Pharmacology Biochemistry and Behavior, Vol. 66, No. 3, pp. 637–643, 2000

0091-3057/00/$–see front matter

PII S0091-3057(00)00252-5

Mecamylamine Blockade of Both Positive and Negative Effects of IV Nicotine in Human Volunteers

LESLIE H. LUNDAHL,* JACK E. HENNINGFIELD† AND SCOTT E. LUKAS*

*Behavioral Psychopharmacology Research Laboratory, McLean Hospital/Harvard Medical School, East House III, 115 Mill Street, Belmont, MA 02478; and
†Pinney Associates, 4800 Montgomery Lane, Suite 1000, Bethesda, MD 20814

Received 11 June 1999; Revised 6 January 2000; Accepted 18 January 2000

LUNDAHL, L. H., J. E. HENNINGFIELD, AND S. E. LUKAS, *Mecamylamine blockade of both positive and negative effects of IV nicotine in human volunteers*. PHARMACOL BIOCHEM BEHAV **66**(3) 637–643, 2000.—The ganglionic blocker mecamylamine blocks the positive reinforcing effects of IV nicotine, but has been shown to increase cigarette smoking behavior under some conditions. The effects of mecamylamine on subjective and physiologic responses to IV nicotine were evaluated in seven healthy male volunteer cigarette smokers who provided informed consent and resided on a clinical pharmacology research unit. On four separate days, each subject was given a different oral dose of mecamylamine (placebo, 5, 10, or 20 mg). One hour later subjects received the first of four doses of IV nicotine (placebo, 0.75, 1.5, and 3.0 mg); the remaining injections were given at 1-h intervals. Both the positive effects following 0.75 mg and negative effects following 3.0 mg of nicotine were significantly reversed by mecamylamine. Thus, the mecamylamine-induced increase in smoking may be due both to competitive blockade of nicotinic receptors and nicotine's reversal of aversive effects. © 2000 Elsevier Science Inc.

Nicotine Mecamylamine Craving Tobacco Human subjects

THE nondepolarizing ganglionic receptor blocker mecamylamine has been shown to block a number of physiological, behavioral, and subjective effects of nicotine in humans and animals (5,6,14–16,23). For example, mecamylamine reverses nicotine-induced increases in heart rate and blood pressure (7,17), as well as nicotine-induced decreases in skin temperature (7). In terms of subjective effects, mecamylamine reverses nicotine-induced increases in reports of drug liking and estimates of dose strength, and decreases the positively reinforcing aspects of nicotine as well, including smoking satisfaction and liking (17).

Other studies have demonstrated that mecamylamine can influence smoking behavior. As expected of a receptor antagonist, oral doses of mecamylamine increased cigarette smoking behavior in a controlled laboratory environment (12,15,24) and in a treatment setting (18). Although some measures of puff topography differed in these studies, it was clear that subjects compensated for the lack of nicotine effects by attempting to extract more nicotine from the cigarettes. Using a discrimination paradigm, Rose et al. (16) demonstrated that acute doses of mecamylamine increased the preference for nicotine and decreased nicotine discrimination.

The above studies involved self-administration of nicotine via tobacco smoking. As many factors play a role in the amount of nicotine that is absorbed via this route, it is possible that mecamylamine may be altering factors other than by blocking nicotinic receptors (e.g., puff depth, number of puffs, interpuff interval). A recent study by Rose et al. (19) demonstrated that a peripheral nicotinic receptor antagonist, trimethaphan, may alter smoking satisfaction by affecting airway sensations associated with the nicotine in tobacco. In this regard, IV nicotine challenge studies can provide an insight into the possible mechanism of actions of potentially new therapies for smoking (8). Nevertheless, one caveat of such studies is the fact that the reinforcing effects of a drug that is self-administered are usually more pronounced than when the drug is administered by the investigator (2).

Requests for reprints should be addressed to Scott E. Lukas, Ph.D., Associate Professor of Psychiatry (Pharmacology), Director, Behavioral Psychopharmacology Research Laboratory, McLean Hospital/Harvard Medical School, East House III, 115 Mill Street, Belmont, MA 02478.

Prior studies have focused on the impact of mecamylamine on the positive effects of nicotine that contribute to nicotine self-administration. However, the ability of mecamylamine to alter negative effects of IV nicotine has not been studied, and could have an impact on smoking behavior, particularly as mecamylamine is currently being used as an adjunct in the treatment of tobacco dependence (18,20,21). The present study was conducted to evaluate the effects of three doses of mecamylamine on the subjective and physiologic responses to three doses of IV nicotine with the aim of determining the full spectrum of mecamylamine's effects on nicotine-induced behavior.

METHOD

Subjects

Subjects were seven (four Caucasians, three African Americans) healthy male volunteer cigarette smokers (35 ± 9.67 years of age; body mass index = 23.2 ± 2.9 kg/m^2), who provided informed consent and resided on a clinical pharmacology research unit for a 4-week period. After extensive telephone and in-person screening, potential subjects underwent physical and psychological evaluations. All subjects were free of Axis I diagnoses, and were medically cleared.

Subjects reported smoking an average of 33 cigarettes (±19.87) per day, and smoked daily for 19.60 years (±10.92). Additionally, subjects reported using a variety of illicit drugs (heroin, alcohol, and marihuana) on a regular basis. Potential subjects who met criteria for current drug or alcohol dependence were excluded from the study.

Experimental Design and Data Analysis

The overall goal of the study was to evaluate the effects of three doses of mecamylamine on three doses of nicotine. Because of the complexity of the study design, all of the IV nicotine doses were administered in 1 day following a single dose of mecamylamine. This procedure is valid as long as IV nicotine has a short duration of action and mecamylamine has a relatively long duration of action (25). To verify these two assumptions, a pilot study was conducted using two of the subjects who received a 10-mg dose of mecamylamine followed by four IV injections of 1.5 mg nicotine spaced at 1-h intervals. Return to baseline before each nicotine injection with simultaneous blockade of nicotine effects for 4 consecutive hours would support the validity of the proposed nicotine/mecamylamine dosing procedure.

The main study involved testing each subject individually during a 4-h session at each mecamylamine dose (four sessions). Each session was separated by at least 3 days (range 3–14 days). Both mecamylamiine and nicotine dose orders were randomly assigned. However, for safety reasons, subjects never received the highest nicotine dose (3.0 mg) first.

Subjects were compared at baseline to determine whether or not they differed on physiologic and subjective responses prior to pretreatment and drug administration. Although the study is a repeated measures design, several factors precluded the use of ANOVA in the data analyses. Specifically, due to the small number of subjects, lack of between-subject factors, and the fact that subjects differed significantly at baseline on subjective measures, paired comparisons of change from baseline scores were used to investigate differences among within-subject drug doses. All analyses were conducted using SPSS (22) software programs, and all effects were tested at the $p < 0.05$ level of significance.

Procedure

Subjects abstained from caffeine for 12 h prior to each test session, and were not allowed to eat food or smoke tobacco cigarettes for 1 h before the test session began. Prior to receiving the pretreatment (mecamylamine or placebo), subjects completed the short form of the Addiction Research Center Inventory (11) and vital signs were measured. Mecamylamine was administered orally, and vital signs and questionnaire data were collected 45 min later. The first nicotine or placebo injection was given at 60 min after the pretreatment. The remaining injections followed at 1-h intervals.

During each 4 h session, subjects were seated in a chair and were asked to keep their eyes closed. Nicotine or placebo injections were administered by a physician who was blind to the dose conditions. Subjects manipulated a joystick device with their free hand to report detection of nicotine effects; data were recorded on a polygraph. Subjective drug responses were collected at 10 and 45 min postinjection, and physiologic data were recorded at 10 and 40 min postinjection. Staff observations were made for 10 min preceding, during, and 30 min after each injection. All data were collected by research-trained nurses.

Drug Preparation and Administration

Mecamylamine hydrochloride tablets, in doses of 5, 10, and 20 mg, were placed inside gelatin capsules with lactose filler to maintain the blind. Placebo capsules contained just the lactose filler. Nicotine hydrogen tartrate was mixed with bacteriostatic saline to provide unit doses of 0.0 (placebo), 0.75, 1.5, and 3.0 mg (expressed as the nicotine free base). The volume of the injections was 1.0 ml, and injections were delivered via an intravenous catheter placed in a forearm vein at a rate of 1 ml/10 s. A 2-ml saline flush followed to ensure complete administration of the drug. All pretreatments and IV injections were administered under double-blind conditions.

Subjective Dependent Variables

Subjective responses to IV nicotine and oral mecamylamine were evaluated using standardized questionnaires. Measures included various scales of the Addiction Research Center Inventory (ARCI) including the morphine benzedrine group (MBG) scale, which measures euphoria, the lysergic acid diethylamide (LSD) scale, a measure of dysphoria, and the pentobarbital, chlorpromazine, alcohol group (PCAG) scale, which measures sedation. The Addiction Research Center Single Dose Questionnaire (SDQ) also was administered, and includes items assessing the effects of drugs of abuse, including drug liking, perceived drug effects, reports of dose strength, and craving for tobacco and cigarettes. Subjects also were asked to rate the equivalence of the IV drug to cigarettes. Trained nurses rated the extent to which subjects appeared to like the drug (i.e., "observed liking") and recorded subjects' behavior before, during, and after IV nicotine administration.

Physiologic Dependent Variables

Both heart rate and blood pressure were collected manually at baseline and again at 5 min before and at 10 and 40 min after each nicotine injection.

RESULTS

Study I. Mecamylamine Time Course

Paired comparisons indicated that the oral doses of mecamylamine blocked all of the effects of IV nicotine for at least 4 h, confirming its relatively long duration of action (25), and support the use of a multidose experimental design to study various doses of nicotine within a single session. Two representative measures ("drug detection" and "nicotine effects") are shown in Fig. 1.

Study II. Mecamylamine Alteration of Nicotine Effects

Effects of mecamylamine alone. Subjective responses: comparisons of placebo and active doses of mecamylamine during the placebo nicotine condition indicated that mecamylamine did not have any subjective effects of its own. There were no significant differences between placebo and active doses of mecamylamine on any measure of subjective mood state (data not shown).

Physiological responses: paired comparisons indicated that there were no significant mecamylamine effects on heart rate, diastolic, or systolic blood pressure. Table 1 provides data on the effects of mecamylamine alone on heart rate, systolic, and diastolic blood pressure. As none of the subjects had hypertension, the effects of mecamylamine on resting physiologic measures were negligible.

Effects of nicotine alone. Subjective responses: Fig. 2 shows the effects of mecamylamine on nicotine-induced changes on the MBG and LSD scales of the ARCI. Paired comparisons indicated that there was a significant biphasic effect of nicotine on MBG scores with significantly lower change scores following the 3.0-mg dose than at the 0.75-mg dose, $t(6) = 3.46$, $p = 0.013$. This finding indicates that acute administration of 3.0 mg nicotine was not euphorigenic in this population, and likely induced some dysphoria, as evidenced by the increase in the LSD Scale (Fig. 2, right panel). Dose-related responses to nicotine also were observed on drug liking scores (Fig. 3, left panel), with significantly lower liking scores after 3.0 mg nicotine than at both placebo nicotine, $t(6) = 2.49$, $p < 0.02$, and 0.75 mg nicotine, $t(6) = 2.24$, $p < 0.07$. Subjective reports of tobacco craving were reduced in a dose-related manner with significantly lower levels of craving following 3.0 mg nicotine compared to placebo, $t(6) = 3.24$, $p < 0.02$, and 0.75 mg nicotine, $t(6) = 3.87$, $p < 0.01$. Finally, Fig. 4 depicts the finding that subjective reports of cigarette craving were significantly lower following 3.0 mg nicotine compared to placebo, $t(6) = 3.17$, $p < 0.02$.

Physiological responses: Paired comparisons indicated that there were no significant changes in heart rate (Fig. 4, right panel), systolic, or diastolic blood pressure at 10 min postadministration of the nicotine doses (data not shown).

Effects of mecamylamine/nicotine combinations. Subjective responses: paired comparisons were used to determine whether or not different doses of mecamylamine exerted differential effects on nicotine-induced subjective responses. Results of these analyses indicated that mecamylamine attenuated the dose-related increases in both the MBG scale (euphoria) (Fig.

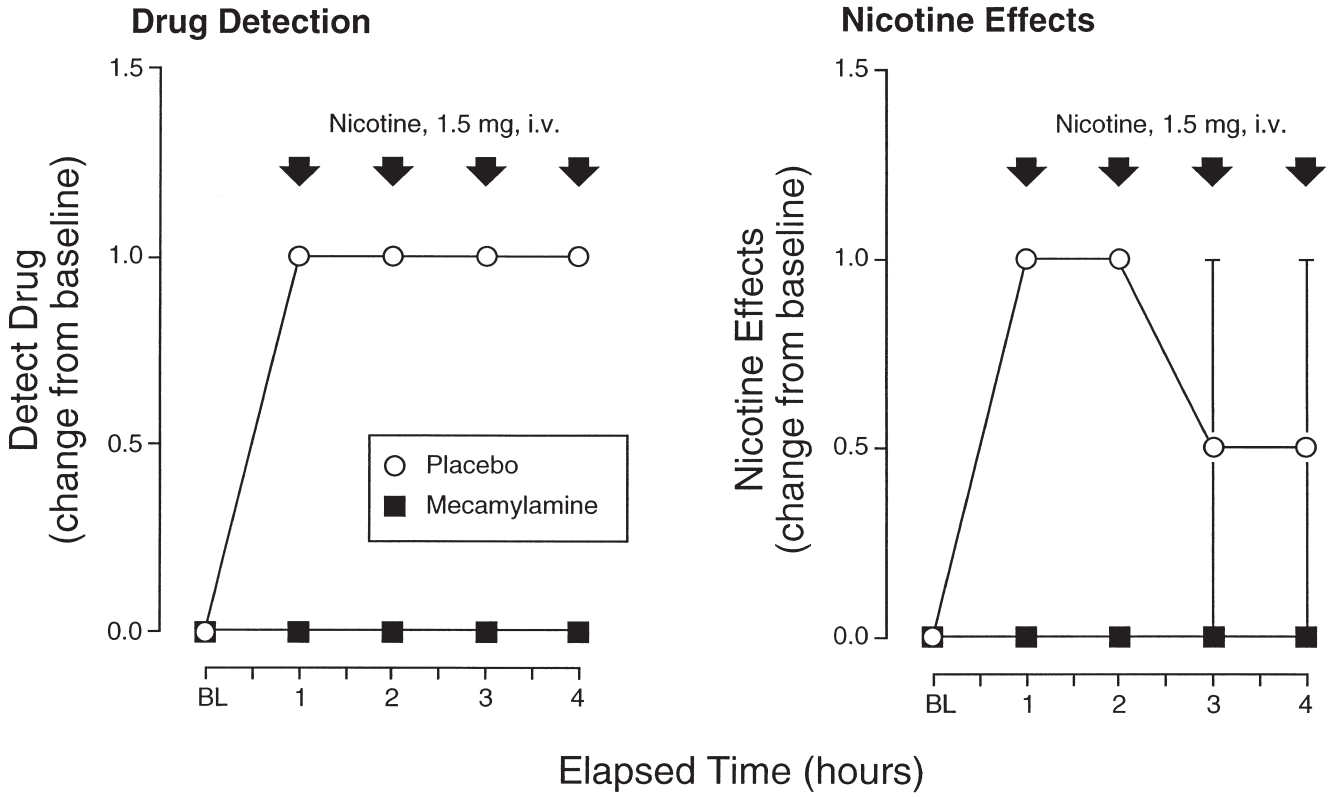

FIG. 1. Demonstration of mecamylamine's long duration of effects. Left panel: 10 mg mecamylamine completely blocked the "drug detection." Right panel: 10 mg mecamylamine completely blocked "nicotine effects" after 4 consecutive IV doses of nicotine. Data are mean ± SEM of two subjects who participated in this preliminary study.

TABLE 1
PHYSIOLOGIC MEASURES BEFORE AND AFTER MECAMYLAMINE PRETREATMENT

	Mecamylamine Pretreatment		
Mecamylamine Dose	Premean (SD)	Postmean (SD)	*p*
Heart Rate			
Placebo	73.67 (9.50)	84.00 (10.04)	0.016*
5 mg	81.33 (4.84)	85.00 (6.90)	0.280
10 mg	83.33 (3.27)	84.33 (5.13)	0.733
20 mg	75.67 (7.63)	82.67 (9.00)	0.189
Systolic blood pressure			
Placebo	118.33 (8.34)	114.33 (8.14)	0.400
5 mg	124.00 (4.90)	117.33 (13.00)	0.233
10 mg	124.33 (11.48)	101.00 (40.18)	0.225
20 mg	121.67 (9.75)	119.67 (7.53)	0.624
Diastolic blood pressure			
Placebo	79.33 (3.17)	72.00 (7.90)	0.123
5 mg	81.00 (7.87)	80.00 (7.38)	0.723
10 mg	80.67 (9.18)	75.00 (10.33)	0.330
20 mg	78.00 (8.67)	76.33 (9.33)	0.633

*Significant difference

2, left panel) and drug liking (Fig. 3, left panel), and tempered the dose-related decrease in cigarette craving (Fig. 4, left panel). Mecamylamine did not appear to have any significant effects on the observed response to nicotine effects (Fig. 3, right panel).

With respect to changes in MBG scores, 5 mg of mecamylamine attenuated the reported euphoria, which was evident at both the 0.75 mg, $t(6) = 2.50$, $p < 0.05$ and the 1.5 mg, $t(6) = 2.50$, $p < 0.05$, nicotine doses, and also blocked the 3.0-mg dose-induced reduction in MBG scores, $t(6) = -2.49$, $p <$

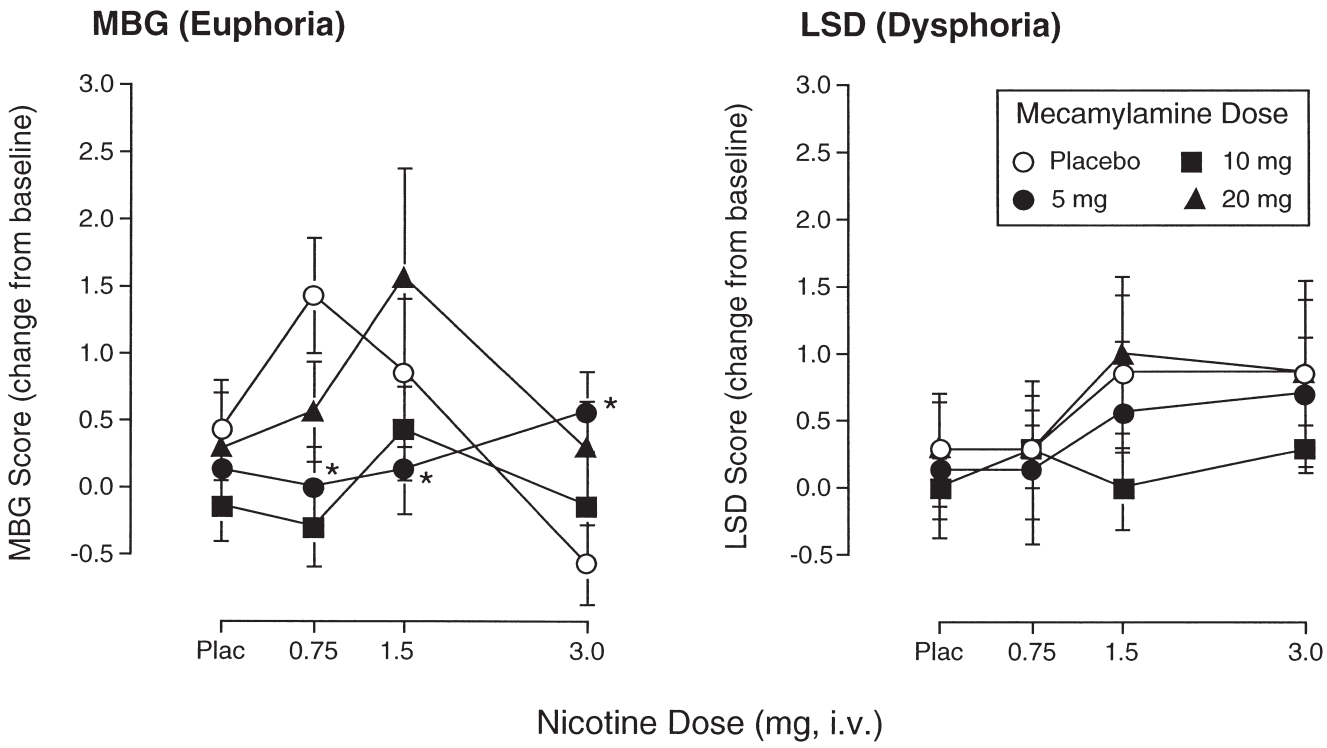

FIG. 2. Mecamylamine effects on IV nicotine-induced changes on MBG (morphine benzedrine group; Left panel) and LSD (lysergic acid diethylamide; right panel) Scales of the ARCI. Data are mean ± SEM of seven subjects. *Denotes significant differences from placebo mecamylamine.

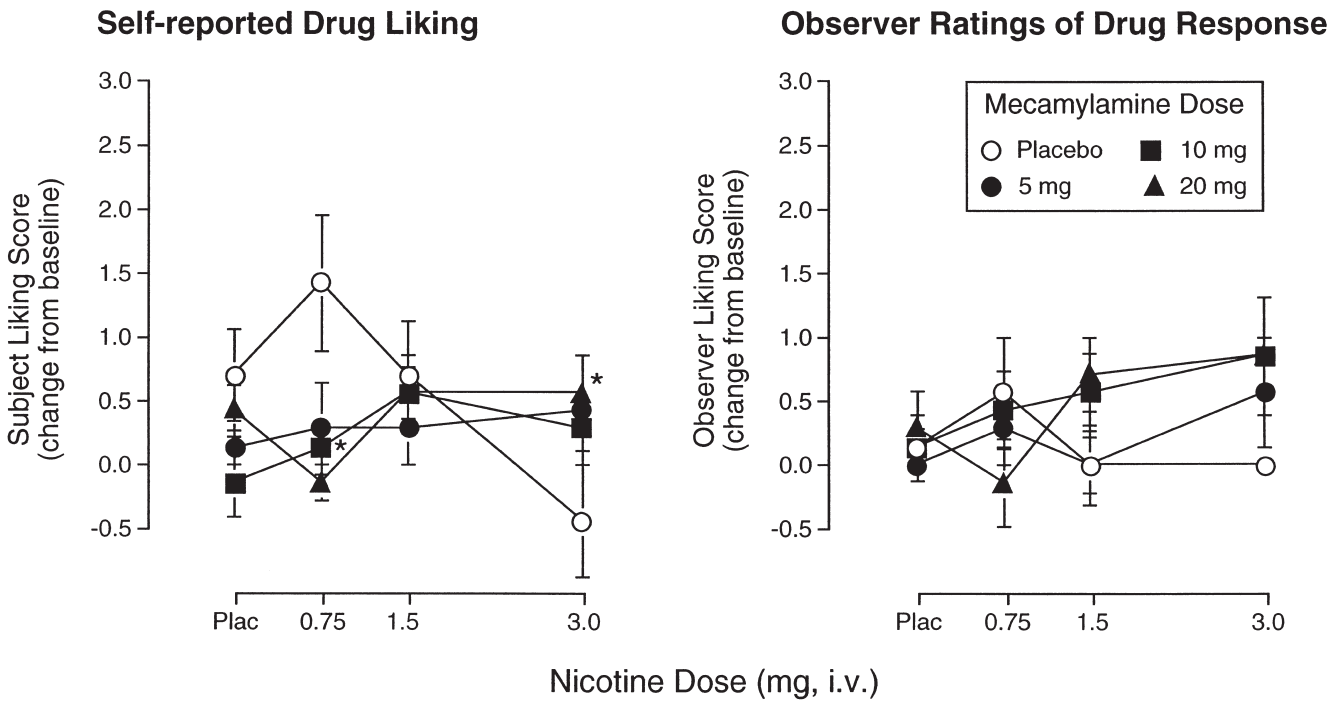

FIG. 3. Mecamylamine effects on IV nicotine-induced changes in "drug liking" (left panel) and "observed response" of nicotine effects. Data are mean ± SEM of seven subjects. *Denotes significant differences from placebo mecamylamine.

0.05 (Fig. 2, left panel). Neither 10 nor 20 mg mecamylamine significantly altered the change scores on the MBG Scale of the ARCI at any nicotine dose.

All doses of mecamylamine attenuated the "drug liking" reported after the 0.75 mg dose of nicotine, although only the 10-mg mecamylamine dose produced a statistically significant decrease on this measure, $t(6) = 2.71$, $p < 0.04$ (Fig. 3, left panel). Similarly, the 20-mg dose of mecamylamine significantly reversed the nicotine-induced reduction in liking scores observed after the 3.0 mg nicotine, $t(6) = -2.29$, $p < 0.06$. These results indicate that mecamylamine not only reduced "liking" of the lower doses of nicotine, but also made the negative effects of the 3.0-mg nicotine dose more tolerable.

Although 5- and 10-mg doses of mecamylamine reversed the significant 3.0-mg nicotine-induced decrease in tobacco craving, only the 20-mg dose of mecamylamine significantly increased tobacco craving, $t(6) = -2.83$, $p < 0.03$. Conversely, the 3.0-mg nicotine-induced reduction in cigarette craving was significantly reversed by all three mecamylamine doses (5, 10, and 20 mg) following the 3.0 nicotine dose, $t(6) = -3.06$, $p < 0.03$; $t(6) = -2.52$, $p < 0.05$; $t(6) = -2.29$, $p < 0.06$, respectively (Fig 4, left panel).

Physiological responses: paired comparisons were used to determine whether or not different doses of mecamylamine exerted differential effects on nicotine-induced physiological effects. Results of these comparisons indicated that the 10 mg mecamylamine pretreatment significantly decreased the heart rate effects of 3.0 mg nicotine, $t(5) = 3.73$, $p < 0.02$ (Fig. 4, right panel). This dose of mecamylamiine also attenuated the heart rate increases observed after the 0.75-mg nicotine dose, $t(6) = -3.50$, $p < 0.02$. Finally, 20 mg mecamylamine significantly decreased systolic blood pressure compared to placebo mecamylamine, $t(6) = -3.84$, $p < 0.02$, 5.0 mg mecamylamine, $t(5) = -2.61$, $p < 0.05$, and 10.0 mg mecamylamine, $t(5) = -2.41$, $p < 0.06$, following 3.0 mg nicotine (data not shown).

DISCUSSION

The present study was designed to document the profile of subjective and physiologic effects of IV nicotine in human volunteers, and to investigate the effects of the ganglionic receptor blocker, mecamylamine, on nicotine-induced subjective and physiologic effects.

The dose-related changes in positive mood state subsequent to IV nicotine administration are consistent with the study by Henningfield and Goldberg (9), which demonstrated that nicotine is self-administered by human tobacco smokers, presumably as a result of its positive mood effects. In the present study, only the lowest nicotine dose (0.75 mg) resulted in significant increases in euphoria, as indicated by increased MBG scores, and the highest dose (3.0 mg) suppressed MBG scale scores below baseline levels. This finding supports a prior report that high doses of nicotine are avoided due to their noxious effects (9), and suggests that nicotine has a biphasic effect on mood state not unlike many other psychoactive drugs (4).

Although physiologic effects of IV nicotine are well documented (6), robust changes in heart rate were not observed after any dose in the present study. This discrepancy may be because physiologic measures were obtained at least 10 min postinjection, and IV nicotine metabolism is rather fast in humans (10); as such, the effects of nicotine are very short-lived (5). There are two additional reasons for the less robust effect of nicotine in the present study. First, the subjects in this

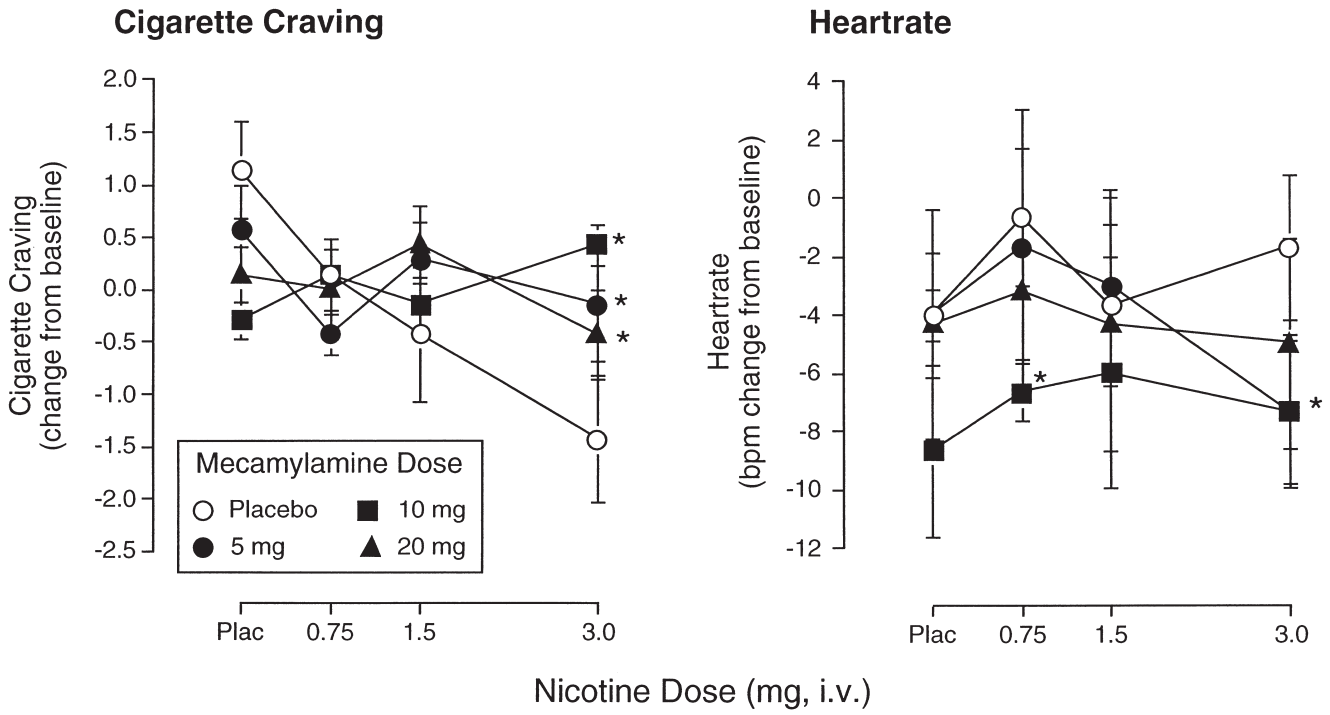

FIG. 4. Mecamylamine effects on IV nicotine-induced changes in "cigarette craving" (left panel) and heart rate (right panel). Data are mean ± SEM of seven subjects except for heart rate (right panel), where data are mean ± SEM of six subjects. *Denotes significant differences from placebo mecamylamine.

study had extensive drug use histories in addition to their tobacco smoking. Thus, their tolerance to nicotine, as well as other drugs, may have blunted their responses to IV nicotine. Second, the fact that the nicotine was administered by a physician and was not self-administered by the subject, may also have contributed to the attenuated responses, as suggested by the preclinical data (2).

By itself, the blockade of nicotine-induced euphoria (not unlike naltrexone blockade of heroin's effects) by mecamylamine may have an immediate implication for the development of a novel strategy to treat nicotine dependence. However, acute treatment with mecamylamine results in a transient increase in self-administration (12,15,24) that has been attributed to an attempt to overcome the blockade of nicotine's positive effects. The increased smoking was reflected in an elevation of plasma nicotine levels in smokers who had been treated with mecamylamine (15). The plasma nicotine levels were so high that subjects should have experienced nausea—yet they did not, presumably because the mecamylamine also blocked the negative effects of nicotine, as was demonstrated in the present study.

Although not measured in the present study, plasma nicotine levels were most likely similar to those in prior studies using comparable doses and procedures (3,8). As plasma nicotine levels after IV nicotine are similar to the levels achieved after smoking usual cigarettes [i.e., 24–26 ng/ml; (1,13)], the results of the present study are likely generalizable to smoking studies.

For individuals who have successfully completed treatment and are highly motivated to remain abstinent, mecamylamine may be used as an adjunct to relapse prevention especially when combined with a nicotine transdermal patch (20,21). As mecamylamine attenuated nicotine-induced measures of euphoria, it would likely block the reinforcing effects of nicotine and decrease the incidence of relapse should the treated individual experience a "slip," and smoke a cigarette while on mecamylamine. However, the complex action of mecamylamine is evident in a recent study in which prequit date mecamylamine treatment prolonged the duration of continuous abstinence of a combined mecamylamine/nicotine patch treatment (18).

Finally, although positively reinforcing effects are generally a primary variable of focus in abuse liability studies because this characteristic is predictive of abuse potential, behavior can be controlled by both positively and negatively reinforcing effects. In fact, within the smoking of a single cigarette, the decision to initiate smoking behavior might be controlled by the negatively reinforcing effects of nicotine for the nicotine-deprived cigarette smoker, whereas the cigarette might be extinguished before the cigarette has been depleted of its nicotine reservoir either because the smoker has become sated or perhaps is beginning to experience adverse effects of cumulated nicotine. Mecamylamine administration could thus acutely increase cigarette smoking by reducing the positive or negative effects of nicotine or both. Results of the present study not only have an impact on the search for new and more effective treatments of tobacco dependence, but provide another perspective on the manner by which current pharmacological treatments are working and may be better implemented.

ACKNOWLEDGEMENTS

The authors thank the support staff of the NIDA Addiction Research Center Treatment Research Unit, Baltimore, MD. Portions of this study were previously reported at the Annual CPDD Meeting (June, 1996, San Juan, Puerto Rico). This work was supported by Grants DA 03994 and DA 00343 from the National Institute on Drug Abuse.

REFERENCES

1. Benowitz, N. L.; Jacobs, P., III.: Nicotine and carbon monoxide intake from high- and low-yield cigarettes. Clin. Pharmacol. Ther. 36:265–270; 1984.
2. Dworkin, S. I.; Mirkis, S.; Smith, J. E.: Response-dependent versus response-independent presentation of cocaine: Differences in the lethal effects of the drug. Psychopharmacology (Berlin) 117:262–266; 1995.
3. Gourlay, S. G.; Benowitz, N. L.: Arteriovenous differences in plasma concentrations of nicotine and catecholamines and related cardiovascular effects after smoking, nicotine nasal spray, and intravenous nicotine. Clin. Pharmacol. Ther. 62:453–463; 1997.
4. Griffiths, R. R.; Bigelow, G. E.; Henningfield, J. E.: Similarities in animal and human drug-taking behavior. In: Mello, N. K., ed. Advances in substance abuse, vol. 1. Greenwich, CT: JAI Press, Inc.; 1980.
5. Henningfield, J. E.; Miyasato, K.; Jasinski, D. R.: Cigarette smokers self-administer intravenous nicotine. Pharmacol. Biochem. Behav. 19:887–890; 1983.
6. Henningfield, J. E.; Miyasato, K.; Johnson, R. E.; Jasinski, D. R.: Rapid physiologic effects of nicotine in humans and selective blockade of behavioral effects by mecamylamine. In: Harris, L. S., ed. Problems of drug dependence, 1982. NIDA research monogr. No. 43. Washington, DC: Government Printing Office; 1983:259–265.
7. Henningfield, J. E.; Goldberg, S. R.: Nicotine as a reinforcer in human subjects and laboratory animals. Pharmacol. Biochem. Behav. 19:989–992; 1983.
8. Henningfield, J. E.; Katsumasa, M.; Jasinski, D. R.: Abuse liability and pharmacodynamic characteristics of intravenous and inhaled cocaine. J. Pharmacol. Exp. Ther. 24:1–12; 1985.
9. Henningfield, J. E.; Goldberg, S. R.: Control of behavior by intravenous nicotine injections in human subjects. Pharmacol. Biochem. Behav. 19:1021–1026; 1983.
10. Jacob, P.; Benowitz, N. L.; Shulgin, A. T.: Recent studies of nicotine metabolism in humans. Pharmacol. Biochem. Behav. 30:249–253; 1988.
11. Martin, W. R.; Sloan, J. W.; Sapira, J. D.; Jasinski, D. R.: Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. Clin. Pharmacol. Ther. 12:245–258; 1971.
12. Nemeth-Coslett, R.; Henningfield, J. E.; O'Keefe, M. K.; Griffiths, R.: Effects of mecamylamine on human cigarette consumption. Psychopharmacology (Berlin) 88:420–425; 1986.
13. Perkins, K. A.; Sexton, J. A.; Reynold, W. A.; Grobe, J. E.; Fonte, C.; Stiller, R. L.: Comparison of acute subjective and heart rate effects of nicotine intake via tobacco smoking versus nasal spray. Pharmacol. Biochem. Behav. 47:295–299; 1994.
14. Pickworth, W. B.; Herning, R. I.; Henningfield, J. E.: Mecamylamine reduces some EEG effects of nicotine chewing gum in humans. Pharmacol. Biochem. Behav. 30:149–153; 1988.
15. Pomerleau, C. S.; Pomerleau, O. F.; Majchrzak, M. J.: Mecamylamine pretreatment increases subsequent nicotine self-administration as indicated by changes in plasma nicotine level. Psychopharmacology (Berlin) 91:391–393; 1987.
16. Rose, J. E.; Sampson, A.; Levin, E. D.; Henningfield, J. E.: Mecamylamine increases nicotine preference and attenuates nicotine discrimination. Pharmacol. Biochem. Behav. 32:933–938; 1989.
17. Rose, J. E.; Levin, E. D.; Behm, F. M.; Westman, E. C.; Stein, R. M.; Lane J. D.; Ripka, G. V.: Combined administration of agonist-antagonist as a method of regulating receptor activation. Ann. NY Acad. Sci. 757:218–221; 1995.
18. Rose, J. E.; Westman, E. C.; Behm, F. M.: Nicotine-mecamylamine treatment for smoking cessation: The role of pre-cessation therapy. Exp. Clin. Psychopharmacol. 6:331–343; 1998.
19. Rose, J. E.; Westman, E. C.; Behm, F. M.; Johnson, M. P.; Goldberg, J. S.: Blockade of smoking satisfaction using the peripheral nicotinic antagonist trimethaphan. Pharmacol. Biochem. Behav. 62:165–172; 1999.
20. Rose, J. E.; Behm, F. M.; Westman, E. C.; Levin, E. D.; Stein, R. M.; Ripka, G. V.: Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone. Clin. Pharmacol. Ther. 56:86–99; 1994.
21. Rose, J. E.; Behm, F. M.; Westman, E. C.; Levin, E. D.; Stein, R. M.; Lane, J. D.; Ripka, G. V.: Combined effects of nicotine and mecamylamine in attenuating smoking satisfaction. Exp. Clin. Psychopharmacol. 2:328–344; 1994.
22. SPSS: SPSS Version 6.1. 1995.
23. Stolerman, I. P.: Could nicotine antagonists be used in smoking cessation? Br. J. Addict. 81:47–53; 1986.
24. Stolerman, I. P.; Goldfarb, T.; Fink, R.; Jarvik, M. E.: Influencing cigarette smoking with nicotine antagonist. Psychopharmacologia 28: 247–259; 1973.
25. Taylor, P.: Agents acting at the neuromuscular junction and autonomic ganglia. In: Hardman, J. G.; Limbird, L. E.; Molinoff, P. B.; Ruddon, R. W.; Gilman, A. G., eds. The pharmacological basis of therapeutics, 9th ed. New York: McGraw-Hill; 1996: 177–197.