ELSEVIER

Pharmacology Biochemistry and Behavior, Vol. 53, No. 2, pp. 309–315, 1996

0091-3057/96 $15.00 + .00

0091-3057(95)02027-7

Dissociating the Nicotine and Airway Sensory Effects of Smoking

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Received 30 December 1994; Revised 8 May 1995; Accepted 30 May 1995

WESTMAN, E. C., F. M. BEHM AND J. E. ROSE. *Dissociating the nicotine and airway sensory effects of smoking.* PHARMACOL BIOCHEM BEHAV **53**(2) 309–315, 1996.—This study examined the subjective and cardiovascular effects of two of the components of cigarette smoking when given separately: nicotine and airway sensations. Using a within-subjects design, six healthy volunteer smokers, age 18–45 years, who smoked at least 20 cigarettes per day were given six conditions in a randomized, counterbalanced order. The effects of IV nicotine, IV saline, and denicotinized cigarettes were compared to a standard 1-mg cigarette. The standard cigarette produced more of a calming effect and more irritability reduction than either the nicotine or airway sensations alone. The denicotinized cigarette was similar to the standard cigarette condition, except the cigarette condition was associated with higher feelings of "exhilaration." Many of the positive subjective effects from a denicotinized cigarette were comparable to that of a standard cigarette. These data support the hypothesis that replacement of the sensory cues of smoking with "airway sensory replacement" may be useful for smoking cessation.

Nicotine Smoking Intravenous Infusion

SMOKING is currently understood as a drug addiction to nicotine (18). However, nicotine replacement therapy alone for smoking cessation is only partially successful. For example, the average success rate at 6 months combining 17 nicotine patch studies is only about 22% (6). Nicotine replacement therapy may be only partially successful for smoking cessation because it does not replicate the rapid, high doses of nicotine delivered by cigarette smoking. Alternatively, nicotine replacement may be only partially successful for smoking cessation because nicotine only partially explains the smoking addiction.

The low success rates with nicotine replacement alone may be due to the lack of adequate attention to the sensory and motor components of smoking. These sensory and motor components are then linked to the primary reinforcing drug: nicotine. From the smoker's perspective, these sensory and motor cues may be equally as reinforcing as nicotine. In previous studies from our laboratory using airway anesthesia to block airway sensations, smoking was less enjoyable, and by inference less reinforcing, without the usual associated airway sensations of smoking (11,12). The observation that many of the major reinforcing sensory cues are in the smoker's airway led to the "airway sensory hypothesis" of smoking (13).

If nicotine alone could explain the smoking addiction, then smoking cessation research should continue to focus on ways to replace nicotine. On the other hand, if the airway sensory hypothesis also explains part of the smoking addiction, then research efforts should also be placed upon reproducing the airway sensations of smoking.

The purpose of this study was to examine the subjective effects of two of the components of smoking when given separately: nicotine and airway sensations. In this study, overnight-deprived smokers were studied under conditions of: 1) IV nicotine without the airway sensory components of smoking; 2) the airway sensory components of smoking without the nicotine; 3) the combined nicotine and airway sensory components of smoking, and 4) a standard nicotine-containing cigarette. We hypothesized that the administration of nicotine and airway sensations alone would reproduce many of the effects of a standard cigarette.

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METHOD

Subjects

Six healthy volunteer smokers, age 18–45 years, who smoked at least 20 cigarettes per day, were recruited by newspaper advertisement. Subjects were screened by history, physical, serum chemistries, complete blood count, and resting electrocardiogram prior to study enrollment. Light smokers were excluded if the baseline (afternoon) exhaled carbon monoxide level was less than 15 ppm. The six subjects had a mean age of 34.3 years (range 19–43 years); all were male; five were Caucasian, one was African-American. Subjects smoked 28.5 cigarettes per day on average (range 20–40), and had been smoking for an average of 20.3 years (range 3–35). The mean baseline carbon monoxide level was 27.7 ppm (range 17–40); the mean Fagerstrom score (FTND) was 6.5 (range 5–9) (7). Two subjects were college graduates; two had completed some college, one some high school, and one eighth grade or less. Subjects were paid $10/h for compensation. Informed consent approved by the local Institutional Review Board was read and signed prior to participation.

Design

Using a within-subjects design, each subject was given six conditions in a randomized, counterbalanced order using a Latin square (Table 1). Nicotine IV was given during conditions A, B, D, and E; saline IV was given during conditions C and F. The dose of 1 mg nicotine was chosen to approximate the nicotine delivery from a medium strength cigarette, and was given either as: 1) 1-mg nicotine base solution continuously infused over 10 min (conditions A, D) or 2) 0.1-mg nicotine base solution pulse injected every minute for 10 min (conditions B, E). There was no smoking during conditions A and B, smoking of a denicotinized cigarette during conditions C, D, and E, and smoking of a standard 1-mg nicotine (by FTC analysis) cigarette during condition F. The denicotinized cigarettes were similar to the medium strength cigarettes in tar, draw, and other nonnicotine sensory features (1).

Conditions A and B were designed to assess the effect of nicotine alone when given without the airway sensations. Condition C assessed the effect of airway sensations of a denicotinized cigarette alone. Conditions D and E assessed the combination of the IV nicotine and denicotinized smoke. Condition F served as the nicotine cigarette reference.

The study staff administering the conditions and questionnaires were unaware of the study hypotheses, and the study physician administering the infusions had little interaction with the subjects.

Procedures

Subjects reported to the Nicotine Research Laboratory at 0730 h after overnight smoking abstinence (verified by self-report of no smoking since 2400 h of the study day and exhaled carbon monoxide < 20 ppm). After completing a baseline craving and side effect questionnaire, the subjects were seated in a chair in the semirecumbent position. Two 22-ga IV catheters (one in each antecubital vein) were inserted 30 min prior to the infusions. During all conditions, cardiac rhythm was monitored continuously, and blood pressure and pulse were measured each minute via an automated oscillometric blood pressure recorder (Dinamap model 1846sx, Critikon, Tampa, FL).

The conditions were administered every 30 min over a 3.5-h period. The IV solutions were delivered via infusion pump (conditions A, C, D, F) or syringe (conditions B, E), and in the syringe conditions were started approximately 5–10 s prior to each puff to approximate the usual 7-s time interval between puffing and arrival of nicotine at the brain (normal range of arm to brain circulation time = 9–16 s; estimated lung to brain circulation time = 7 s) (5). The cigarettes were smoked through a cigarette holder positioned at the subject's mouth. One puff was inhaled every minute for 10 min, and five puffs were taken from each of two cigarettes to maintain consistency of puff delivery of nicotine.

Measures

Venous nicotine levels. Blood samples were taken immediately before and after each condition. Samples were centrifuged, frozen, and sent for nicotine determination by gas chromatography (Clinical Pharmacology Unit of the Medical Service, San Francisco Hospital Medical Center).

Exhaled carbon monoxide. Carbon monoxide levels (Vitalograph, Lanexa, KS) were measured before and after each condition after 10 s of breath holding.

Vital signs. Blood pressure and pulse were measured upon arrival to the laboratory, 10 min prior to each condition, then every minute during the conditions.

Satisfaction and liking. Questionnaire items assessing satisfaction and liking were completed at the end of each condition. The items asked "Was it satisfying?," "How much did you like the puffs that you just took?" The items were rated on a scale from 1 ("not at all") to 7 ("extremely").

TABLE 1

STUDY CONDITIONS AND NICOTINE AND EXHALED CARBON MONOXIDE BOOST

Condition	Intravenous Solution	Airway Sensations	Venous Nicotine Boost* [ng/ml (sd)]	Exhaled CO Boost† [ppm (sd)]
A	Nicotine infusion	No smoking	4.2 (2.9)	0.7 (4.2)
B	Nicotine pulses	No smoking	8.9 (3.0)	−0.8 (1.5)
C	Saline infusion	Denic cigarette	0.2 (5.2)	12.7 (7.0)
D	Nicotine infusion	Denic cigarette	7.1 (4.0)	7.8 (0.8)
E	Nicotine pulses	Denic cigarette	7.6 (2.9)	9.8 (0.8)
F	Saline infusion	Cigarette	16.7 (3.5)	7.2 (1.2)

*Venous nicotine boost comparisons: AB vs. C, $p = 0.001$; AB vs. F, $p = 0.0001$; C vs. F, $p = 0.0001$; DE vs. F, $p = 0.0001$; DE vs. C, $p = 0.0003$.

†Exhaled CO boost comparisons: AB vs. C, DE, or F, $p < 0.0001$; C vs. DE, $p = 0.03$; C vs. F, $p = 0.01$.

Craving reduction. One item asked "Did it immediately reduce your craving?," rated from 1 ("not at all") to 7 ("extremely"). A modified Shiffman-Jarvik smoking withdrawal questionnaire was administered after each condition to measure postcondition craving (15). From this questionnaire, a craving subscale was used containing six items (craved a cigarette, would have liked a cigarette, thought of cigarettes, missed a cigarette, had urges to smoke and, scored oppositely, would have refused a cigarette). The items were also rated on a scale from 1 ("not at all") to 7 ("extremely").

Airway sensory effects. A questionnaire regarding the strength of sensations in the mouth and tracheobronchial tree was completed at the end of each condition: "Rate how strong the puffs were in the following places: tongue, nose, back of mouth & throat, windpipe, chest." Another item asked "Did you enjoy the sensations of the smoke in your throat and chest?" These items were rated from 1 ("not at all") to 7 ("extremely").

Other effects. A questionnaire was administered after each condition asking if the subjects experienced calming effects ("calm you down," "a feeling of relaxation," "a feeling of comfort," "less irritable," "a sense of well-being"), arousing effects ("more awake," "help you concentrate," "exhilaration," "pleasurable excitement"), or adverse effects ("dizziness," "lightheadedness," "nausea," "nervousness"). "The items were scored from 1 ("not at all") to 7 ("extremely"). After each condition, an open-ended side effect questionnaire was given, and subjects were asked if they thought they had received nicotine.

Analysis Plan

Each of the outcome measurements was compared first in an overall repeated-measures analysis of variance (ANOVA) model (Superanova, Abacus Concepts Inc., Berkeley, CA) Because there was no significant difference in nicotine delivery between the IV infusion and the IV bolus injections, the IV nicotine conditions (A, B) were combined, and the IV + denicotinized cigarette conditions (D, E) were combined. If the overall model was significant, the following planned comparisons were made:

1. Nicotine alone vs. nicotine and airway sensory cues (AB vs. DE).
2. Nicotine effect with airway sensory cues held constant (C vs. DE).
3. Nicotine alone vs. standard nicotine cigarette (AB vs. F).
4. Airway sensory cues vs. standard nicotine cigarette (C vs. F).
5. Airway sensory cues + nicotine vs. standard nicotine cigarette (DE vs. F).

All comparisons were two-tailed, using a $p = 0.05$ as the level of statistical significance.

RESULTS

Venous Nicotine Levels

The combined mean nicotine levels of conditions A + B (6.6 ng/ml) and conditions D + E (7.3 ng/ml) were significantly higher than the saline condition C (0.2 ng/ml), and were significantly lower than the standard nicotine cigarette condition F (16.7 ng/ml) (Table 1). The mean nicotine levels of the IV infusion conditions (A and D) were not significantly different from the nicotine pulse conditions (B and E).

Exhaled Carbon Monoxide

The highest mean carbon monoxide level was observed in the denicotinized cigarette condition (C), and was significantly higher than the other smoking conditions (D, E, and F) (Table 1). The mean carbon monoxide levels from the combined nicotine/sensory conditions (D, E) were not significantly different from the cigarette condition (F). All of the smoking conditions (C, D, E, F) had significantly higher carbon monoxide boosts than the nonsmoking conditions A and B ($p < 0.0002$).

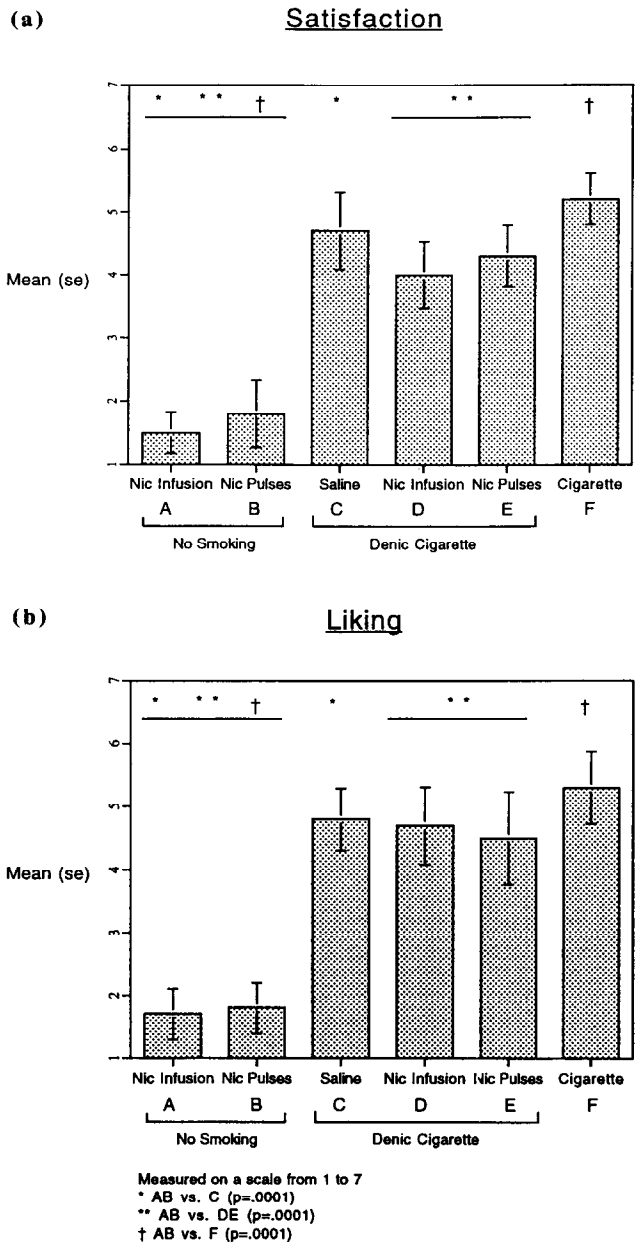

FIG. 1. (a) Mean ± SEM subjective satisfaction for the six study conditions ($n = 6$). (b) Mean ± SEM subjective liking for the six study conditions ($n = 6$).

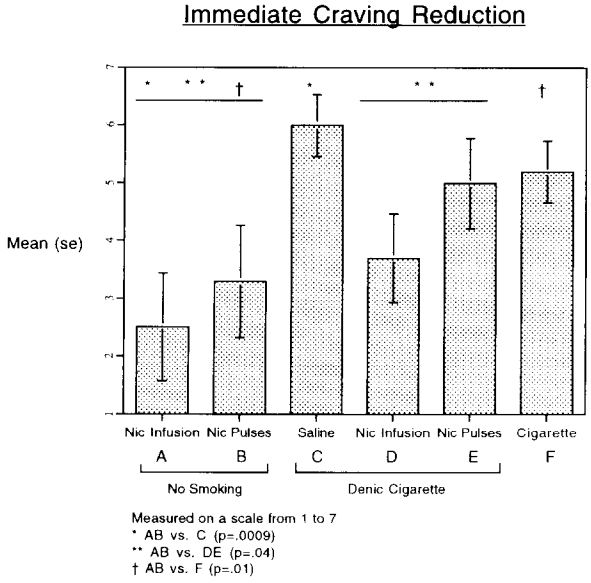

FIG. 2. Mean ± SEM subjective immediate craving reduction for the six study conditons (n = 6).

Vital Signs

There were no statistically significant overall model differences among the conditions for mean maximal rise in pulse, systolic blood pressure, or diastolic blood pressure. The maximal rise in pulse (bpm) for condition A was 12.2, condition B was 11.2, condition C was 11.3, condition D was 13.0, condition E was 12.8, and condition F was 15.5. The maximal rise in systolic blood pressure (mmHg) for condition A was 6.5, condition B was 15.2, condition C was 7.8, condition D was 11.2, condition E was 10.0, and condition F was 9.5. The maximal rise in diastolic blood pressure (mmHg) for condition A was 7.3, condition B was 9.5, condition C was 7.8, condition D was 12.3, condition E was 6.7, and condition F was 7.8.

Satisfaction and Liking

Satisfaction and liking were both significantly higher for the four smoking conditions (C, D, E, and F) than for the two IV nicotine conditions (Fig. 1a,b). There were no significant differences among the four smoking conditions for satisfaction or liking.

Craving Reduction

On the single item of immediate craving reduction, there were no significant differences among any of the smoking conditions (C, D, E, and F), but craving reduction was higher for all of the smoking conditions than the IV nicotine conditions alone (A, B) (Fig. 2). There were no differences among the conditions on the postcigarette craving subscale, with scores ranging from 3.7 to 3.9.

Airway Sensory Effects

There were no significant differences for strength in the tongue, nose, back of mouth & throat, windpipe, and chest among any of the smoking conditions (C, D, E, and F), but these sensations were significantly higher for all of the smoking conditions than the IV nicotine alone conditions (A, B). The chest sensations are shown in Fig. 3a. The enjoyment of chest sensations was similar for any type of smoking, and significantly higher for the smoking conditions than the IV nicotine conditions (Fig. 3b). Good taste was similar for the smoking conditions, and significantly higher for the smoking conditions than the nonsmoking conditions. Good taste for condition A was 1.8, condition B was 1.3, condition C was 4.3, condition D was 3.3, condition E was 3.6, and condition F was 4.3.

Other Effects

The cigarette condition (F) was consistently higher than the IV conditions (A, B) for four of the five calming items ["calm

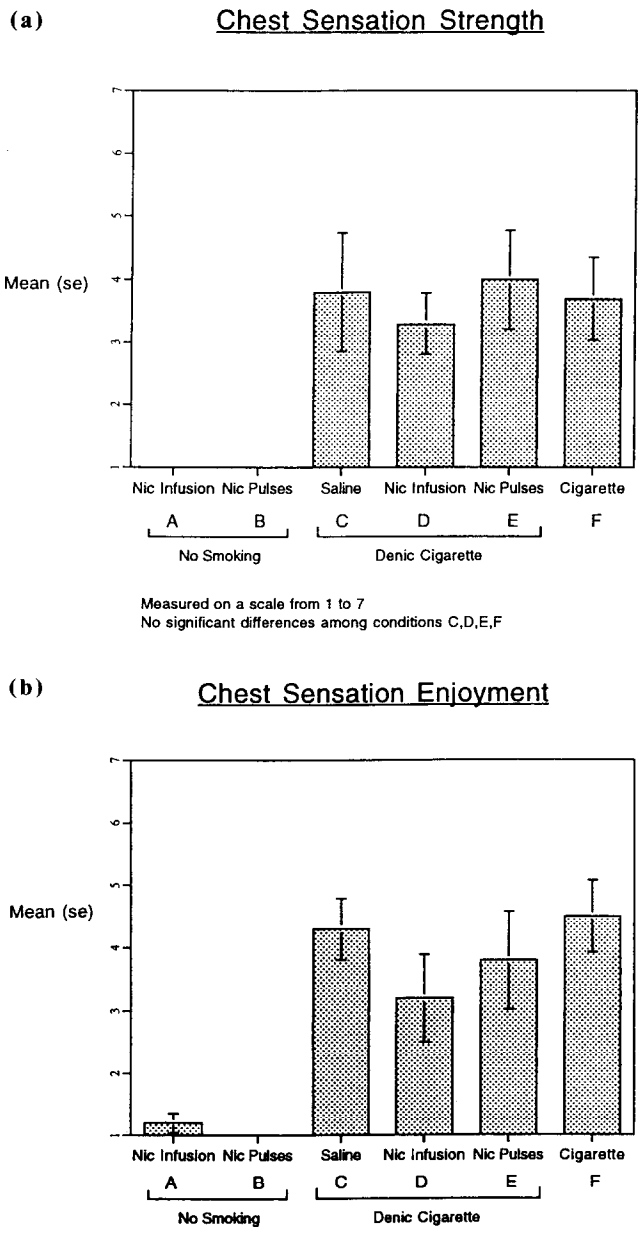

FIG. 3. (a) Mean ± SEM subjective chest sensation strength for the six study conditions (n = 6). (b) Mean ± SEM subjective chest sensation enjoyment for the six study conditions (n = 6).

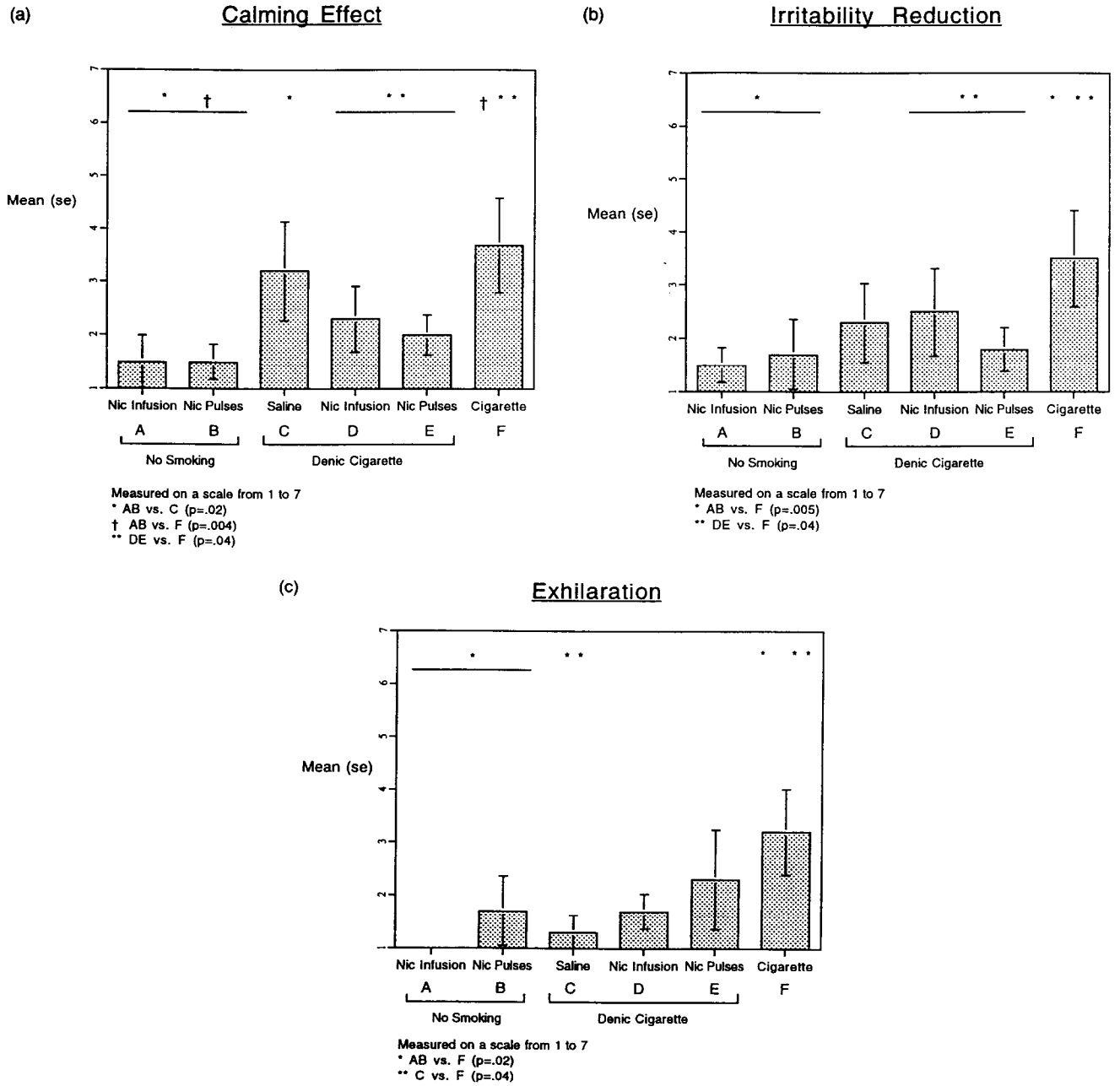

FIG. 4. (a) Mean ± SEM subjective calming effect for the six study conditions (n = 6). (b) Mean ± SEM irritability reduction for the six study conditions (n = 6). (c) Mean ± SEM subjective exhilaration for the six study conditions (n = 6).

you down" (p = 0.004), "a feeling of relaxation" (p = 0.02), "a feeling of comfort" (p = 0.01), "less irritable" (p = 0.005)], three of four arousing items ["more awake" (p = 0.03), "help you concentrate" (p = 0.03), "exhilaration" (p = 0.02)], and one of four adverse items ["dizziness" (p = 0.006)].

The cigarette condition (F) was similar to the nicotine/sensory conditions (D, E) except it had higher scores for the items "calm you down," and "less irritable" (Fig. 4a,b). Additionally, the cigarette condition (F) was similar to the denicotinized cigarette condition (C), except the cigarette condition had higher feelings of "exhilaration" (Fig. 4c).

All conditions were well tolerated. Mild burning at the catheter site occurred in several subjects, but there was no significant difference among the conditions. Of the other adverse effects, there were no differences for lightheadedness, nausea, or nervousness. For dizziness, the cigarette (F) and denicotinized cigarette (C) conditions were significantly higher than the IV nicotine conditions (p = 0.006, p = 0.04, respectively). Dizziness for condition A was 1.2, condition B was

1.8, condition C was 3.2, condition D was 2.2, condition E was 2.7, and condition F was 3.8.

Subjects were generally well blinded to the drug administration. In ascertaining the presence or absence of nicotine, the percent correct for each subject (out of six conditions) was 16.7%, 33.3%, 50%, 50%, 50%, and 83.3%. Subjects correctly identified nicotine being present or absent 50% of the time (6/12) for conditions A and B, 33.3% of the time (2/6) for condition C, 41.7% of the time (7/12) for conditions D and E, and 66.7% of the time (4/6) for condition F.

DISCUSSION

In this study, we attempted first to recreate the experience of cigarette smoking, and then to focus on the sensory and nicotine components independently. Although we were unable to replicate the nicotine levels of smoking, we were able to reproduce many of the subjective experiences of cigarette smoking. Because satisfaction and immediate craving reduction were reproduced by a denicotinized cigarette, we conclude that the airway sensations of smoking may be just as important as nicotine for short-term smoking satisfaction and craving reduction.

Many of the effects of a standard 1-mg cigarette were reproduced by the denicotinized cigarette in this study. The denicotinized cigarette produced airway sensations, craving reduction, arousal, and relaxation similar to the standard 1-mg cigarette. However, the standard 1-mg nicotine cigarette produced more calming effect and irritability reduction than the combined sensory/nicotine conditions, and more "exhilaration" than the denicotinized cigarette. Because some of the airway sensations of a cigarette arise from nicotine, a denicotinized cigarette should not be expected to entirely reproduce the airway sensations of a nicotine cigarette. Differences between the two cigarettes in this study may result from the greater nicotine and tar delivery from the standard cigarette, or may be due to the unique qualities of the airway sensations of nicotine-containing smoke.

By design, the subjects were able to adjust their intake of cigarette smoke in this study by controlling the depth and duration of inhalation. As a result, subjects achieved higher boosts in carbon monoxide while smoking a denicotinized cigarette than while smoking a standard 1-mg nicotine cigarette. This increase in inhalation may have been the subjects' attempts to increase nicotine intake from the denicotinized cigarette. An alternative hypothesis may be that the subjects were compensating for the loss in nicotine stimulation by increasing the amount of airway sensations received. This ability to control smoke intake may have allowed the subjects to receive more craving reduction and higher satisfaction in the smoking conditions than the nonsmoking conditions.

Intravenous nicotine had a small effect on craving reduction, satisfaction, and liking. Although the subjective effects of IV nicotine were subtle, IV nicotine decreased the amount of smoked inhaled: the mean carbon monoxide level after condition C was 12.7 compared to 8.8 for conditions D and E combined ($p = 0.03$).

Intravenous nicotine can be a useful tool for studying the pharmacological reinforcement of smoking in the absence of the usual behavioral components of cigarette smoking (3,4,8,9,14). In this study we used a nicotine dose and rate of delivery similar to the dose and rate expected from smoking a cigarette, but did not entirely achieve nicotine levels comparable to smoking. Although in previous studies higher doses of IV nicotine were sometimes used, these studies did not use standard measures to assess craving, satisfaction, and other subjective effects.

We used IV nicotine to study the effects of nicotine alone without the sensory components of smoking. Although nicotine could be replaced with nicotine sprays or inhalers, the associated sensory effects of these delivery systems would then need to be taken into account in the effect of nicotine: the nasal spray produces an aversive nasal mucosa irritation; the nicotine inhaler can elicit the cough reflex (16,17). To optimize cerebral blood nicotine levels, further studies should use higher peripheral venous IV doses or even pulmonary artery infusion of nicotine.

The extrapolation of our study findings to smoking is limited because we only addressed the short-term administration of nicotine and airway sensations. Long-term administration may diminish the conditioned cues over time such that the same effect may not be observed. In addition, by not incorporating the holding and manipulating of the cigarette usually associated with smoking, we may have reduced the magnitude of satisfaction and craving reduction, thereby decreasing the power for finding significant results.

Our laboratory has focused on the importance of airway sensations to the smoking behavior in developing new methods for smoking cessation. The airway sensory hypothesis of smoking has led to the promising initial studies of an ascorbic acid inhaler, and a citric acid inhaler (2,10). In another study, a citric acid inhaler combined with the nicotine patch improved short-term smoking cessation rates over the nicotine patch alone (19). If devices like these, which only partially substitute for the sensory effects of smoking, have robust effects on craving, then sensory replacements that are more similar to smoking may have even greater effectiveness.

In this study, we examined the subjective effects of the nicotine and airway sensory components of smoking in combination and separately. We found that many of the positive subjective effects from a denicotinized cigarette were comparable to that of a standard cigarette. Therefore, we hypothesize that replacement of the conditioned sensory cues of smoking with "airway sensory replacement" may improve the effectiveness of nicotine replacement for smoking cessation.

ACKNOWLEDGEMENTS

This study was supported by NIDA grant DA 02665 and the Medical Research Services of the Department of Veterans Affairs.

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