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Mecamylamine acutely increases human intravenous nicotine self-administration

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Abstract

Previous studies of human cigarette smoking have shown that administration of the nicotinic acetylcholine receptor antagonist mecamylamine produces acute increases in smoking behavior. In contrast, studies of intravenous nicotine self-administration in animals typically show an immediate decrease in self-administration behavior following mecamylamine administration. To investigate whether this discrepancy might be due in part to the mode of nicotine self-administration (intravenous vs. cigarette smoke), we measured the rate of intravenous nicotine self-administration in tobacco-dependent human smokers. After being trained in a preliminary session to self-administer puff-sized bolus doses of nicotine, 16 subjects were exposed to two sessions (4 h duration) in which they could self-administer intravenous nicotine ad lib. Two hours prior to one session, subjects swallowed a capsule containing 10 mg mecamylamine, and before the other session they took a placebo capsule. Rates of responding for nicotine were assessed, as were subjective reports of withdrawal symptoms and plasma nicotine levels. There was a significantly higher rate of nicotine self-administration in the mecamylamine condition, and mecamylamine attenuated the reduction in craving over the session that occurred during nicotine self-administration. These results indicate that route of administration is not likely the major source of the discrepancy between findings from animal and human studies of nicotine administration. Instead, it is likely that the higher rates of nicotine self-administration induced by mecamylamine were due to an attenuation of the effects of nicotine (e.g., alleviation of withdrawal symptoms) in nicotine-dependent subjects. Thus, animal models of nicotine dependence may need to be employed in conjunction with self-administration procedures in order to duplicate the effects of mecamylamine observed in studies of human smokers.

Keywords: Nicotine; Self-administration; Dependence; Craving; Cigarette smoking

1. Introduction

The role of nicotine self-administration in tobacco dependence is well documented, and yet relatively few studies have explored the determinants of nicotine self-administration outside the context of cigarette smoking. A rodent model of nicotine self-administration was initially developed by Corrigall and Coen (1989), and there have been several studies exploring the effects of various drugs, including antagonists, on self-administration behavior. For example, the nicotinic acetylcholine receptor antagonist mecamylamine was shown to decrease lever pressing for intravenous nicotine (Corrigall and Coen, 1989; Donny et al., 1999), as was local injection of the nicotinic antagonist dihydro-β-erythroidine into the ventral tegmental area, a region that is believed to play a critical role in mediating reinforcement (Corrigall, 1995). Administration of mecamylamine has also been shown to diminish nicotine self-administration in monkeys (Goldberg et al., 1983).

In contrast, studies of human cigarette smoking have consistently shown that nicotinic blockade acutely increases cigarette smoking behavior (Nemeth-Coslett et al., 1986; Pomerleau et al., 1987; Rose et al., 1988; Stolerman et al., 1973). The apparent discrepancy between the immediate responses to nicotinic antagonist

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treatment of animals self-administering nicotine, and humans smoking cigarettes, suggests several possible explanations. The critical difference might be related to the obvious species differences, to differences between limited access schedules often used in animal models, as opposed to continuous access procedures employed in human smoking studies, or to differences in the cumulative doses of nicotine that are administered. Alternatively, an important factor may be the difference between cigarette smoking behavior, with its attendant stimulus cues and unique pharmacokinetics (pulmonary delivery) and intravenous nicotine self-administration.

To explore this issue, a laboratory model of intravenous nicotine self-administration in humans is needed. Henningfield et al. (1983) showed that under some conditions, human volunteers self-administered intravenous nicotine to a greater extent than saline, thus demonstrating the reinforcing effects of nicotine. However, in these investigations, the nicotine-dosing parameters employed were different from those in cigarette smoking: doses of 0.75–3.0 mg nicotine were administered as bolus injections in contrast to the puff-sized doses of approximately 0.1 mg of nicotine inhaled by cigarette smokers. Measurements of arterial nicotine concentrations during smoking and intravenous nicotine administration strongly suggest that the nicotine levels attained by rapid injection of 0.75–3.0 mg nicotine would far exceed the levels usually reached during smoking (Rose et al., 1999).

Recently, we have developed a laboratory paradigm for studying intravenous nicotine self-administration in human volunteers, using nicotine doses and rates of delivery similar to those obtained when smokers inhale each puff of cigarette smoke. Intravenous administration of puff-sized nicotine injections produces very similar peak arterial blood nicotine levels as does cigarette smoking, with an onset of 10–15 s after injection (Rose et al., 1999). In the present study, we sought to measure the effects of mecamylamine on intravenous self-administration in human cigarette smokers using this intravenous self-administration procedure. After an initial training session, ad lib self-administration was monitored in response to the administration of mecamylamine or placebo capsules. A dose of 10 mg mecamylamine hydrochloride was chosen inasmuch as previous studies have shown doses in the range of 5–20 mg acutely increase ad lib cigarette smoking (Rose et al., 1988). We hypothesized that mecamylamine administration would cause subjects to increase their self-administration of intravenous nicotine. However, it was a plausible alternative hypothesis that mecamylamine might acutely reduce or eliminate nicotine self-administration, as it has been shown to do in animal studies. In either case, studying the effects of mecamylamine on human intravenous nicotine self-administration might be a potentially useful method of studying smokers' dependency on the pharmacologic effects of nicotine, devoid of the usual sensorimotor cues accompanying cigarette smoking.

2. Methods

2.1. Subject recruitment

Sixteen healthy male and female smokers were recruited from the community by newspaper and radio advertisements and by word of mouth. Subjects were required to be 18–55 years of age, smoke at least 20 cigarettes per day, and be in good general health based on a physical examination, ECG, serum chemistries, CBC, and urinalysis. Exclusion criteria included the following: hypertension, hypotension, coronary artery disease, cardiac rhythm disorder, any other major medical condition, current psychiatric disorder other than nicotine dependence (DSM-IV criteria), pregnancy or nursing mothers, and current smokeless tobacco use. Subjects were paid US$20 per hour for participation in the laboratory sessions. The study was approved by the Duke University Medical Center Institutional Review Board and written informed consent was obtained from every subject prior to participation in the study.

2.2. Intravenous nicotine delivery

A solution of 0.05% nicotine base in saline was prepared by the Duke University Pharmacy Services. The solution was pH adjusted to 7.0 using acetic acid, sterilized by filtration and autoclaving, and finally tested for bacterial growth and pyrogens. The nicotine solution was diluted to a concentration based on each subject's per-puff nicotine dose when smoking ad lib. A syringe pump (Harvard Apparatus Model 22, Holliston, MA) was used to deliver nicotine infusions or pulsed 2-s injections.

The doses of nicotine administered in each pulsed intravenous injection were set equal to the per-puff nicotine dose each subject obtained from their usual brands of cigarettes. This dose was calculated by taking cigarette puffs from the same type of cigarettes using a syringe, with the same average puff volume and interpuff intervals that had been measured in an ad lib smoking baseline session. The smoke particulate matter was trapped in Cambridge filters (Federal Trade Commission, 1976), and after extraction with ethanol, a spectrophotometer was used to measure the absorbance of the solution at a wavelength of 400 nm, which is an accurate measure of "tar" concentration (Rose et al., 1987). Using published values for the nicotine/tar ratio for each brand of cigarette (Federal Trade Commission, 2000), the nicotine delivery per puff could then be estimated.

2.2.1. Procedure

Four sessions were held in the morning after overnight abstinence from smoking. Abstinence was assessed at the beginning of each session by expired CO sampling and subsequently confirmed by plasma nicotine assay. Saliva and blood samples were collected at 1-h intervals throughout the session; subjective measures of side effects were

Table 1
Subject characteristics

	Mean (S.D.)
$n = 16$	
Sex	7 males/9 females
Race	10 White/6 Black
Age (year)	37 (10.6)
No. of cigarettes per day	24.7 (6.4)
Years smoked	18.1 (9.5)
FTC nicotine (mg)	0.9 (0.3)
FTND score	4.2 (2.0)
Baseline CO (ppm)	28.6 (12.8)

collected every hour and subjective withdrawal symptoms were rated every 30 min.

2.2.1.1. Session 1. Subjects smoked their preferred brand of cigarette ad lib in order to assess per-puff nicotine dose. Using a smoking topography measurement device, puff volumes were recorded and the average per-puff nicotine dose was calculated by reproducing these puffing parameters in the laboratory with the same brand of cigarettes and by trapping the "tar" and nicotine in Cambridge filters for subsequent assay. To maintain the experimental environment between sessions, a saline intravenous catheter was introduced in this session.

2.2.1.2. Session 2. A pilot study suggested that participants required a training session before administering intravenous nicotine ad lib, as they needed to be instructed that it would be necessary to press the response manipulandum several times within a 10-min period in order to maintain their usual rate of nicotine intake. In this session, subjects were instructed to administer intravenous nicotine doses according to the same timing and number as they had taken puffs from cigarettes of their preferred brand during the first session (using an audible tone and visual cue to signal the time of each administration).

2.2.1.3. Sessions 3 and 4. In these last two sessions, subjects were allowed to self-administer intravenous nicotine ad lib, subject to a safety constraint that the maximum session dose not exceed twice that of the baseline session. An FR1 schedule of nicotine self-administration was used.

Approximately 2 h before their session, subjects swallowed a capsule containing either 10 mg mecamylamine hydrochloride or placebo (order counterbalanced across sessions). A member of the investigator's staff telephoned subjects to remind them to take the capsules.

2.2.1.4. Dependent measures. The main dependent measure was self-administration behavior, indexed by the number of intravenous nicotine infusions that the subjects received during the session (automatically counted by a computer program that operated the infusion pump). Salivary nicotine concentrations served as a secondary measure of nicotine intake: nicotine levels in saliva correlate highly with those in blood and are typically eight times higher (Rose et al., 1993). Plasma nicotine could not be utilized because there was only one intravenous catheter inserted into each subject, which was also used to administer nicotine. Due to insufficient sample volumes, a complete set of saliva nicotine assays for mecamylamine and placebo sessions was obtained for only 10 subjects, which limited the statistical power for this analysis. However, this provided confirmation of nicotine delivery. Gas chromatography was utilized to measure nicotine, following the methods of Jacob et al. (1981).

Subjects were also asked to rate their subjective mood and withdrawal symptoms every 30 min using a modified version of the Shiffman–Jarvik questionnaire (Shiffman and Jarvik, 1976), which assessed craving, negative affect, arousal, and appetite. In addition, a side effects questionnaire was administered hourly, which had subjects rate "pain" at the intravenous catheter site (nicotine is irritating, even at physiological pH), "comfort," and "exhilaration," the latter ratings designed to assess euphorigenic effects of nicotine. All items were rated using seven-point scales ranging from "not at all" to "extremely."

2.2.1.5. Statistical analysis. All statistical analyses were performed using Superanova and Statview (SAS Institute, Cary, NC). A multivariate approach to repeated measures analysis ANOVA was used, which appropriately took into account the correlation pattern among repeated measurements (Maxwell and Delaney, 1990). The number of nico-

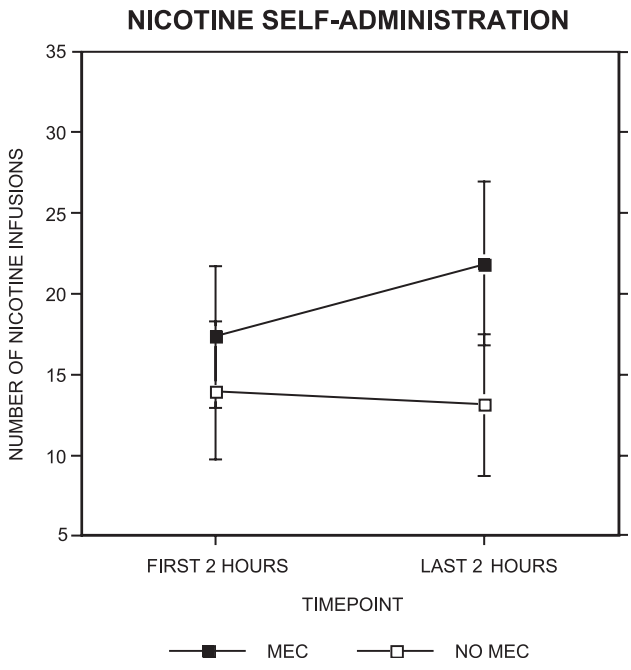

Fig. 1. Mean (± S.E.M.) number of nicotine doses self-administered during each 2-h portion of each session.

tine doses self-administered was tabulated for the first and second half of the session to detect possible temporal trends in the response to mecamylamine administration. Withdrawal symptoms and side effects ratings were also analyzed with time point as a factor. When significant interactions between mecamylamine condition and time were detected, an analysis of simple effects of mecamylamine at each time point was conducted (Keppel, 1982).

3. Results

3.1. Subject characteristics

Table 1 presents information on characteristics of the subject sample.

3.2. Compliance with overnight abstinence

Baseline expired air CO levels, averaged across all four sessions, were 11 ppm (S.D. = 3.6), and baseline plasma nicotine levels averaged 5 ng/ml (S.D. = 3.5), indicating overall compliance with the overnight smoking abstinence requirement. There were no systematic differences between conditions.

3.3. Smoke/nicotine intake during baseline session

During the baseline ad lib smoking session, subjects took, on average, 44 puffs (S.D. = 13.2) of smoke, with a mean puff volume of 45 ml (S.D. = 10.4). This cumulative smoke intake corresponded to a total nicotine dose (expressed as the base) of 4.7 mg (S.D. = 1.96). Plasma

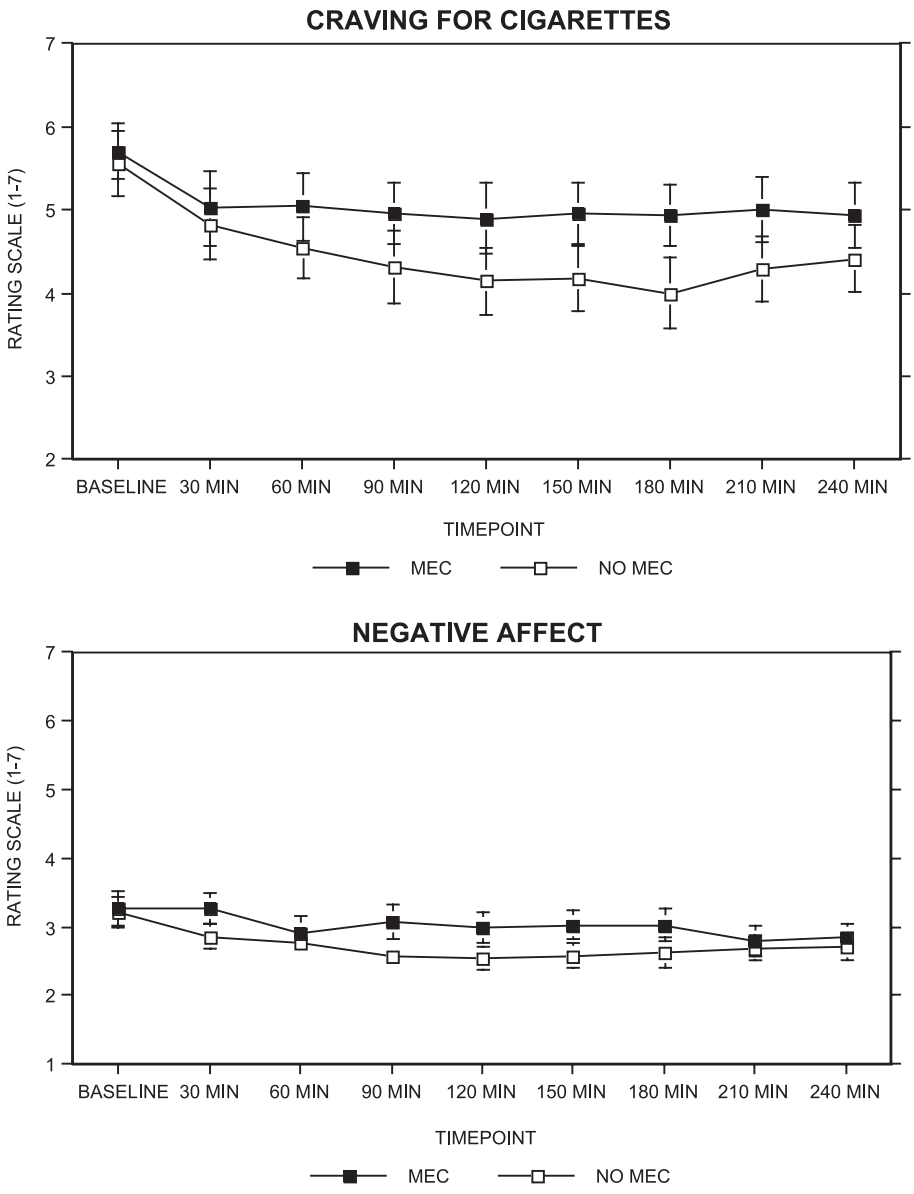

Fig. 2. Mean (± S.E.M.) ratings of craving and negative affect during each experimental session.

nicotine levels at the end of the session averaged 21 ng/ml (S.D. = 8.3). The mean nicotine dose per puff, which was equal to the per-infusion nicotine dose in subsequent sessions, was 0.1 mg (S.D. = 0.03, range 0.04–0.15).

3.4. Nicotine self-administration

In analyzing nicotine self-administration behavior, we attempted to minimize the confounding effects of pain at the intravenous site. Although pain ratings were low on average (mean = 2.0, S.D. = 0.86) and there were no systematic effects of mecamylamine, some subjects reported considerable pain during portions of the session (in one case, the maximum rating of 7 was given). Moreover, for some subjects, average pain ratings were higher in one of the nicotine self-administration sessions than in the other self-administration session. This between-session difference presented a potential confound in comparing nicotine self-administration between mecamylamine and placebo conditions. Indeed, we observed a significant correlation between the intensity of pain reports and the tendency to decrease the number of nicotine infusions self-administered during the latter half of each session [$F(1,14) = 6.26$, $r = -.6$, for the correlation between pain and the change in number of infusions taken between first 2 h and last 2 h, $P = .03$]. Therefore, we excluded the data from subjects for whom mean ratings of pain differed by more than one point between sessions (six subjects).

The subsequent analysis of the number of nicotine infusions self-administered in each 2-h portion of the sessions revealed a significant interaction of Mecamylamine × Time [$F(1,9) = 5.77$, $P = .04$]. Follow-up tests showed that the number of nicotine infusions self-administered in the last 2 h of the mecamylamine condition was significantly greater than in the placebo condition [$F(1,9) = 8.42$, $P = .02$]. Fig. 1 shows the mean number of infusions self-administered, broken down by the first and second half of the session. The dose of nicotine taken in during the entire session averaged 4.3 mg (S.D. = 3.17) in the mecamylamine session versus 3.4 mg (S.D. = 3.52) in the placebo session.

A similar Mecamylamine × Time interaction was seen for saliva nicotine concentrations, although the large number of missing data points due to insufficient volume limited the power of this test [$F(1,5) = 4.15$, $P = .1$]. However, for the samples assayed, nicotine levels were higher at the end of the session in the mecamylamine condition [258 ng/ml (S.D. = 239.3) vs. 149 ng/ml (S.D. = 260.3)], confirming that subjects self-administered a higher nicotine dose after mecamylamine administration than placebo.

3.5. Withdrawal symptoms

Ratings of craving for cigarettes showed a significant Mecamylamine × Time interaction [$F(4,56) = 2.89$, $P = .03$]. As shown in Fig. 2, craving declined to a greater extent over time in the placebo condition than in the mecamylamine condition. An analysis of simple effects showed that the differences were significant at 120, 150, 180, and 210 min.

Negative affect was also higher overall in the mecamylamine condition [$F(1,56) = 4.60$, $P = .05$].

3.6. Side effects

There was a significant effect of mecamylamine on ratings of exhilaration [$F(3,45) = 6.38$ for the Mecamylamine × Time interaction, $P = .02$], with ratings being significantly lower in the mecamylamine condition at 4 h [$F(1,15) = 6.36$, $P = .02$]. However, ratings were low in both conditions: the mean value was 1.2 (S.D. = 0.44) in the mecamylamine condition versus 1.4 (S.D. = 0.79) in the placebo condition at 4 h. No effects on other subjective measures were noted.

4. Discussion

The main finding of this study was that mecamylamine maintained a higher rate of intravenous nicotine self-administration relative to placebo. The number of nicotine doses self-administered and plasma nicotine levels at the end of the self-administration period were higher in the mecamylamine condition. The acute increase in nicotine self-administration we observed is consistent with the results of studies that have measured increases in cigarette smoking following mecamylamine administration but contrasts with the results from studies of animals trained to self-administer nicotine.

One potential explanation for the lack of increased responding in studies of animals self-administering intravenous nicotine is that the subjects may not have been dependent on nicotine. Without dependence, the nicotine deprivation state maintained by mecamylamine administration would not necessarily be expected to elicit more vigorous responding to obtain nicotine. Studies of nicotine self-administration in rats have often used schedules, whereby the daily dose of nicotine is relatively low. In contrast, other dosing procedures have been used to induce signs of dependence (Malin, 2001; Markou and Paterson, 2001). It would be interesting to measure self-administration behavior in response to mecamylamine in rats that have been exposed to a dosing regimen that produces dependence. Conversely, the hypothesis that dependence is critical for observing a rate-increasing effect of mecamylamine could be tested by studying nondependent human smokers (“chippers”) (Shiffman et al., 1990). These smokers should show less effect of mecamylamine because they are hypothesized to lack a drive state based on nicotine deprivation or withdrawal symptoms. We are aware of no studies that have compared chippers and dependent smokers in response to mecamylamine.

An alternative explanation of the difference between results of human and rat self-administration studies is that the high doses of mecamylamine used in rat studies may have produced a more complete blockade of the effects of nicotine, thereby hastening extinction of self-administration responding. Although human studies with smokers have shown a monotonic increase in compensatory smoking over the range of doses tested (Nemeth-Coslett et al., 1986; Rose et al., 1988), the maximal dose of mecamylamine (22.5 mg) used in previous laboratory studies of cigarette smoking may have produced incomplete blockade. Support for this interpretation was provided by the analysis of craving results from the present study. The effect of nicotine in relieving craving for cigarettes was significantly attenuated by mecamylamine (Fig. 2), but craving nonetheless declined across the session, which may have been due to the partial blockade of the effects of nicotine. These results are consistent with our previous findings from a study that administered to smokers combinations of different doses of nicotine patch and mecamylamine: mecamylamine attenuated but did not completely block the effects of nicotine on craving (Rose et al., 2001). Again, however, this result may be dependent on the dose of mecamylamine used. Mecamylamine is thought to block nicotine effects through a noncompetitive action entailing occlusion of the ion channel portion of the receptor rather than competing with nicotine for binding to the recognition sites of the receptors (Martin et al., 1989). Therefore, a sufficiently high dose of mecamylamine might not be overcome by increasing the dose of nicotine self-administered and hence might produce a more immediate decrease in self-administration behavior. If smaller doses were to be used in animal studies, then it is conceivable that partial blockade may lead to increased nicotine self-administration, even in the absence of dependence, reflecting an attempt to compensate for the reduced positive effects of nicotine.

It is interesting that while mecamylamine attenuated the effect of nicotine on craving, it did not appear to increase craving for cigarettes above the baseline level associated with overnight cigarette deprivation. This finding is in agreement with the results from previous studies reporting that mecamylamine does not induce more intense withdrawal symptoms than those produced by overnight cigarette deprivation (Eissenberg et al., 1996; Rose et al., 2001). Thus, it appeared that mecamylamine interacted with nicotine to prevent the relief of withdrawal symptoms, thereby maintaining higher rates of nicotine self-administration, particularly later in the session.

The acute effects of mecamylamine observed in this study, as well as studies of acute effects on smoking behavior, should not be taken to infer that chronic mecamylamine administration would produce long-term compensatory increases in smoking. Quite to the contrary, it would make sense that after time, smoking behavior (or nicotine self-administration) should decline due to the reduction in reinforcing potency of nicotine in the presence of mecamylamine. This prediction was borne out in a study we conducted in which smokers received 4 weeks of treatment with oral mecamylamine (5–10 mg/day). After a slight initial increase in smoking behavior during the first 2 days (relative to placebo treatment), rates of smoking gradually declined over 4 weeks (Rose et al., 1998).

One limitation of the current study is that the procedure did not provide access to a second response manipulandum that would have administered intravenous saline. Such a control condition would have helped evaluate the specificity of the reinforcing effect of nicotine and would also have helped rule out direct effects of mecamylamine that could have affected response rates (e.g., sedation). In another work, we have found that subjects infrequently self-administer saline infusions (Rose, 2003); thus, the self-administration behavior in the present study was likely controlled by the reinforcing effects of nicotine, as opposed to being controlled by the instructional set to which subjects were exposed. This conclusion is also supported indirectly by the finding that the rate of self-administration was sensitive to mecamylamine. Moreover, Newhouse et al. (1994) reported only minimal cognitive/behavioral effects of 10 mg mecamylamine in young, normal, healthy volunteers. However, we cannot completely rule out the influence of direct effects of mecamylamine in this study.

In summary, the present results demonstrate that intravenous nicotine self-administration in humans shows the same response to mecamylamine administration as does cigarette smoking behavior. This finding shows that the unique sensory cues accompanying smoking behavior are not essential for compensation to occur. Moreover, the results suggest that the discrepancy between animal and human studies of nicotine self-administration is not likely due to the difference between smoking and intravenous self-administration, but rather to species differences, differences in levels of dependence, or differences in the extent of nicotinic blockade achieved with the dose of antagonist employed.

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