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Blockade of Smoking Satisfaction Using the Peripheral Nicotinic Antagonist Trimethaphan

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ROSE, J. E., E. C. WESTMAN, F. M. BEHM, M. P. JOHNSON AND J. S. GOLDBERG. *Blockade of smoking satisfaction using the peripheral nicotinic antagonist trimethaphan.* PHARMACOL BIOCHEM BEHAV **62**(1) 165–172, 1999.—The present study was conducted to investigate the role of peripheral nicotinic receptors in mediating the rewarding effects of cigarette smoking. Twelve cigarette smokers rated cigarettes after intravenous infusion of the short-acting peripheral nicotinic receptor antagonist trimethaphan and after placebo (saline) infusions. Subjects were blinded to the infusion and cigarette conditions. Cigarette conditions included subjects' usual brand of cigarette, denicotinized tobacco cigarettes, and nicotine-injected cigarettes that had a tar delivery equal to that of the denicotinized cigarettes but with an enhanced nicotine delivery equal to that of subjects' usual brands. The latter cigarettes were rated as extremely harsh due to the high nicotine/tar ratio. Trimethaphan significantly attenuated the airway sensations associated with nicotine, and eliminated the difference in smoking satisfaction between the usual brand of cigarette and the other two cigarettes. These findings suggest that nicotinic receptors on peripheral nerve endings in the respiratory tract modulate smoking satisfaction and may be important in the maintenance of cigarette addiction. © 1998 Elsevier Science Inc.

Nicotine Smoking Addiction Antagonist Trimethaphan

RECENT views of tobacco dependence, and of cigarette smoking in particular, have stressed the role of nicotine addiction in the maintenance of smoking behavior (36). Moreover, an almost exclusive emphasis is usually placed on the role of CNS nicotinic receptors, which mediate a variety of reinforcing effects of nicotine (7). It is generally assumed that nicotine acts at CNS receptors to induce dependence in a manner similar to that of opiates and cocaine. Indeed, evidence for nicotine's actions in the CNS is considerable; nicotine interacts directly with several subtypes of nicotinic receptors, consisting of various combinations of α and β subunit proteins (40). Nicotine acts on these receptors to trigger a cascade of neurophysiologic effects, including facilitating the release of neurotransmitters such as dopamine, norepinephrine, acetylcholine, glutamate, GABA, and serotonin (11,19,25). The role of CNS dopamine release has received special attention inasmuch as there is considerable evidence that activation of mesolimbic reward pathways contributes to the reinforcing efficacy of a variety of abused drugs, including nicotine (21,26,31). In a rodent model of nicotine self-administration, specific lesions in the mesolimbic dopamine system selectively block nicotine self-administration behavior (8).

Despite this evidence for direct CNS reinforcement of nicotine self-administration, it is likely that in humans the reinforcing effects of tobacco use are multifaceted. In addition to the direct CNS actions of nicotine, the peripheral actions of cigarette smoke, accompanied by perceptions labeled as "taste" and "impact," may be important conditioned or unconditioned reinforcing cues (28,33). Smokers report enjoying the "feel" of cigarette smoke as it is inhaled, and when these sensory effects are blocked, as with local anesthesia, smoking satisfaction is blunted (27). Conversely, studies in our laboratory have also shown that stimulation of peripheral respiratory tract sensations relieves craving for cigarettes and can facilitate smoking cessation (3,32,38). Other studies have shown that there are nicotinic receptors on vagal nerve endings in the respiratory tract. Ginzel (10), for example, showed that injection of nicotinic agonists into the right heart of cats caused

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an immediate skeletal muscle relaxation response, even before the nicotine reached the cerebral circulation. Lee (22) has shown in human subjects that the irritating actions of nicotine in the respiratory tract can be blocked with the antagonist hexamethonium.

Thus, there is considerable uncertainty as to the relative importance of peripheral sensory actions of cigarette smoke, the nicotinic components of these peripheral sensations, and the direct CNS action of nicotine in providing the reinforcing effects that maintain cigarette addiction.

We conducted the present study to explore the effect of trimethaphan, a peripherally acting nicotinic antagonist (20), on the immediate subjective effects of cigarette smoking. Trimethaphan has been used clinically in the control of blood pressure; it has both ganglion-blocking effects as well as direct vasodilating actions, but the ganglionic blocking action predominates at low doses (2). Neurophysiologic studies suggest that trimethaphan is primarily a competitive antagonist of nicotine (37). An advantage of trimethaphan for laboratory-based studies of human smoking behavior is its brevity of action; the effects of trimethaphan dissipate within several minutes after the intravenous infusion is terminated (2), making it well suited for repeated-measures experimental designs. Also, because trimethaphan is a sulfonium compound with a permanent positive charge (20), it is likely that trimethaphan has limited penetration into the CNS.

Theories of smoking motivation that exclusively involve the CNS actions of nicotine would predict that trimethaphan should have little or no effect on the rewarding effects of smoking (whether assessed by subjective ratings or by behavioral measures of reinforcement), given that trimethaphan does not prevent inhaled nicotine from reaching the brain and providing primary reinforcement. However, based on the previous work in our laboratory, blockade of the peripheral sensory effects of nicotine was hypothesized to modify the pleasurable effects of smoking and reduce reported satisfaction. In this study we focused on the subjective satisfaction obtained from cigarette smoking as an index of reward. To gain as much information as possible regarding the effects of trimethaphan, subjects rated their usual brand of cigarette as well as research cigarettes that varied nicotine delivery while holding "tar" delivery constant, accompanied by either trimethaphan or saline infusions.

METHOD

Design

A 3 (usual brand of cigarette vs. nicotine-injected research cigarette vs. denicotinized cigarette) $\times$ 2 (trimethaphan vs. saline infusion) factorial design. A within-subjects design was used, with all six conditions presented to subjects in a single session.

Subjects

Twelve healthy male and female smokers were recruited from a pool of subjects previously contacted through responses to newspapers advertisements, who were interested in participating in a smoking cessation trial involving treatment with nicotine skin patches and mecamylamine. Subjects were offered the opportunity to participate in this laboratory study for monetary payment ($10/h) prior to the initiation of smoking cessation treatment. Subjects were screened according to the following criteria: inclusion criteria: age 18–55 years old; smoke at least 20 cigarettes per day on average, with nicotine delivery at least 0.7 mg; afternoon expired carbon monoxide (CO) level $\geqslant$20 ppm; desire to quit smoking; general good health, based on physical examination, EKG, serum chemistries, CBC, and urinalysis. Exclusion criteria: hypertension (systolic $>$140 mmHg, diastolic $>$90 mmHg); hypotension (systolic $<$90 mmHg, diastolic $<$60 mmHg); coronary artery disease; cardiac rhythm disorder; history of urinary retention; prostatic hypertrophy; glaucoma; impaired renal function; history of skin allergy; active skin condition (psoriasis) within the last 5 years; other major medical condition; current psychiatric disease; pregnancy or nursing mothers; use of oral contraceptives; current alcohol or drug abuse; current smokeless tobacco use, nicotine replacement therapy, or other smoking cessation treatment. Assessment of eligibility: Each potential subject was screened by telephone to determine compatibility with the inclusion and exclusion criteria. If the criteria were met, the potential subject was scheduled for the screening history and physical examination at the study center. At this session, potential subjects completed a medical history form; blood pressure, pulse, blood, and urine tests were also taken, as well as an EKG with rhythm strip.

Subject characteristics were as follows: 10 males and 2 females participated in the study; the mean age was 41.6 years (SD = 10.64) and subjects had smoked for an average of 27.2 years (SD = 10.57). They smoked on average 28 cigarettes/day, with a mean cigarette nicotine delivery (assessed by FTC method) of 0.94 mg (SD = 0.297). The mean score on the Fagerström test for nicotine dependence (14) was 5.7 (SD = 1.56).

Controlled Puff-Volume Apparatus

Puff volume was controlled with a simple apparatus validated in previous studies (23). The device uses a glass syringe preloaded with a measured amount of air that is supplied to the burning cigarette with each puff. When the subject takes a puff, the syringe barrel slides within the glass housing until the specified volume of air (smoke) has been drawn into the mouth, and no further smoke can be obtained until the device is reset for the next puff. While the cigarettes are in the controlled puff delivery apparatus, a low air flow rate (5 cc/s) was provided to prevent the cigarette from extinguishing while keeping side stream smoke from escaping. The apparatus was held in place with a ring stand situated conveniently in front of the subject, who could take puffs by leaning forward and drawing from a disposable plastic mouthpiece having a diameter comparable to a cigarette. This apparatus was used in a previous study of mecamylamine and nicotine administration, in which we found that subjects reported substantial smoking satisfaction taking puffs through the apparatus, and smoking satisfaction was significantly blocked by prior administration of mecamylamine or nicotine (29).

Puff volume was equated across nicotine-containing and denicotinized cigarettes; puff volume, number of puffs, and interpuff interval were individualized as described below. To minimize variability in nicotine absorption from variations in inhalation, subjects in all conditions were instructed to inhale deeply and hold their breath for 5 s after each puff. Gilbert (9) found that this manipulation was adequate to ensure consistent boosts in plasma nicotine levels after smoking nicotine-containing cigarettes.

Individualized Nicotine Dosing

Cigarette smokers vary enormously in the nicotine extracted from cigarettes during ad lib smoking; in a study con-

ducted by Benowitz (4), typical nicotine deliveries per cigarette were found to range from approximately 0.4 mg/cigarette to 1.6 mg/cigarette, with a mean of 1.0 mg. We have also found similar variability in smokers' nicotine intake during ad lib smoking in previous studies. In view of these findings, spurious results might be obtained if the same dose of nicotine were administered to all subjects, ignoring individual differences in sensitivity to nicotine. Therefore, we devised a procedure for administering nicotine doses equal to that self-administered by each subject during ad lib smoking. Nicotine intake after ad lib smoking was quantified by measuring puff volume, number of puffs, and interpuff intervals. This measurement was conducted directly using the same spirometric apparatus described above. When employed to measure puff volume, as opposed to controlling it, the air-containing syringe was initially filled with 70 cc prior to each puff, and the reading after each puff indicated the volume provided to the cigarette. The number of puffs and interpuff interval were also recorded, and during the controlled smoke presentations the same total number of puffs and average interpuff interval were used. In previous work we have verified that individualizing nicotine delivery using this method produces increases in plasma nicotine highly correlated with those of ad lib smoking ($r \approx 0.8$), and the mean plasma nicotine boosts agree within 10%.

Trimethaphan

Trimethaphan camsylate (Arfonad®) ampules were obtained from Roche Laboratories (Nutley, NJ). Each ampule contained 500 mg trimethaphan camsylate, which was diluted before intravenous administration.

Cigarettes

Three types of cigarettes were used: 1) subject's customary brand, 2) denicotinized tobacco cigarettes, and 3) denicotinized cigarettes injected with nicotine to raise their nicotine delivery to match subjects' usual brands. We used denicotinized cigarettes manufactured by Phillip Morris, Inc., which our laboratory and others have studied previously (13,28). These cigarettes contain tobacco from which the nicotine has been selectively extracted by high-pressure CO_2. The tar delivery of these cigarettes, when smoked by FTC criteria, is 9 mg. However, the nicotine delivery is extremely low, less than 0.1 mg. Hasenfratz et al. (13) measured smoking behavior and nicotine intake after smoking denicotinized vs. nicotine-containing cigarettes, and found that plasma nicotine levels increased less than 2 ng/ml after smoking the denicotinized cigarette. In studies using these cigarettes we have verified that they produce no significant boosts in plasma nicotine levels.

The technique for manipulating cigarette nicotine delivery of these cigarettes, which we have validated in several previous studies [e.g (15)], involved injecting a measured amount of nicotine base into the filter of the control (denicotinized) cigarettes. As smoke particles pass through the filter, they absorb some of the nicotine and the nicotine delivery of the cigarette is thereby enhanced. A graded effect is seen with different amounts of nicotine injected. The standard FTC nicotine delivery of each subject's habitual brand of cigarette was matched by injecting a known amount of nicotine into a denicotinized cigarette. In this manner, nicotine dose was manipulated in a controlled way while also keeping nonnicotine constituents constant. To blind participants to the cigarette conditions, distinctive markings were covered with opaque strips of cigarette paper, taking care not to block visible ventilation holes in the cigarette filter.

Dependent Variables

Expired air carbon monoxide. Expired air carbon monoxide, an objective index of smoke intake (16), was measured with a breath carbon monoxide monitor (Vitalograph, Lenexa, KS). While sitting, patients held a deep inspiration for a minimum of 10 s, then exhaled through the monitor. Exhaled CO was calculated by subtracting the background (ambient) CO from the exhaled CO reading.

Cardiovascular measures. Measurement of pulse and blood pressure was taken each minute during trimethaphan infusion, and every 15 min between cigarette presentations. Continuous ECG monitoring was also performed.

Cigarette evaluation. A cigarette evaluation questionnaire was administered after smoking each cigarette, which included seven-point item ratings that clustered (based on previous factor analytic studies) into the following scales: satisfaction ("was it satisfying?," "did it taste good?"); similarity to usual brand ("how similar to your own brand?"); psychological reward ("did it calm you down?," "did it help you concentrate?," "did it make you feel more awake?," "did it reduce your hunger for food?," "did it make you feel less irritable?"); aversion ("did it make you nauseous?," "did it make you dizzy?"); enjoy respiratory sensations ("did you enjoy the sensations of the smoke in your throat and chest?"); craving reduction ("did it immediately reduce your craving for cigarettes?"); and perceived strength on "tongue," "nose," "back of mouth and throat," "windpipe," and "chest" (39).

Procedure

After the screening physical, subjects participated in two sessions that were conducted after overnight abstinence from smoking. Smoking abstinence was confirmed at the beginning of each session by expired air CO measurement and subsequently by plasma nicotine analysis. The first session served to characterize the individual nicotine intake of each subject, upon which to base subsequent dosing. Subjects were allowed to smoke ad lib one cigarette of their usual brand, using the spirometric device (described above) that was later used to control smoke dose in the second session.

An intravenous line was established for infusion of trimethaphan (or saline) and for collection of blood samples for plasma nicotine assay. The study was conducted in the Durham Veterans Affairs Medical Center, with a physician present during the procedure.

Six cigarettes were presented at 30-min intervals; three of the smoking conditions (one of each type of cigarette) were accompanied by trimethaphan infusion and the other three smoking periods were accompanied by saline infusions (subjects were blind to the infusion condition). Before lighting each cigarette, intravenous trimethaphan infusions were started at a rate of 3–4 mg/min and titrated up until a mild hypotensive effect (5–10 mmHg reduction in systolic blood pressure) was observed, continuing throughout the cigarette smoking period. The order of conditions was counterbalanced using a Latin square design. However, because previous studies had suggested that the nicotine-injected cigarettes, having a much higher nicotine/tar ratio, were extremely harsh (15), these cigarettes were always presented during the last hour of the session (the order of trimethaphan vs. saline infusion was counterbalanced for these cigarettes).

Subjects rated the rewarding and/or aversive effects of each cigarette using the cigarette evaluation questionnaires described above.

Samples of venous blood (10 cc) were collected immediately before and after each cigarette (a total of 120 cc) to assess nicotine concentrations.

Data Analysis

Quality checks were made in the process of data handling to minimize errors. The data were entered into a database twice, and the two resulting datasets were compared. Data points that were discrepant were reviewed and corrected by referring to the original data forms. Data analysis was performed using SUPERANOVA (Abacus Concepts Inc., Berkeley, CA). This statistical software applies a multivariate approach to repeated measures analysis, which is generally appropriate regardless of the correlation pattern among repeated measurements (1,24). The effects of the repeated measures factors Cigarette and Infusion were analyzed, and, if significant main effects or interactions were found, follow-up tests were conducted according to the protected least significant difference test (18). For each dependent measure, contrasts were also conducted to determine whether trimethaphan influenced the pattern of significant differences between cigarette conditions that were apparent in the saline infusion condition. The alpha criterion for assessing drug effects was taken to be 0.05 (two tailed). Nonsignificant trends ($p < 0.1$) were also noted in some cases if they suggested potential mechanisms underlying the actions of trimethaphan.

RESULTS

Nicotine Delivery and Plasma Nicotine Boosts for the Three Types of Cigarette

The plasma nicotine boost following smoking of the usual brand cigarette was comparable in trimethaphan and saline infusion conditions, and was also similar to the nicotine boost in the nicotine-injected cigarette conditions (see Fig. 1). The mean boost of approximately 10 ng/ml is in good accord with the values reported in previous studies of cigarette smokers. The denicotinized cigarette had negligible effects on plasma nicotine, also confirming previous studies using these cigarettes. The plasma nicotine boost was highly correlated with the cigarette nicotine delivery, estimated by the multiplying the FTC nicotine rating by the number of puffs and puff volume ($r = 0.69, p = 0.01$). Subjects took an average of 6.2 puffs (SD = 1.76), with a mean puff volume of 42.8 ml (SD = 10.66) and mean interpuff interval of 67.2 s (SD = 28.28).

The change in expired air CO following smoking was also similar in trimethaphan and saline infusion conditions [1.8 ppm (SD = 1.70) vs. 2.2 ppm (SD = 1.71), $F(1, 11) = 1.00, p > 0.3$].

Cigarette Rratings

Before assessing the influence of trimethaphan on cigarette ratings, the three cigarette conditions were first compared using data from the saline infusion conditions to characterize the effects of the cigarettes per se. There were pronounced differences in satisfaction ratings, which differed across cigarettes, $F(2, 22) = 11.10, p = 0.0005$; the usual brand was rated more satisfying than the denicotinized cigarette, $F(1, 22) = 10.68, p = 0.003$) or the nicotine-injected cigarette ($F(1, 22) = 20.93$, $p = 0.0005$). The cigarettes were also rated differently in terms of the degree of similarity to the subjects' usual brand of cigarette, $F(2, 22) = 10.38, p = 0.0007$, with the usual brand being rated, not surprisingly, as significantly more similar than either the denicotinized cigarette, $F(1, 22) = 16.25$, $p = 0.0006$, or the nicotine-injected cigarette, $F(1, 22) = 14.87$, $p = 0.0009$.

Subjects reported enjoying the airway sensations of smoking their usual brand more than the other two-cigarette conditions, $F(1, 22) = 7.24$, $p = 0.01$ for the comparison of usual brand vs. denicotinized cigarette, and, $F(1, 22) = 14.42$, $p = 0.001$, for the comparison of usual brand vs. nicotine-injected cigarette.

Ratings of the strength of regional respiratory tract sensations also differed across cigarette conditions, $F(2, 22) = 3.53$, $p = 0.05$ for tongue; $F(2, 22) = 5.09$, $p = 0.02$ for nose; $F(2, 22) = 6.83$, $p = 0.005$ for back of mouth and throat; $F(2, 22) = 4.19$, $p = 0.03$ for windpipe; and $F(2, 22) = 4.62$, $p = 0.02$ for chest. In contrast to the ratings of enjoyment previously de-

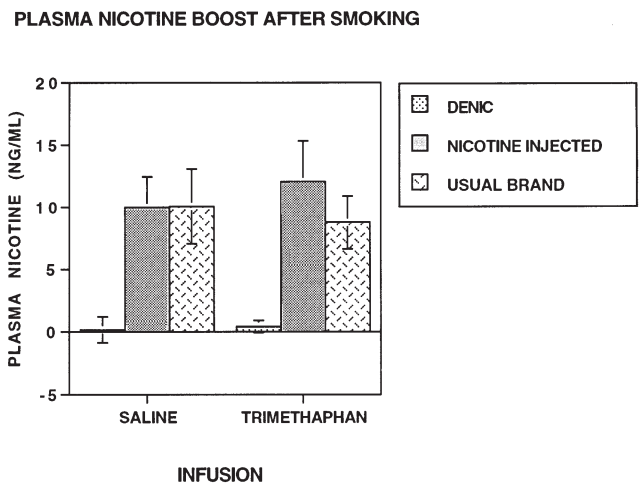

FIG. 1. Plasma nicotine boosts (mean ± SEM) resulting from smoking the three types of cigarette used in the study. Nicotine boosts were similar for the two nicotine-containing cigarettes and negligible for the denicotinized cigarette.

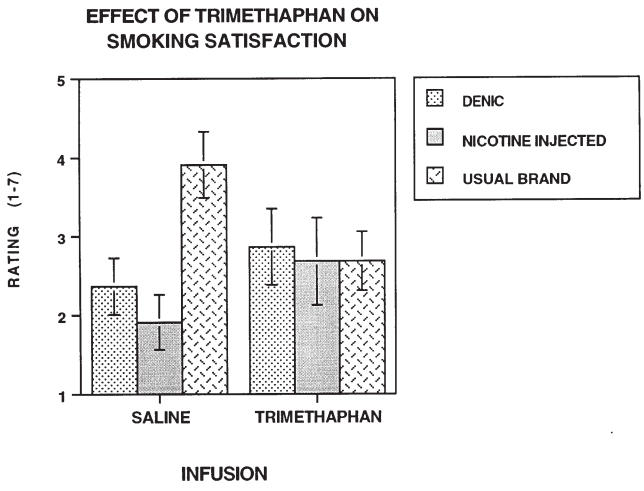

FIG. 2. Smoking satisfaction (mean ± SEM) reported after smoking each type of cigarette in trimethaphan and saline infusion conditions. The increased satisfaction for the usual brand of cigarette was abolished by trimethaphan.

scribed, which distinguished the usual brand from the other two cigarettes, in the case of respiratory tract sensations the nicotine-injected cigarette was generally rated stronger than the other two cigarettes in all regions; they were rated stronger than the denicotinized control cigarette for the tongue, $F(1, 22) = 6.03$, $p = 0.02$; nose, $F(1, 22) = 10.11$, $p = 0.004$; back of mouth and throat, $F(1, 22) = 16.67$, $p = 0.004$; windpipe, $F(1, 22) = 6.28$, $p = 0.02$; and chest, $F(1, 22) = 9.04$, $p = 0.006$). They were also rated as significantly more intense than the usual brand cigarettes with respect to sensations on the tongue, $F(1, 22) = 4.43$, $p = 0.05$; back of mouth and throat, $F(1, 22) = 10.25$, $p = 0.004$; and windpipe, $F(1, 22) = 6.28$, $p = 0.02$, with trends in the same direction for nose, $F(1, 22) = 3.30$, $p = 0.08$, and chest, $F(1, 22) = 3.60$, $p = 0.07$.

There was a difference between conditions in the immediate craving-reducing effect of smoking, with the two nicotine-containing cigarettes reducing craving more than the denicotinized cigarette, $F(1, 22) = 5.42$, $p = 0.03$).

Effects of Trimethaphan on Cigarette Ratings

The effects of trimethaphan were assessed with respect to the differences between cigarettes noted above: 1) for satisfaction ratings, the difference between the usual brand and the two control cigarettes was contrasted between trimethaphan and saline infusion conditions; 2) for respiratory tract strength ratings, the difference between the nicotine-injected cigarettes and the other two cigarettes was contrasted between trimethaphan and saline conditions; also, the two nicotine-containing cigarette conditions were contrasted with the denicotinized control cigarette; and 3) for immediate craving reduction, the two nicotine-containing cigarettes were contrasted with the denicotinized control cigarette.

Smoking Satisfaction

There was a significant interaction of infusion × cigarette condition, $F(1, 20) = 4.73$, $p = 0.04$, such that the difference between the usual brand and other cigarette conditions was abolished by trimethaphan (see Fig. 2). In the saline condition, the contrast between the usual brand and the other two cigarettes was highly significant, $F(1, 20) = 9.51$, $p = 0.006$, whereas the three cigarettes were rated similarly in terms of satisfaction during the trimethaphan infusions, $F(1, 20) = 0.02$, $p = 0.9$. Thus, there was a strong trend for trimethaphan to reduce smoking satisfaction in the usual brand condition,

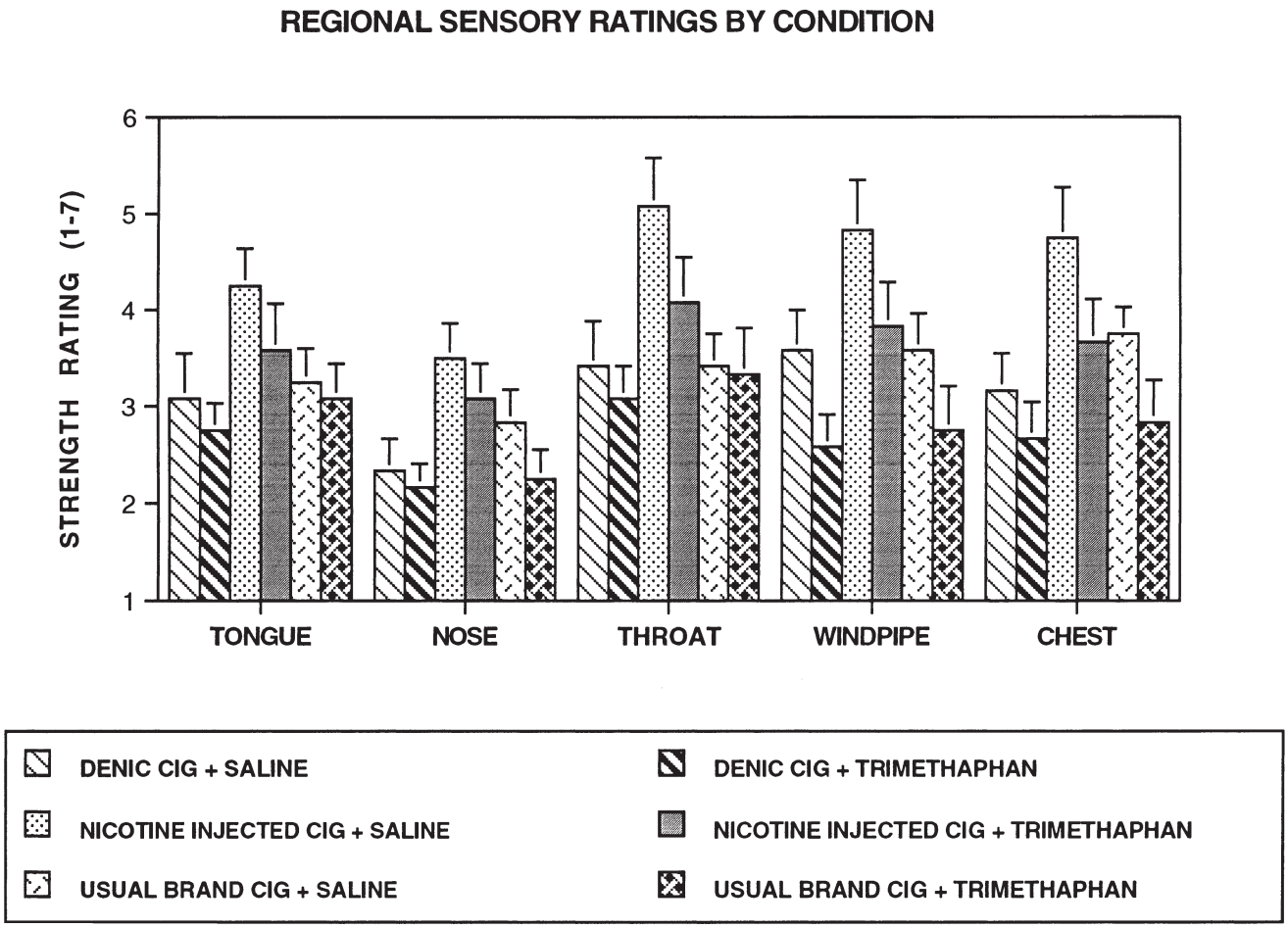

FIG 3. Regional airway sensory ratings (mean ± SEM) for the three types of cigarette, in both saline and trimethaphan infusion conditions (for each type of cigarette and region, the rating for the trimethaphan condition is depicted immediately adjacent to the saline infusion condition to illustrate the attenuation of sensations by trimethaphan).

$F(1, 18) = 4.21$, $p = 0.06$, while tending to increase satisfaction for the nicotine-injected cigarettes, $F(1, 18) = 2.93$, $p = 0.1$.

A similar finding held with regard to similarity to the usual brand cigarette; the difference between the usual brand and the other two cigarettes was significantly attenuated by trimethaphan, $F(1, 22) = 5.03$, $p = 0.04$. In the saline condition, the contrast between the usual brand and the other two cigarettes was highly significant, $F(1, 22) = 12.11$, $p = 0.002$, but in the trimethaphan condition, the cigarettes did not differ from each other in similarity ratings, $F(1, 22) = 0.22$, $p = 0.6$.

The relatively greater enjoyment of the respiratory sensations reported for the usual brand of cigarette was also attenuated by trimethaphan, $F(1, 20) = 6.46$, $p = 0.02$ for the trimethaphan vs. saline comparison of the difference between the usual brand and other two cigarettes.

To evaluate the hypothesis that trimethaphan would block the perception of nicotine in the respiratory tract, the reported intensity of sensations in the different respiratory regions was analyzed. In Fig. 3, for each type of cigarette and region, the rating for the trimethaphan condition is depicted immediately adjacent to the saline infusion condition to illustrate the attenuation of sensations by trimethaphan. There was a significant main effect of trimethaphan infusion, decreasing strength ratings for all cigarettes in several regions, especially in the windpipe and chest—$F(1, 11) = 6.36$, $p = 0.01$ for the windpipe, and $F(1, 11) = 8.68$, $p = 0.01$ for the chest. However, the difference in ratings between the nicotine-injected cigarette and the other two cigarettes was unaffected by trimethaphan (ps > 0.1 for all regions). On the other hand, for the chest, the difference between the two nicotine-containing cigarettes and the denicotinized control cigarette was attenuated by trimethaphan, $F(1, 22) = 5.63$, $p = 0.03$.

With respect to the immediate craving reduction after smoking, the effect of nicotine was not altered by trimethaphan, as shown in Fig. 4, $F(1, 20) = 0.41$, $p = 0.5$, for the contrast between the effect of nicotine in the saline infusion condition vs the effect of nicotine in the trimethaphan condition; thus, there was still a significant effect of nicotine (contrasting the two nicotine-containing cigarettes with the denicotinized cigarette) in both the trimethaphan condition, $F(1, 20) = 4.74$, $p = 0.04$, and in the saline condition, $F(1, 20) = 6.56$, $p = 0.02$.

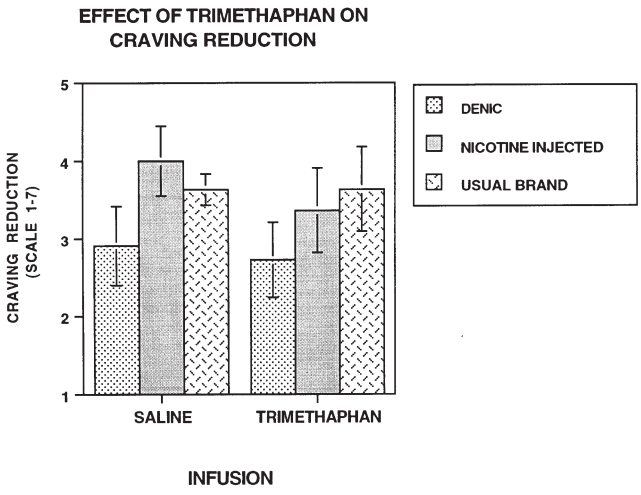

FIG. 4. Ratings of craving reduction (mean ± SEM) obtained by smoking the three types of cigarette in the trimethaphan and saline infusion conditions. Trimethaphan did not block the craving reduction produced by the nicotine-containing cigarettes relative to the denicotinized control cigarette, suggesting a CNS site of action for nicotine.

Blood Pressure and Heart Rate

There was a mild hypotensive effect of trimethaphan (relative to saline infusion) prior to cigarette smoking. Systolic blood pressure was lowered on average by trimethaphan from a mean of 115.6 mmHg (SD = 2.05) to 110.7 mmHg (SD = 1.76), $F(1, 11) = 17.18$, $p = 0.002$. Diastolic blood pressure was lowered from a mean of 71.5 (SD = 10.92) to 66.5 mmHg (SD = 10.71), $F(1, 11) = 16.60$, $p = 0.002$. Smoking had no consistent effect on blood pressure.

Heart rate was increased by trimethaphan from an average (presmoking) of 67.2 bpm (SD = 8.61) to 72.9 bpm (SD = 9.04), $F(1, 11) = 22.2$, $p = 0.0006$. Cigarette smoking also increased heart rate in the nicotine-containing cigarette conditions relative to the denicotinized control, $F(1, 20) = 8.82$, $p = 0.008$; the heart rate boost after smoking averaged 6.6 bpm (SD = 6.31) in the usual brand condition, 5.6 bpm (SD = 5.73) in the nicotine-injected cigarette condition, and 3.5 bpm (SD = 4.08) in the denicotinized cigarette condition.

DISCUSSION

The main conclusion of the present study is that peripheral actions of nicotine are extremely important in mediating the immediate subjective effects of cigarette smoking. The importance of peripheral actions of nicotine was demonstrated by the attenuation of smoking satisfaction for the usual-brand cigarette condition accompanying trimethaphan infusions. In addition, the fact that the usual-brand cigarette was rated so much more enjoyable than the nicotine-injected cigarette, despite having equal nicotine delivery (and presumably similar direct actions on the central nervous system), further highlights the importance of peripheral sensory cues in determining hedonic effects of cigarette smoking. The nicotine-injected cigarettes were rated as excessively harsh (relative to both the usual brand cigarettes and the denicotinized control cigarettes), which probably accounts for the low ratings of liking and satisfaction.

The harshness of the nicotine-injected cigarettes also explains why trimethaphan had opposite effects on reactions to the usual brand vs. injected nicotine cigarettes. The usual brand cigarettes, which were rated high in satisfaction in the saline condition, showed a strong trend to be rated less satisfying in the trimethaphan condition, possibly due to the lack of the unique "feel" of nicotine in the lungs. In contrast, the nicotine-injected cigarettes, which produced excessive harshness, tended to become more enjoyable and satisfying when sensations were reduced to a more tolerable level by trimethaphan (see Fig. 2).

The finding that sensory cues are important determinants of the hedonic effects of smoking leaves open the question of whether these cues are primary reinforcing stimuli (10), or instead become reinforcing over time due to their familiarity or because they serve as a conditioned reinforcers signaling the rewarding CNS actions of nicotine. Studies examining whether the rewarding effects of peripheral cues extinguish over time, if presented in the absence of the CNS effects of nicotine, will be useful in addressing this issue.

Interestingly, the ability of a cigarette to relieve craving may depend on different processes than those that mediate enjoyment and satisfaction. This was shown by the fact that

trimethaphan did not attenuate the nicotine-related component of craving reduction (see Fig. 4). Thus, for the usual brand of cigarette, the peripheral actions of nicotine appear to be critical for mediating satisfaction, but the nicotine component of craving reduction is likely to be CNS mediated. Evidence from other studies involving nicotine administration via skin patches, a mode of nicotine delivery that presents few peripheral sensations, but which reduces cigarette craving (28), also suggests that at least a portion of nicotine's effects on craving is centrally mediated. Additionally, there is a nonnicotine sensory component of craving reduction, as evidenced by the ratings of craving reduction for the denicotinized cigarette [which, although statistically lower, were nearly as high as for the usual brand; see also (6,13)].

Although brain concentrations of trimethaphan were not measured, there are several reasons for concluding that the marked effects on subjective ratings of smoking were due to peripheral nicotinic receptor, as opposed to CNS receptor, blockade: 1) molecules having a permanent positive charge such as trimethaphan and low lipid solubility generally show little penetration into the brain in the short term (5); 2) the opposite effects of trimethaphan on the desirability of the harsh, nicotine-injected cigarettes vs. subjects' usual brands is consistent with an interpretation in terms of blockade of peripheral respiratory tract sensations, but would be difficult to explain in terms of CNS blockade inasmuch as both the nicotine-injected cigarettes and usual brand cigarettes had comparable nicotine delivery and presumably similar CNS actions; 3) the lack of effect of trimethaphan on the nicotine component of craving reduction is consistent with a lack of CNS blockade. Although this could also be explained by assuming that nicotine was acting peripherally but at a different nicotinic receptor subtype, not affected by trimethaphan, the most parsimonious account is that trimethaphan did not block the CNS actions of nicotine.

The effect of trimethaphan in attenuating sensations in the windpipe and chest, and specifically the attenuation of nicotine-related sensations in the chest (as shown by the comparison between trimethaphan and saline conditions in the difference between the denicotinized cigarette and the two nicotine-containing cigarettes) is consistent with the existence of nicotinic receptors on vagal nerve endings (10). However, the fact that trimethaphan also had a main effect in reducing the sensory intensity of all cigarettes (including the denicotinized cigarette), suggests that sensory input arising from nonnicotine stimuli may, nonetheless, be mediated through nicotinic pathways. It has been reported that there are nicotinic receptors in the solitary nucleus, a target of vagal afferent terminals (35), part of which is located in a region of the brain where the blood–brain barrier is absent (12). Moreover, sensory ganglia contain nicotinic receptors that relay signals arising from nicotine and well as nonnicotine stimuli (17). Thus, it is conceivable that trimethaphan would have access to these neural relay stations and could have attenuated sensations produced by the denicotinized cigarette, even though these sensations were almost certainly elicited by smoke constituents other than nicotine.

The present results have several implications for smoking cessation treatment. First, these results, along with previous studies, suggest that the peripheral effects of nicotine are important to smokers and that adjuncts that can replace these sensations may be helpful smoking cessation aids (38). Second, the aversive irritation that can result from some existing nicotine-containing smoking cessation aids, such as the nicotine nasal spray, might best be attenuated by nicotinic antagonist treatment to enhance compliance with effective use.

Third, these results suggest that selective nicotinic antagonists might be developed that block the enjoyment of smoking by blocking the nicotinic receptors in the respiratory tract. Previous research in our laboratory has shown that the nicotinic antagonist mecamylamine can be used fruitfully in smoking cessation treatment (30,34). Initiation of blockade treatment 2 weeks prior to smoking cessation appears to enhance subsequent abstinence, suggesting that extinction of smoking behavior resulting from blockade of smoking reward mediates the therapeutic effect of mecamylamine. However, mecamylamine blocks both central and peripheral nicotinic receptors, and the question is left open as to how much of the action of mecamylamine might be mediated by blockade of peripheral nicotinic receptors. Blockade of these receptors alters the sensory characteristics of cigarette smoke and may account for a significant portion of the blockade of smoking satisfaction we have previously reported using mecamylamine. If the therapeutic effect of mecamylamine were shown to result in large part from its action on peripheral nicotinic receptors, then more selective antagonists might be developed to target these receptors with minimal side effects. Thus, further studies using chronic administration of peripheral nicotinic receptor antagonists will be important for evaluating theories of tobacco dependence, for understanding the mechanisms underlying nicotine antagonist treatment, and potentially for developing still more efficacious therapies.

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