicotine administration. The latter finding seems initially difficult to reconcile with the results from a study reported by Eissenberg et al. (1996), which reported no effect of 10- or 20-mg doses of mecamylamine on craving for cigarettes. However, in their study, nicotine patches were not used, and

the only source of nicotine was from previous smoking, which ended 30 min prior to mecamylamine administration. If mecamylamine absorption required an additional 1–2 h, plasma nicotine levels (which were not reported) might have been low by the time effective plasma mecamylamine levels were reached. Under these conditions, our results suggest that mecamylamine will not increase craving for cigarettes.

Mecamylamine significantly increased ad lib smoke intake in two of the nicotine patch conditions (0 and 42 mg), possibly reflecting compensation for the partial blockade of the effects of smoking. In the 42-mg patch condition, increased ad lib nicotine intake may have also resulted from the partial blockade of the craving–reducing effects of the nicotine patches prior to smoking. The greater plasma nicotine boost was only partially accounted for by measures of nicotine preference and expired air CO, suggesting other subtle manipulations of smoking topography that subjects may have used to alter nicotine intake. Several previous studies have reported increases in ad lib smoking and nicotine intake following acute mecamylamine administration (Nemeth-Coslett et al., 1986; Pomerleau et al., 1987; Rose et al., 1988; Stolerman et al., 1973), although these studies did not involve NRT.

In interpreting the effects of nicotine patches on the various dependent measures, it must be borne in mind that the order of nicotine doses was not counterbalanced. Thus, it is not possible to unambiguously separate a nicotine dose effect from an order effect. However, this concern is mitigated by the fact that the values for most of the dependent measures at the beginning of each session remained similar across sessions.

Overall, the results support the hypothesis that nicotine replacement has demonstrable effects even in the context of mecamylamine administration. Although the effect of nicotine skin patches on craving was attenuated in the mecamylamine condition, there was a clear dose-related suppressive effect of transdermal nicotine on craving, with the 42-mg nicotine condition having a significantly greater effect than the 21-mg dose. This suggests that the nicotine patch administered in previous clinical trials of nicotine/mecamylamine combination treatment (Rose et al., 1994b, 1998) was likely providing some functional degree of nicotine replacement. The tolerability of high-dose nicotine in combination with mecamylamine was supported by the absence of any adverse reaction to the high nicotine dose among subjects in the mecamylamine condition. Thus, if nicotine/mecamylamine therapy were ultimately shown to be efficacious in smoking cessation treatment, investigation of the effects of higher doses of nicotine replacement (e.g., 42 mg/24 h) would be warranted.

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