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Smoking Without Nicotine Delivery Decreases Withdrawal in 12-hour Abstinent Smokers

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BUTSCHKY, M. F., D. BAILEY, J. E. HENNINGFIELD AND W. B. PICKWORTH. *Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers.* PHARMACOL BIOCHEM BEHAV **50**(1) 91-96, 1995.—The contribution of sensory factors to smoking satisfaction and nicotine withdrawal symptoms was assessed by evaluating responses to three types of cigarettes: a regular cigarette, a de-nicotinized cigarette (de-nic), and a lettuce leaf cigarette. Doses were varied by requiring subjects to smoke cigarettes using a five-port cigarette manifold. The ratio of the regular or de-nic cigarettes to the lettuce cigarettes was varied across the following values: zero, one, two, and four of five. Seven male smokers were tobacco-deprived for 12 h before testing. On one test day they smoked the de-nic cigarettes, and on another day they smoked the regular cigarettes. Ratings of satisfaction and cigarette liking were directly related to the number of regular or de-nic cigarettes, but were generally higher after the regular cigarette. The regular and de-nic cigarettes were equivalent in reducing acute withdrawal symptoms. Expired CO was similar on both experimental days. The regular cigarette dose-dependently increased plasma nicotine, but the de-nic cigarette did not increase plasma nicotine. These results indicate that sensory characteristics of cigarettes contribute to the abuse liability of smoke-delivered nicotine. The results suggest that smoking cigarettes that do not provide nicotine may temporarily suppress cigarette withdrawal symptoms.

De-nicotinized cigarette Tobacco withdrawal Sensory factors Smoking behavior

AS DESCRIBED in the Surgeon General's Report on the Health Consequences of smoking (25), cigarette smoking is a process involving both behavioral and pharmacologic factors. For example, reinforcement of cigarette smoking and the discriminative stimulus effects of nicotine depend on nicotinic receptor activation (24) and sensory factors (19). Similarly, the strength of withdrawal symptoms varies as a function of both pharmacologic and environmental factors (6,15). Systematic study of "non-pharmacologic" factors has been confounded by the lack of palatable control cigarettes—for example, lettuce-leaf cigarettes (9).

A new cigarette, Next (Philip Morris, Richmond, VA) was test marketed as a "de-nicotinized" cigarette from which most of the nicotine had been removed from the tobacco. Its nicotine yield rating in machine tests is similar to the widely available "ultralight" cigarettes. The tobacco of ultralight cigarettes, which may contain more than 8 mg nicotine, can actually deliver significant amounts of nicotine to cigarette smokers. Presumably, the Next cigarette would be incapable of delivering significant levels of nicotine to smokers because it is made of de-nicotinized tobacco. The tar yield (10.8 mg) is in the range of medium-yield cigarettes. This de-nic cigarette may provide the taste and odor sensations and cues of a subject's preferred brand of cigarette better than the nontobacco control cigarettes often used in research studies.

Presumably, smoking a de-nicotinized cigarette would evoke all the sensory and environmental cues of smoking, without substantial nicotine delivery. For example, Robinson et al. (18) reported that a de-nicotinized cigarette caused minimal increases in plasma nicotine and heart rate compared with a low-nicotine control cigarette. Robinson et al. did not systematically measure subjective effects. One purpose of the present study was to evaluate the subjective effects from smoking the de-nic cigarette by comparing subjects' responses on a tobacco withdrawal scale (16) and on several "liking" scales after smoking de-nic and regular cigarettes.

Benowitz et al. (1) showed that low-FTC yield nicotine cigarettes (< 0.4 mg/cigarette) produce blood cotine levels equivalent to those produced by high-nicotine yield cigarettes. Herning et al. (13) reported that blood nicotine levels are controlled by how a cigarette is smoked, and that smokers adjust their smoking behavior to optimize nicotine delivery. There-

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fore, a second purpose of this study was to determine whether experimentally directed smoking of this de-nic cigarette would deliver pharmacologically active doses of nicotine to human cigarette smokers.

METHOD

Subjects

Seven male residential subjects participated in the study. All were recruited from the research ward of the Addiction Research Center to participate before or after their scheduled primary study. Subjects were consistent smokers of at least one pack (mean ± SD = 2 6.4 ± 8.5 cigarettes) per day, and their mean Fagerstrom (5) score was 8.43 ± 1.99, indicating a high level of dependence. Nicotine delivery ratings of subjects' usual brand of cigarettes averaged 1.15 ± .19 mg. Subjects' mean age was 35.7 ± 4.3 years. They weighed an average of 79.5 ± 10.0 kg. Before beginning the study, subjects gave informed consent in accordance with guidelines of the Department of Health and Human Services and the local institutional review board. The day before the experimental sessions started, the subjects were familiarized with the testing room, equipment, and smoking procedures.

Cigarette Administration

Cigarettes were smoked five at a time through a five-port manifold similar to one described by Chait and Griffiths (3). Subjects puffed through a mouthpiece centrally located on the side opposite to the ports, thus receiving smoke from all five cigarettes (Fig. 1).

Three brands of nonmenthol cigarettes were used: "regular" (Marlboro King Size Soft Pack [Philip Morris]; nicotine delivery = 1.1 mg/cigarette, tar = 15.9 mg/cigarette); the test "de-nic" cigarette (Next; nicotine = .09 mg/cigarette, tar = 10.8 mg/cigarette) and a "lettuce cigarette" (Bravo, a nontobacco cigarette, Safer Smokes, Inc., Ft. Lee, NJ). The cigarette manifold always contained five cigarettes. On each study day, subjects smoked varying numbers of tobacco cigarettes (regular or de-nic) in the following treatment order: zero tobacco cigarettes (five lettuce cigarettes); one tobacco cigarette and four lettuce cigarettes; two tobacco and three lettuce cigarettes; four tobacco and one lettuce cigarette. Thus, subjects smoked the equivalent of: zero, one, two, or four of five tobacco cigarette during each smoking treatment. The order of tobacco cigarette type varied randomly across subjects.

Procedure

Subjects were required to abstain from tobacco, caffeine, and other drugs for 12 h before the 3.5-h testing sessions. The two testing sessions were completed on two different days. An intravenous catheter was inserted into an arm vein at 0800 h of the study day for blood collection. Testing began at 0900 h and consisted of the four smoking treatments occurring about 45 min apart. Physiologic and subjective measurements were taken throughout the session.

For each smoking treatment, all five cigarettes were lit by the experimenter. The subjects were instructed to puff every 30 s for a total of eight puffs according to the following procedure: puff for 1 s, inhale and hold smoke for 5 s, then exhale. Although during smoking treatments the subjects puffed according to instructions, actual puff duration was recorded by a computer via a "pressure tube" that was connected to simulate activation of the computer mouse, which turned the computer timer on and off. Duration of each puff was then saved to a file.

Systolic and diastolic blood pressure, pulse, oral and skin temperature, and pupil diameter were recorded every 8 min for 45 min after the smoking treatments. Exhaled carbon monoxide (CO) was measured at the beginning and the end of each study day on an Ecolyzer carbon monoxide monitor (National Draeger, Pittsburgh, PA). Venous plasma samples for nicotine and cotinine analysis were obtained immediately before and 10 min after each of the four smoking treatments.

Subjects completed a scale measuring tobacco withdrawal symptoms (16) before and after the testing session and on an orientation day, when subjects were smoking ad lib. Other subjective questionnaires were administered by means of a computer 5 min after smoking treatments. Computerized visual analog scales of cigarette ratings were used; subjects used the computer mouse to place a mark on a 95-mm horizontal line to index their endorsement of the following phrases: "drug strength," "good effects of drug," "bad effects of drug," "like effects of drug," "cigarette strength," "hotness of cigarette," "harshness of cigarette," "draw level of cigarette," "taste of cigarette," "overall satisfaction," "good effects of cigarette," and "bad effects of cigarette." Anchors for visual analog lines were specific to each question; for example, "like effects of drug" was scored between "not at all" and "very much." A short form of the Addiction Research Center Inventory (ARCI) (10), which included the MBG, PCAG, and LSD subscales (17), and the Single Dose Questionnaire (8) were administered after each smoking treatment.

Statistical Analyses

Data from this within-subject, repeated-measure study were analyzed by univariate analyses of variance (ANOVA) with the two main factors of cigarette type (two levels: regular and de-nic) and dose (four levels: zero, one, two, and four of five tobacco cigarettes) using SPSS software. When the ANOVA indicated significant effects of cigarette type, dose, or interaction and adjustments of the degrees of freedom were made for the repeated measure design. Posthoc comparisons were made using a Studentized Tukey's test of critical differences and Student *t*-tests (23).

RESULTS

Both tobacco cigarette types caused similar and significant carbon monoxide boosts (Fig. 2A) over the study day [$F(1, 6) = 23.05$, $p < 0.01$], indicating that subjects smoked with equal rapacity on both days. This result was supported by the puff duration, which averaged 1.3 s over each dose (number of cigarettes) condition and for each cigarette type. For plasma nicotine boosts (from immediately before to 10 min after treatment), the ANOVA showed a cigarette-type effect [$F(1, 6) = 20.66$, $p < 0.01$], a dose effect [$F(3, 18) = 63.76$, $p < 0.001$], and an interaction [$F(3, 18) = 56.96$, $p < 0.001$], indicating that the regular cigarette caused increases in plasma nicotine that were orderly, dose-dependent, and significant. Average increases in venous plasma nicotine levels were: − 1.4ng/ml after the zero treatment, 2.4 ng/ml after the one of five treatment, 6.4 ng/ml after the two of five treatment, and 10.1 ng/ml after the four of five treatment (Fig. 2B). The de-nic cigarette produced no significant increases in venous plasma nicotine. The maximal increase in venous plasma nicotine after de-nic cigarette was 0.8 ng/ml in the four of five

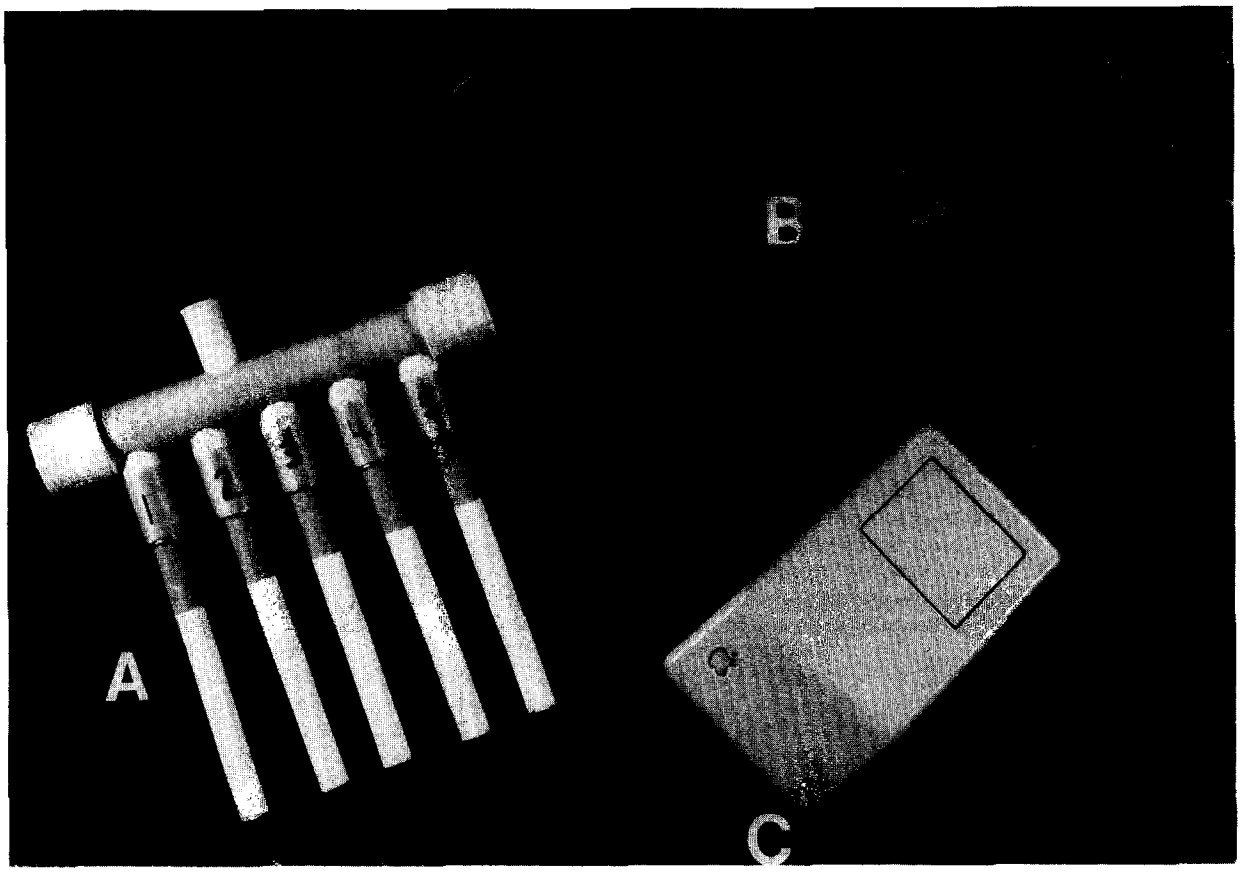

FIG. 1. Five-port cigarette manifold (A) connected to a computer mouse (C) by a plastic tubing (B). Modified after Chait and Griffiths (3).

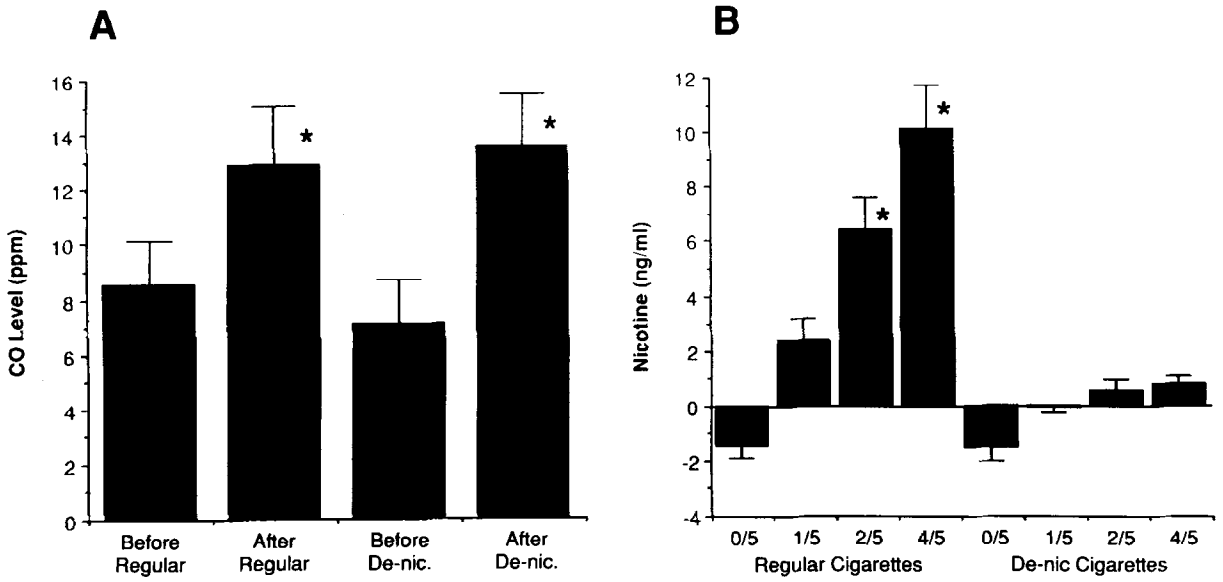

FIG. 2. (A) Mean exhaled carbon monoxide (CO) levels before and after regular and de-nic cigarettes. Measures were collected before and after the four smoking treatments on each experimental day. *Significant differences ($p < 0.01$, Tukey critical difference) from presmoking levels. (B) Venous plasma nicotine increases after each smoking treatment. *Plasma nicotine is significantly different ($p < 0.01$) from zero of five cigarettes (all lettuce cigarette) condition.

de-nic treatment condition. Neither tobacco cigarette significantly increased plasma cotinine levels; in fact, there was a significant decrease in cotinine levels after the zero treatments; the decreases averaged 6.6 and 10.1 ng/ml on regular and de-nic cigarette days, respectively.

Heart rate was significantly higher after the regular cigarette than after de-nic [$F(1, 6) = 22.59, p < 0.01$]. Posthoc paired t-test showed significant increases from 8 min before to 5 min after the two highest doses of regular cigarette (two of five cigarettes: [6 df] t = 7.1; $p = 0.004$, four of five cigarettes: [6 df] t = 3.09, $p = 0.02$). Heart rate was not significantly affected by the de-nic cigarettes. Neither the regular nor de-nic cigarette significantly changed systolic or diastolic blood pressure.

As shown in Fig. 3A, both the regular and de-nic cigarettes significantly reduced scores on the tobacco withdrawal scale (16) to a similar extent [$F(1, 6) = 9.34, p < 0.05$]. After regular cigarette treatments, average total scores decreased from 10.0 to 5.3, and after de-nic, from 10.7 to 6.6. Before either treatment condition, the withdrawal scores were significantly elevated compared with the scores on an orientation day (average score of 2.3) on which the subjects were not deprived (vs. regular, t[6 df] = 3.63, $p < 0.01$; vs. de-nic, t[6 df] = 4.86, $p < 0.01$). Scores for the "craving for nicotine" item of the tobacco withdrawal scale (16) (Fig. 3B) were also significantly reduced after the regular cigarette (from 3.7 to 1.7) and de-nic (from 4.0 to 2.6). The craving item accounted for approximately 36% of subjects' total scores on the tobacco withdrawal scale.

Five subjects completed the Single Dose Questionnaire (8) (Fig. 4A). Subjects rated their "liking of the drug" from "1—not at all" to "5—an awful lot," significantly higher with increasing doses of regular cigarette or de-nic [$F(3, 12) = 6.72$, $p < 0.01$].

Results for the visual analog questions (Figs. 4B–D) generally indicated that both the regular and de-nic cigarettes were more acceptable than the lettuce cigarette; the regular cigarette was rated consistently higher than the de-nic cigarette. For example, subjects dose-dependently rated both regular and de-nic higher than the all lettuce cigarette (zero of five) condition for "How much do you like the effects of the drug?" [$F(3, 18) = 17.52, p < 0.001$]. Subjects' endorsement of "Rate the good effects of the drug" significantly increased with higher doses of either cigarette [$F(3, 18) = 23.14, p < 0.001$], as did responses to "Rate the overall satisfaction of these cigarettes" [$F(3, 18) = 23.32, p < 0.001$]. There were no effects of cigarette type or dose on answers to "Rate how hot these cigarettes are," "Rate the harshness of these cigarettes," "Rate the draw level of these cigarettes," or "Rate the strength of these cigarettes." On the satisfaction question (Fig. 4D) only, there was a significant effect of cigarette type [$F(1, 6) = 8.03, p < 0.05$], indicating that the regular cigarette was, overall, more satisfying than de-nic. There were no significant effects on subject ratings of subscales of the ARCI.

DISCUSSION

The main finding of this study was that a de-nicotinized cigarette that did not increase plasma nicotine levels and had no cardiovascular effects produced subjective effects of liking and satisfaction. The de-nic cigarette significantly reduced acute nicotine withdrawal symptoms in 12-h tobacco-deprived smokers. These results support and extend the observation that contextual and nonpharmacologic factors that are known to influence acute nicotine effects and nicotine craving are also important in the relief of cigarette withdrawal symptoms (6,15).

The smoking procedure in this study caused significant increases in exhaled CO after smoking either regular or de-nic, indicating that smoke inhalation was similar in each of the experimental sessions and to ad lib smoking (25). The regular cigarette delivered nicotine in amounts similar to those reported by Benowitz et al. (2), (boost of 10 ng/ml 10 min after our high dose) and produced an increase in heart rate. Our

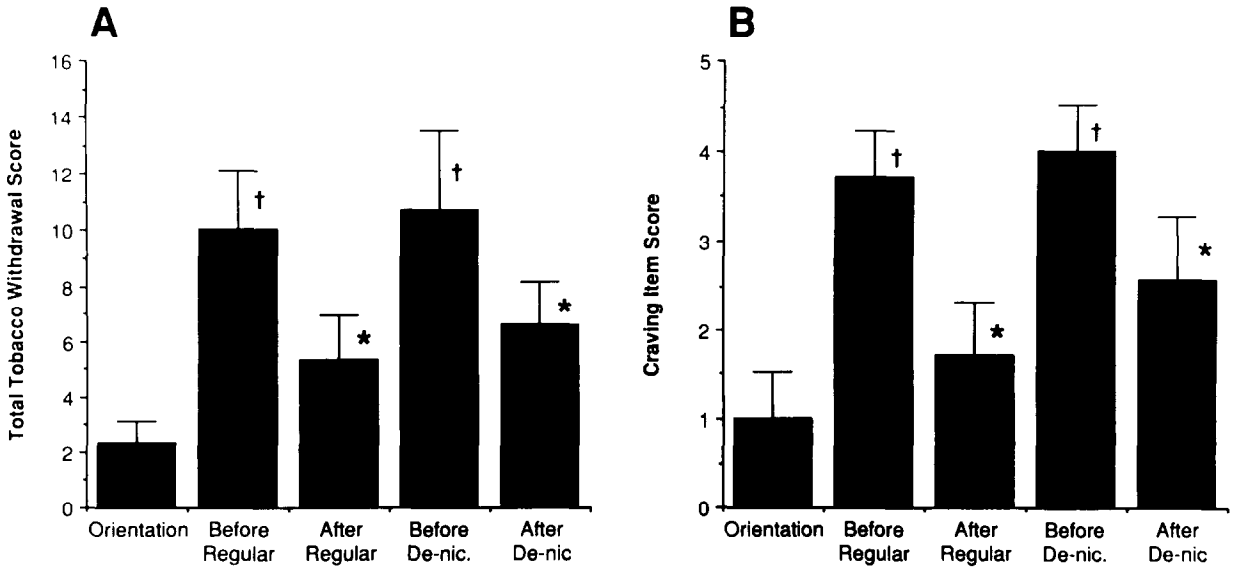

FIG. 3. Mean total tobacco withdrawal scale (A) and craving question (B) scores (16) during ad lib smoking (at orientation), and before and after regular and de-nic cigarettes. Tombstone indicates significant difference between orientation and presession scores. *Significant difference between pre- and postsession scores ($p < 0.05$, paired t-test).

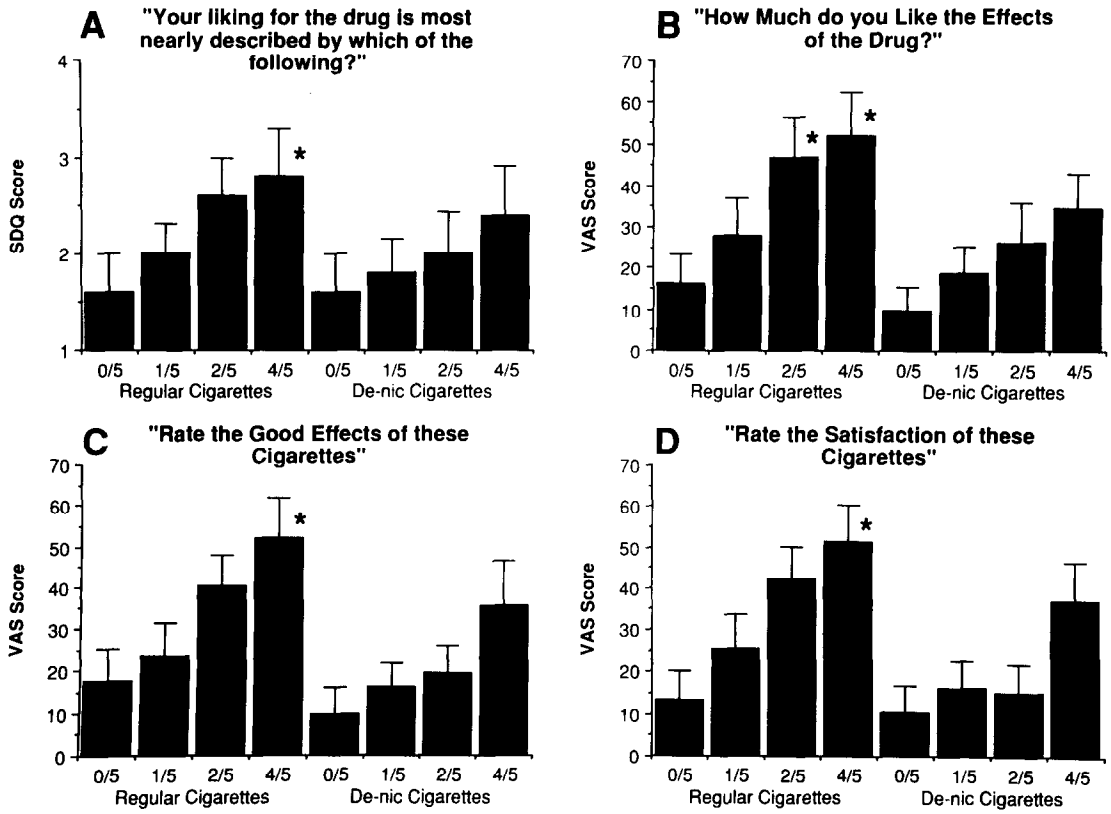

FIG. 4. Mean scores on the drug liking question of the Single Dose Questionnaire (8) (A), and on visual analog scales (B-D). *Mean score is significantly different from zero of five cigarettes, all lettuce cigarette, condition ($p < 0.05$, Tukey critical difference).

results show that the de-nic cigarette did not affect cardiovascular measures. The lack of any physiologic effects after de-nic cigarettes is in concert with the lack of change in nicotine levels. On the other hand, Robinson et al. (18) reported that a de-nicotinized cigarette similar to the one used in the present study caused small but significant increases in plasma nicotine and heart rate, although no EEG changes were reported. It is possible that the paced puffing procedure and the intermixture of the nontobacco smoke from the lettuce cigarettes in the present experiment reduced the amount of nicotine exposure compared with the ad lib smoking of single cigarettes in the study by Robinson et al.

Although the de-nic cigarette did not elevate blood nicotine levels, it decreased total withdrawal scores and scores on the nicotine craving question of a widely used tobacco withdrawal scale (16). The effects of the de-nic cigarette were similar in magnitude to those produced by the regular cigarette. Because nicotine withdrawal was measured before any smoking and at the end of the session, the contribution of the lettuce cigarette to nicotine withdrawal could not be estimated. Nevertheless, these results suggest that contextual, somatosensory, and behavioral cues evoked by the experimental smoke delivery were sufficient to cause short-term reductions in nicotine withdrawal.

Both de-nic and regular cigarettes caused orderly and dose-related increases in scales measuring satisfaction, liking, and positive effects. The Single Dose Questionnaire (8) has been used extensively to assess subjective feeling from and liking for a single dose of a particular drug. It has been used to measure effects of opiates (17) and of IV as well as smoked nicotine (12). In the present study, the regular cigarette increased the "liking" score on this questionnaire dose-dependently, as expected; the de-nic cigarette also significantly increased liking scores in a dose-related manner. On several visual analog scales measuring satisfaction with the cigarette treatments (e.g., "Rate the satisfaction of these cigarettes," "Rate the good effects of the drug," etc.), subjects' scores increased with increasing doses of de-nic and regular cigarettes. Taken together, these findings indicate that subjects can obtain cigarette satisfaction and temporary relief from tobacco withdrawal without the delivery of nicotine. The results are consistent with the conclusion that the high-abuse liability of cigarettes is partly determined by their sensory characteristics (25). These observations are not unique to cigarettes. The role of the drug delivery system itself as a factor in abuse liability and withdrawal symptoms has been documented for cocaine, heroin, and other drugs of abuse (4).

Taste and odor have long been understood to be important determinants of smoking behavior (22). Cigarette smoke delivers thousands of compounds, including nicotine, that evoke strong conditioned associations important for the maintenance of smoking. Thus, both sensory aspects of smoking (e.g., taste, heat, odor, irritation), the conditioned stimuli, and nicotine delivery, the unconditioned stimulus, determine overall smoking behavior (14,22). The importance of sensory factors in tobacco dependence was also confirmed in a study

by Rose and Hickman (21), in which subjects reported that inhaling aerosol puffs of a 15% citric acid solution produced sensations of strength and harshness similar to those produced by smoking cigarettes, and that some pleasure was associated with these sensations. Furthermore, recent results from Hasenfratz et al. (11) suggest that the tar content of cigarettes is more important than nicotine content in the regulation of smoking behavior. In their study, subjects exhibited compensatory smoking behavior when smoking a low-nicotine, low-tar yield cigarette (0.22 mg/cigarette nicotine, 1.83 mg/cigarette tar) but not when smoking the de-nic cigarette, which has low nicotine and medium tar. In the study by Hasenfratz et al. (11), subjects smoked the experimental cigarettes on the day preceding the experiment. Ratings for the liking and satisfaction for the de-nic cigarettes were much lower than those for the nicotine containing cigarette, suggesting that the beneficial effects of de-nic cigarettes on withdrawal we observed may be subject to rapid extinction.

The limited success of nicotine replacement strategies for smoking cessation also indicates that factors other than nicotine delivery modulate smoking behavior. In fact, neither nicotine gum (15), transdermal patch (20), nor intranasal nicotine administration (7) completely abolished cigarette craving. These findings support the importance of sensory factors in the maintaining of smoking behavior and tobacco withdrawal. They also suggest that future smoking cessation aids that provide sensory stimuli that safely mimic the effects of tobacco smoke may be useful in the relief of acute withdrawal symptoms, and possibly in sustaining tobacco abstinence. Such aids might used alone or in combination with a nicotine replacement medication to achieve tobacco abstinence.

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