Nicotine & Tobacco Research Volume 6, Number 2 (April 2004) 309–319

Taylor&Francis healthsciences

Effects of low nicotine content cigarettes on smoke intake

Jed E. Rose, Frederique M. Behm

[Received 2 October 2002; accepted 8 May 2003]

Cigarettes with selective reductions in nicotine delivery have been considered as potential tools to prevent or treat nicotine dependence or to reduce harm by virtue of reduced nicotine and nitrosamine delivery. An important question is whether individuals smoke these products more intensively, as has been shown to occur with ventilated-filter cigarettes. To investigate this issue, we compared conventional highly ventilated filter cigarettes, having very low tar and nicotine yields when smoked by Federal Trade Commission method (1 mg tar, 2 mg carbon monoxide [CO], .2 mg nicotine), with low nicotine content cigarettes, manufactured from a genetically modified strain of tobacco, which had higher tar but lower nicotine yield (14 mg tar, 13 mg CO, .02 mg nicotine). A total of 16 cigarette smokers participated in two 8-hr sessions (order counterbalanced) during which they smoked each type of cigarette ad libitum. Expired-air CO, plasma nicotine, and smoking topography measures were collected. Subjects showed significant increases in smoking when using the highly ventilated filter cigarettes, and puff volume was significantly greater than with the low nicotine content cigarettes. Subjects achieved an expired-air CO level 74% as high as with the low nicotine content cigarettes; the latter produced CO levels similar to those measured at baseline when subjects smoked their habitual brands of cigarettes. Plasma nicotine levels obtained when subjects smoked the highly ventilated filter cigarettes also were significantly higher than when they smoked the low nicotine content cigarettes. These results indicate that the delivery of substantial amounts of smoke, with selective reductions in nicotine yield, appears to prevent compensatory smoking behavior. Further studies should determine whether similar results are obtained in naturalistic environments.

Introduction

The potential use of low nicotine content cigarettes to reduce cigarette smokers' dependence on tobacco has been considered from a variety of perspectives in recent years. Based on the theory that addiction to tobacco results from nicotine reinforcement, researchers have proposed that limiting the total nicotine content of tobacco might prevent the progression from experimentation to dependence in adolescents (Benowitz & Henningfield, 1994; Henningfield et al., 1998).

Jed E. Rose, Ph.D., V.A. Medical Center, and Department of Psychiatry, Duke University Medical Center, Durham, NC; Frederique M. Behm, B.S., Department of Psychiatry, Duke University Medical Center, Durham, NC.

Correspondence: Jed E. Rose, Ph.D., Nicotine Research Program, Duke University and V.A. Medical Centers, 2200 W. Main Street, Suite B-150, Durham, NC 27705, USA. Tel.: +1 (919)-416-1515; Fax: +1 (919)-286-1388; E-mail: jerose@duke.edu

A second possible application of reduced nicotine tobacco might be in smoking cessation treatment, whereby low nicotine content cigarettes might serve as a behavioral weaning tool to reduce relapse and extinguish the reinforcing value of conditioned stimulus cues (Rose & Levin, 1991).

A third application of low nicotine content cigarettes might be as a reduced toxicity product. In this regard, a type of reduced nicotine product has been developed from a genetically engineered strain of tobacco that does not synthesize significant quantities of nicotine (Conkling, Song, & Mendu, 2002). As a result, presumably the tobacco is also relatively free of nicotine-derived nitrosamines, which are potent carcinogens (Hoffmann, Rivenson, & Hecht, 1996). The impact of this manipulation on the health risks associated with smoking is not known, but one important consideration is how individuals would use this or similar products. In particular, a key issue is whether smokers would compensate for the reduced nicotine delivery by smoking more intensively. The present

ISSN 1462-2203 print/ISSN 1469-994X online

DOI: 10.1080/14622200410001676378

study was undertaken to examine smoking topography when subjects were exposed to a reduced nicotine cigarette that had comparable overall smoke delivery to their customary brands of cigarettes. These cigarettes differed in an important respect from conventional low tar and nicotine cigarettes, which are made from tobacco that contains significant quantities of nicotine (Benowitz et al., 1983). The low tar and nicotine ratings are achieved with standardized Federal Trade Commission (FTC) machine-smoking procedures by virtue of ventilation holes in the filter. Therefore, nicotine and tar deliveries can be increased dramatically by covering these holes or taking larger or more frequent puffs (i.e., compensatory smoking; Kozlowski, Pope, & Lux, 1988). We hypothesized that smokers would not engage in compensatory smoking with a low nicotine content cigarette. To test this prediction, we compared smoking topography and nicotine levels obtained when subjects smoked conventional highly ventilated filter cigarettes and low nicotine content cigarettes during 8 hr of ad libitum smoking. We recruited subjects who were not engaged in a quit-smoking attempt, to avoid the potential problem that smokers planning to quit might restrain their smoking behavior in preparation for quitting.

Method

Design

A total of 16 cigarette smokers participated in two all-day (8-hr) sessions and smoked one type of cigarette ad libitum during each session. In one session they had access to low nicotine content cigarettes (Vector Tobacco Co., Mebane, North Carolina). The standardized yield of these cigarettes, when smoked by the FTC method, was .02 mg nicotine, 13 mg tar, and 14 mg carbon monoxide (CO). Following the method of Benowitz et al. (1983), we determined the total nicotine content of the tobacco to be approximately .1–.3 mg/cigarette. On the other day, subjects had access to conventional highly ventilated filter cigarettes (Now brand, R. J. Reynolds Tobacco Co., Winston-Salem, North Carolina); FTC ratings of smoke yield were .2 mg nicotine, 1 mg tar, and 2 mg CO. The total nicotine content of the tobacco was approximately 6–8 mg/cigarette. The order of presentation of the two smoking conditions was counterbalanced across subjects, and brand markings were covered with cigarette paper (taking care not to block filter vent holes) to keep subjects blind to the condition.

Venous blood samples were collected throughout the session to assess the nicotine intake from the two types of cigarettes. Ratings of satisfaction and other sensory qualities, as well as tobacco withdrawal symptoms, were assessed throughout the day.

Subject recruitment

A total of 16 healthy male and female smokers were recruited from the community by newspaper and radio advertisements and by word of mouth. Subjects were aged 18–65 years and were considered for inclusion in the study if they smoked at least 15 cigarettes each day of a brand of cigarette having an FTC nicotine yield of at least .5 mg. Subjects were screened to exclude major medical problems based on physical examination, electrocardiogram, serum chemistries, complete blood count, and urinalysis and were paid US$200 for participation in the laboratory visits. Subjects were asked whether they intended to quit smoking, and anyone indicating a specific intention to quit within the next 6 months was excluded.

Dependent measures

The main dependent variables assessed in the study included pharmacokinetic indices and subjective responses to the cigarettes, as described below.

Plasma nicotine and cotinine concentrations. Venous blood samples (10 ml) were collected every hour, centrifuged, packed on dry ice, and shipped from Durham, North Carolina, to the Clinical Pharmacology Laboratory at the University of California, San Francisco, for assay by gas chromatograph, modified for use with a capillary column.

Cardiovascular measures. Heart rate and blood pressure were measured hourly, using an automated sphygmomanometer.

Expired-air carbon monoxide. Subjects' expired-air CO concentrations were measured hourly as a measure of smoke intake, using a portable CO monitor (Vitalograph, Inc., Lenexa, Kansas).

Smoking topography. At 15 min before the end of the session, subjects were asked to smoke one cigarette through a special holder that monitored smoking topography (Clinical Research Support System, Plowshare Technologies, Inc., Baltimore, MD), including number of puffs, interpuff intervals, and puff volume, to gain information about mechanisms of behavioral compensation.

Subjective measures. We used an abbreviated version of the Shiffman–Jarvik questionnaire (Shiffman & Jarvik, 1976) to assess craving, negative affect, and arousal. A cigarette evaluation questionnaire (Westman, Levin, & Rose, 1992) was administered immediately after smoking to measure satisfaction, psychological reward, nausea or dizziness, craving

relief, and enjoyment of airway sensations. A sensory questionnaire was administered to assess estimated nicotine delivery; similarity to usual brand; and perceived strength on the tongue, nose, back of mouth and throat, windpipe, and chest. All items of these questionnaires were rated on seven-point scales ranging from 1 (not at all) to 7 (extremely).

Statistical analyses

The main hypothesis was that smokers would show compensatory smoking of the highly ventilated filter cigarettes relative to the low nicotine content cigarettes. This hypothesis was tested by conducting two sets of analyses. One set of analyses compared the indices of smoking behavior (expired-air CO, cumulative puff volume, and number of puffs) between the two experimental test sessions. A second set of analyses compared baseline expired-air CO when subjects smoked their customary brands of high-nicotine cigarettes and the end-of-session values from the low nicotine content cigarette condition. Although not part of a counterbalanced design, this approach was informative in determining the extent to which subjects may have compensated in smoking the low nicotine content cigarettes relative to their usual brands. All statistical analyses were performed using SUPERANOVA and STATVIEW (SAS Institute, Cary, North Carolina). For each dependent measure, cigarette type (low nicotine content vs. highly ventilated filter) and time (hr) were entered as factors in the model. A multivariate approach to repeated-measures analysis of variance (ANOVA) was used, which appropriately took into account the correlation pattern among repeated measurements. To interpret significant interactions, we analyzed the simple effects of one factor for different levels of the other factor (Keppel, 1982). Sex and scores on the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) were entered as univariate predictors and retained in the final model if significant.

The subjective ratings of each type of cigarette were compared using a similar approach, with cigarette type and time as repeated factors. Subjective measures of withdrawal symptoms also were analyzed to determine whether the presumed low intake of nicotine from the low nicotine content cigarettes induced withdrawal discomfort.

Additionally, plasma nicotine concentrations were compared across conditions to confirm that the low nicotine content cigarettes produced negligible levels of systemic nicotine relative to the highly ventilated filter product. Heart rate and blood pressure were analyzed similarly as indirect measures of the pharmacological effects of nicotine.

Procedure

After a screening physical exam, subjects came to the laboratory on two occasions after overnight (12-hr) abstinence from smoking. An indwelling intravenous catheter was inserted into the antecubital vein, and blood samples (10 ml) were collected at baseline and hourly throughout the 8-hr session. Baseline measures of smoking withdrawal symptoms and cardiovascular measures also were collected. Next, subjects were provided with cigarettes of a given type and allowed to smoke ad libitum for 8 hr. Participants were allowed to watch television and read magazines, and lunch was provided approximately halfway through the session. At the end of each session, one cigarette was smoked through the smoking topography measurement apparatus.

Results

Subject characteristics

Table 1 shows characteristics of the subject sample, including age, sex, and information about cigarette smoking. Values for FTC nicotine, tar, and CO yields refer to subjects' habitual brands, and baseline expired-air CO was measured in the afternoon.

Assessment of compliance with overnight smoking abstinence

Expired-air CO levels at the beginning of the sessions were generally low; the mean value was 8.9 ppm ($SD=4.74$). Baseline plasma nicotine levels averaged 5.5 ng/ml ($SD=5.31$), also consistent with good compliance.

Ad libitum smoke intake

Number of cigarettes. Subjects smoked significantly more cigarettes in the highly ventilated filter condition than the low nicotine content condition; mean values were 11.9 cigarettes ($SD=3.01$) for the highly

Table 1. Demographic information ($N=16$).

Characteristic	Mean (*SD*)
Sex	8 Males, 8 females
Race	8 White, 8 Black
Age (years)	36 (15)
Number of cigarettes/day	25 (11)
Years smoked	18 (13)
FTC nicotine (mg)	.74 (.15)
FTC tar (mg)	10.5 (3.3)
FTC carbon monoxide (mg)	12.5 (3.9)
Baseline carbon monoxide (ppm)	27 (12)
FTND score	6.4 (2.5)

FTC, Federal Trade Commission; FTND, Fagerström Test for Nicotine Dependence.

ventilated filter cigarettes vs. 10.4 cigarettes (SD= 2.90) for the low nicotine content cigarettes, $F(1, 15) = 7.30$, $p = .02$.

Expired-air carbon monoxide. The end-of-session (8-hr) timepoint was taken as a cumulative measure of smoke intake. To assess compensatory smoking behavior, we divided the expired-air CO values at the end of the session by the values of standardized (FTC) CO delivery for each type of cigarette. This defined a "compensation index"; for example, in the highly ventilated filter condition (FTC delivery of 2 mg CO), if a subject had a CO reading of 10 ppm, this subject would be assigned a compensation index of 10/2 = 5.

The compensation index differed significantly between the low nicotine content and highly ventilated filter conditions, $F(1, 15) = 77.05$, $p = .0001$, and, as shown in Figure 1, compensation was significantly higher in the highly ventilated filter condition. Although compensation was greater with the highly ventilated filter cigarettes than with the low nicotine content cigarettes, absolute CO levels were higher with the latter because of the much higher smoke yield; mean end-of-session CO was 30.6 ppm (SD=11.82) vs. 22.6 ppm (SD=9.49) for the highly ventilated filter cigarettes ($p = .0001$).

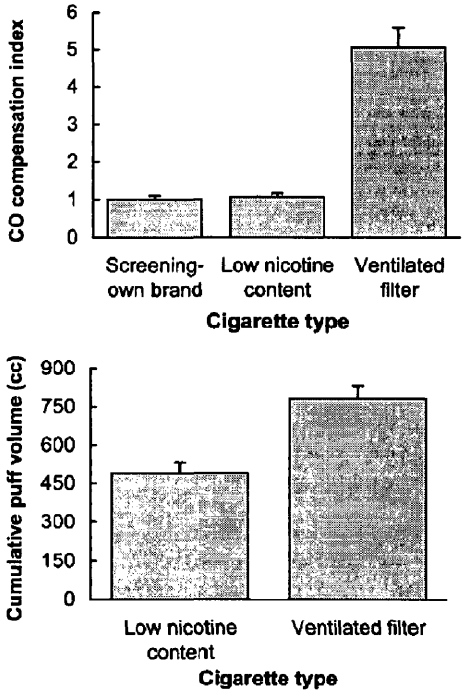

Figure 1. Indices of smoking compensation are depicted for the low nicotine content and highly ventilated filter cigarettes. Top panel shows the mean (±*SEM*) compensation index (ratio of end-of-session expired-air carbon monoxide [CO] to the standardized CO delivery of each type of cigarette); bottom panel shows the mean (±*SEM*) cumulative puff volume taken from a single test cigarette of each type smoked at the end of the session.

We also compared the low nicotine content cigarettes to the usual brand, and the compensation index for the two cigarettes did not differ significantly; mean values were 2.2 (SD=.95) for the usual brand baseline vs. 2.4 (SD=.92) for the low nicotine content condition. At baseline, mean CO levels were 27.1 ppm (SD=12.22) for the usual brand.

Smoke intake from test cigarette. Specific smoking topography parameters were analyzed from the single cigarette smoked through the smoking topography apparatus. As shown in Figure 1, cumulative puff volume was significantly higher for the highly ventilated filter cigarettes, $F(1, 14) = 27.06$, $p = .0001$. A trend was observed in which subjects took a greater number of puffs from this cigarette, $F(1, 14) = 3.72$, $p = .07$.

Plasma nicotine. Plasma nicotine levels were significantly higher in the highly ventilated filter condition relative to the low nicotine content condition, $F(8, 104) = 3.81$, $p = .0006$. The difference emerged as of the first hour (Figure 2) and was maintained consistently throughout the session. Mean plasma nicotine in the highly ventilated filter condition was positively correlated with the smoking compensation index ($r = .8$), $F(1, 13) = 24.33$, $p = .0003$.

Vent blocking. All cigarette butts were examined for signs of filter vent blocking, by which smokers can increase smoke delivery, using observations of filter tar stain patterns as described by Kozlowski et al. (1988). Cigarette butts from 15 out of 16 subjects were found to show some evidence of vent blocking in the highly ventilated filter cigarette condition.

Cigarette ratings. Because different subjects smoked different numbers of cigarettes, we analyzed ratings from the first six cigarettes (all subjects smoked at least six cigarettes), with cigarette number as a repeated factor. This analysis allowed us to look for trends with exposure, such as habituation or extinction.

Ratings of liking showed a main effect of cigarette type; the highly ventilated filter cigarettes were rated higher in liking, as shown in Figure 3, $F(1, 14) = 6.79$, $p = .02$. The satisfaction scale of the cigarette evaluation scale (mean of satisfaction and good taste) showed a significant effect of cigarette type; the highly ventilated filter cigarettes were rated higher in satisfaction, $F(1, 15) = 6.82$, $p = .02$.

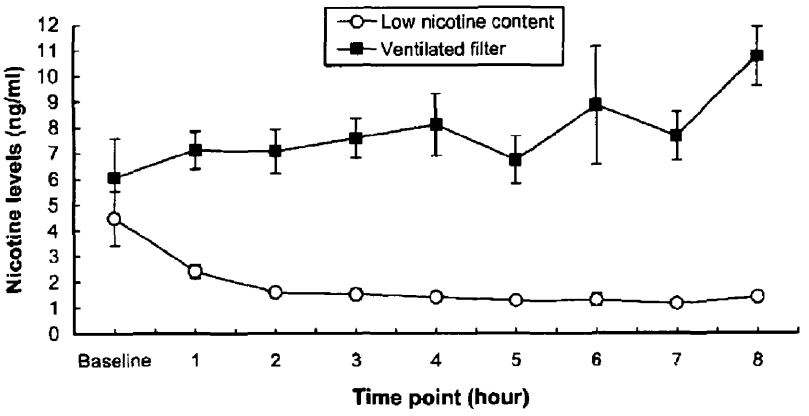

Figure 2. Plasma nicotine levels. Plasma nicotine concentrations (mean ± *SEM*) each hour are depicted for the two cigarette conditions.

No significant difference was observed between the low nicotine content and highly ventilated filter cigarettes in the craving reduction item of the cigarette evaluation questionnaire; mean ratings were 3.3 ($SD = 1.22$) vs. 3.8 ($SD = 1.27$), $p = .2$.

The psychological reward scale showed main effects of cigarette number, $F(5, 75) = 2.55$, $p = .03$, and cigarette type, $F(1, 15) = 4.79$, $p = .04$; ratings decreased across successive cigarettes, and the highly ventilated filter cigarettes scored higher overall.

Subjects also rated the enjoyment of respiratory tract sensations from the highly ventilated filter cigarettes higher initially than for the low nicotine content cigarettes; for the cigarette type × cigarette number interaction, $F(5, 75) = 5.43$, $p = .0003$. A follow-up analysis of simple effects showed that the highly ventilated filter cigarettes were rated higher for cigarette 1, $F(1, 75) = 41.36$, $p = .0001$; cigarette 2, $F(1, 75) = 17.59$, $p = .0001$; and cigarette 4, $F(1, 75) = 6.33$, $p = .01$.

The ratings of the intensity of respiratory tract sensations showed a cigarette type × region interaction, $F(4, 56) = 5.51$, $p = .0008$. The interaction, as shown in Figure 4, reflected the fact that the low nicotine content cigarettes were rated significantly stronger in certain regions of the respiratory tract – that is, in the back of mouth, $F(1, 14) = 8.28$, $p = .01$; in the windpipe, $F(1, 14) = 8.52$, $p = .01$; and on the tongue, $F(5, 70) = 2.40$, $p = .045$, for the cigarette type × cigarette number interaction, but not in the nose or chest. Intensity ratings for the back of the mouth and throat also showed an interaction with FTND score when the latter was included as a covariate, $F(1, 65) = 6.77$, $p = .02$; mean ratings for mouth and throat intensity are broken down by low vs. high FTND score in Figure 5.

Ratings of estimated nicotine delivery also showed a significant cigarette type × FTND score interaction, $F(1, 72) = 6.93$, $p = .02$. When broken down by low vs. high FTND score (above or below the mean), the low-FTND subjects tended to rate the highly ventilated filter cigarettes higher in nicotine delivery, whereas the high-FTND subjects showed the opposite trend (Figure 5).

No significant differences were found between the two cigarettes in ratings of similarity to subjects' usual brands, and no significant effects of the aversion scale of the cigarette evaluation questionnaire were observed.

Smoking withdrawal symptoms

Craving. Craving for cigarettes showed a significant main effect of hour, $F(8, 122) = 16.9$, $p = .0001$, but the effect of cigarette type was not significant (Figure 6).

Negative affect. Negative affect showed a significant main effect of hour, $F(8, 112) = 4.77$, $p = .0001$, and a significant cigarette type × hour interaction, $F(8, 112) = 2.31$, $p = .02$. This interaction reflected the fact that negative affect declined over time in the highly ventilated filter condition to a greater extent than in the low nicotine content condition (note in Figure 6 the trend for a difference at baseline). An analysis of simple effects at each hour indicated that negative affect in the highly ventilated filter condition was significantly lower than in the low nicotine content condition from hour 2 on.

Arousal. No significant effects of cigarette type or hour were detected for subjective arousal.

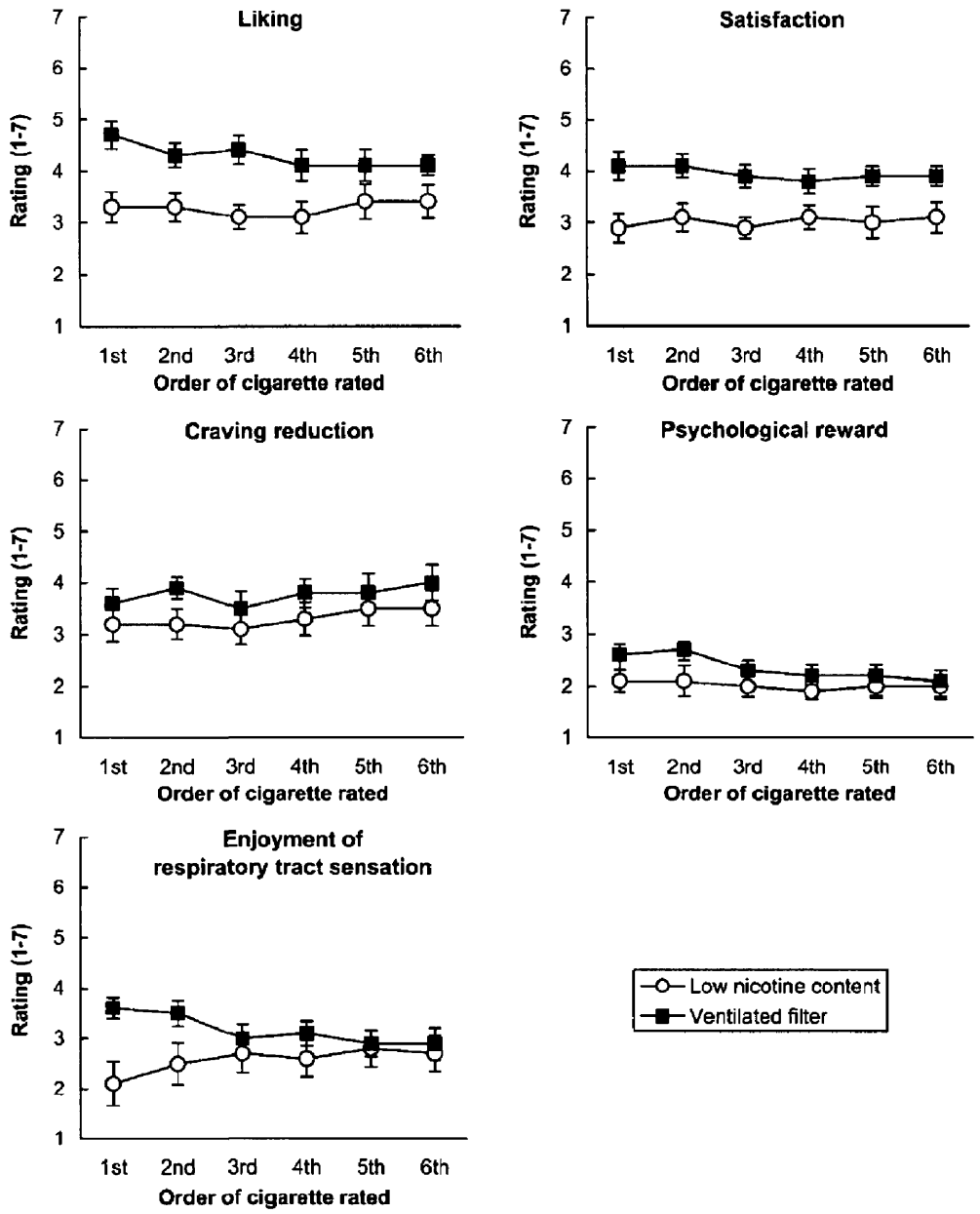

Figure 3. Ratings (mean ± *SEM*) of the first six cigarettes smoked during each condition.

Appetite. Appetite showed a significant main effect of hour, $F(8, 112) = 17.04$, $p = .0001$, with appetite increasing over the morning and decreasing after lunch, but no effect was observed for cigarette type.

Cardiovascular measures. Aside from a significant main effect of hour, $F(8, 112) = 9.16$, $p = .0001$, heart rate (measured while seated) showed a trend to be higher in the highly ventilated filter condition: 68.8 beats per minute (bpm) ($SD = 11.13$) vs. 66.7 bpm ($SD = 11.40$), $F(1, 30) = 3.56$, $p = .08$. Systolic blood pressure also showed a trend to be higher in the highly ventilated filter condition: 121 mmHg ($SD = 15.2$) vs. 116 mmHg ($SD = 10.8$), $F(1, 15) = 3.85$, $p = .07$. Diastolic blood pressure showed only an effect of hour, $F(8, 120) = 2.03$, $p = .048$.

Discussion

The main result of this study was that smokers showed the expected compensatory increase in smoking behavior when using highly ventilated filter

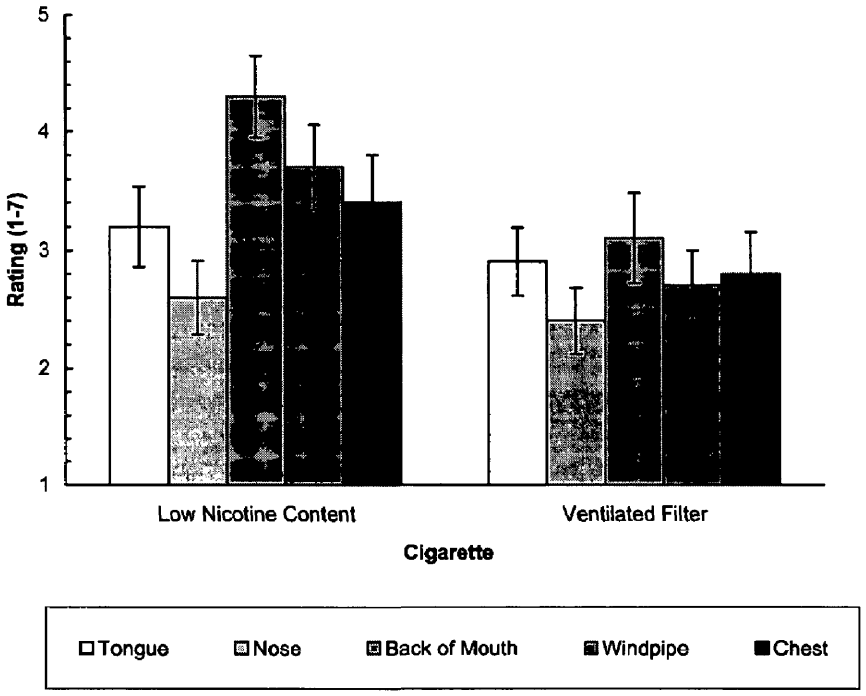

Figure 4. Ratings (mean ± *SEM*) of the intensity of respiratory tract sensations when smoking the low nicotine content and highly ventilated filter cigarettes (ratings averaged over the first six cigarettes smoked).

cigarettes relative to the low nicotine content cigarettes. This result was shown by a significantly higher ratio of expired-air CO level to FTC ratings and by greater cumulative puff volume as measured with a test cigarette using the smoking topography apparatus. If subjects had smoked all cigarettes equivalently, their expired-air CO with the highly ventilated filter cigarettes should have been only 17% of that for the low nicotine content cigarettes, but in fact it was 74% as high. Moreover, cumulative puff volume for the test cigarette was 59% greater with the highly ventilated filter cigarettes.

Although the study design did not include a third session presenting the usual-brand cigarettes, the comparison with baseline measures was informative. The expired-air CO levels at the end of the session with the low nicotine content cigarettes were similar to baseline levels, which are representative of CO levels in other studies (Rose, Behm, & Westman, 1998). Cumulative puff volume also was in the range typically reported for high nicotine yield cigarettes (Buchhalter & Eissenberg, 2000; Herning, Jones, Bachman, & Mines, 1981; Russell, Sutton, Iyer, Feyerabend, & Vesey, 1982). These findings suggest not only that subjects compensated when smoking the highly ventilated filter cigarettes but also that no appreciable compensation occurred when subjects used the low nicotine content cigarettes.

Other differences in smoke chemistry or cigarette parameters (e.g., burn characteristics, pressure drop) might have influenced the results obtained with the low nicotine content cigarettes. However, the findings regarding compensation are in accord with results from other studies of denicotinized cigarettes (manufactured from tobacco from which the nicotine was extracted), showing that low nicotine content cigarettes were smoked similarly to high nicotine content cigarettes (Nil & Battig, 1989; Pickworth, Fant, Nelson, Rohrer, & Henningfield, 1999; Robinson, Pritchard, & Davis, 1992; Robinson, Houtsmuller, Moolchan, & Pickworth, 2000). For example, Pickworth et al. (1999) reported similar CO levels after smoking standard nicotine containing and denicotinized cigarettes.

The present results agree with those of previous studies conducted in our program. In one laboratory study, subjects did not compensate when exposed to a high sensory and low nicotine smoking condition but did compensate in a low sensory and low nicotine condition, with cigarette pressure drop equated across conditions (Rose, Behm, & Levin, 1993). In another study in which cigarette smokers attempting to quit smoking were first switched for 2 weeks to denicotinized cigarettes, indices of smoking behavior (cigarettes smoked per day, expired-air CO) showed no evidence of compensation (Rose, Westman, & Behm, 2001). The present study, which involved only participants who

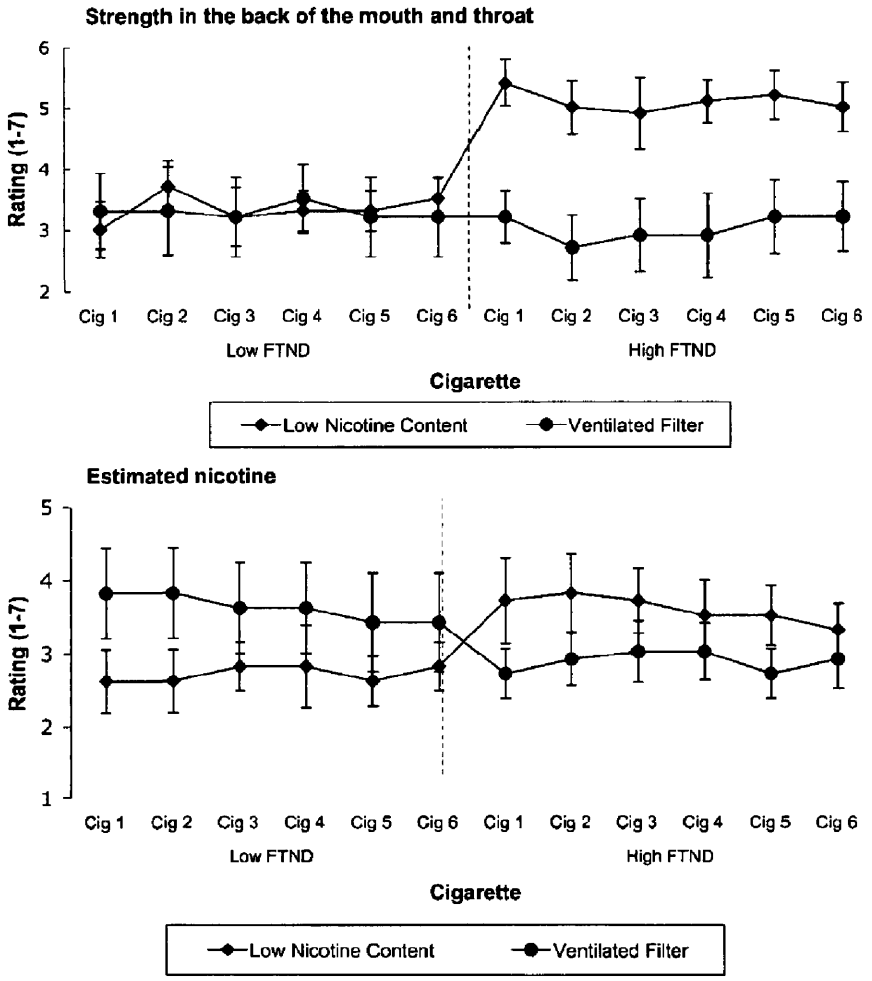

Figure 5. Ratings (mean ± *SEM*) of the intensity of sensations in the back of mouth and throat, and estimated nicotine delivery, for the low nicotine content and highly ventilated filter cigarettes. Results are plotted separately for subjects with low (≤6) or high (≥7) scores on the Fagerström Test for Nicotine Dependence (FTND).

were not trying to quit smoking, lends additional support to the conclusion that smokers do not compensate when using low nicotine content cigarettes.

Recent investigations of longer-term smoking (over several weeks) of products having selective reductions in nicotine yield, over a range of nicotine deliveries, are bolstering the conclusion that compensation (assessed by CO measurement) does not occur when FTC tar delivery is maintained (Benowitz, 2003; Rose, 2003). However, additional studies will be needed to delineate fully the range of conditions under which low nicotine content cigarettes are smoked without compensation.

Our results raise the intriguing question of why smokers do not smoke the low nicotine content cigarettes more intensively. At least four plausible explanations may be considered:

1. The nicotine delivery may have been so low that compensation was discouraged because smokers perceived any attempts at so doing as being ineffectual (i.e., a 350-cc puff would have been needed to obtain as much nicotine as from a standard 35-cc puff of the highly ventilated filter cigarettes, which was not feasible).
2. Taking larger puffs would not result in an immediate perception of higher nicotine impact, because the sensory "signal" of nicotine was obscured by the "noise" of the tar (Gullotta, Kuhn, von Holt, & Heintze, 2000).
3. The substantial smoke delivery of the low nicotine content cigarettes provided sensorimotor cues that satisfied craving for cigarettes and reduced the motivation to smoke more intensively than usual. Sensory ratings (e.g., sensations in back of mouth and

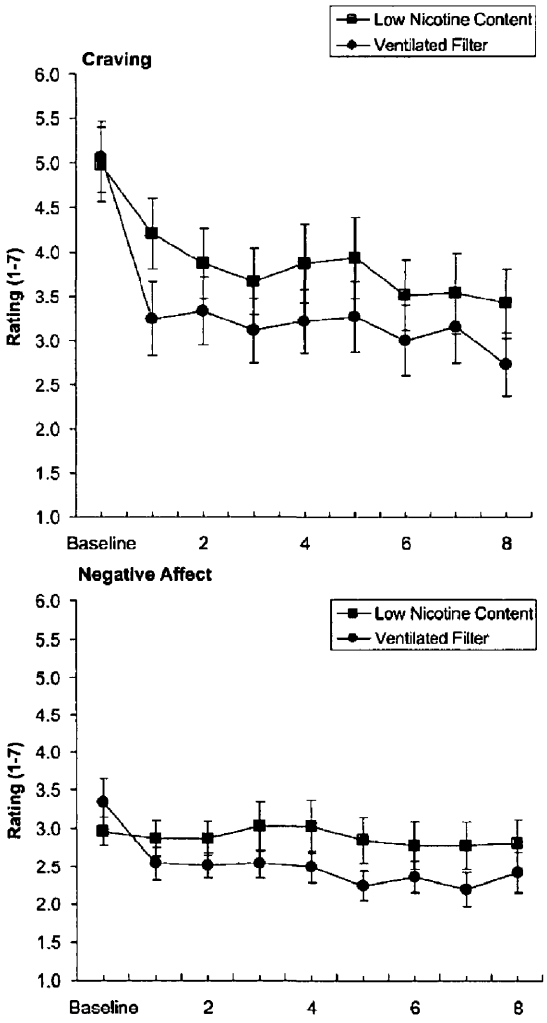

Figure 6. Craving for cigarettes and negative affect (mean ± *SEM*) while smoking the low nicotine content and highly ventilated filter cigarettes.

throat) were indeed higher for the low nicotine content cigarettes than for the highly ventilated filter cigarettes.

4. The low nicotine content cigarettes were perceived as aversive, relative to the other brands of cigarettes, which discouraged more intensive smoking.

Poststudy interviews conducted with participants offered some support for all of these explanations. Recent results from a field study (Rose, 2003) of cigarettes having .6 mg, .3 mg, and less than .05 mg nicotine delivery, but having equal tar delivery, indicated that expired-air CO concentrations did not change relative to baseline, during at least 2 weeks of exposure to each product. These results lend support to explanations 2, 3, or 4 over explanation 1, because it would not have been difficult to compensate when smoking cigarettes having .3 mg or .6 mg FTC nicotine yields.

Although a significant degree of smoking satisfaction was provided by the low nicotine content cigarettes, the enjoyment of respiratory tract sensations was initially less than for the highly ventilated filter cigarettes. This finding supports the view from previous research that nicotine-related sensations are part of the enjoyment of smoking (Ginzel & Eldred, 1977; Jones, Lo, & Simon, 2002; Pritchard, Robinson, Guy, Davis, & Stiles, 1996; Rose, Westman, Behm, Johnson, & Goldberg, 1999; Wang et al., 2001).

Aside from sensory effects, negative affect was significantly higher in the low nicotine content cigarette condition, which was expected, given that negative mood is a well-documented nicotine withdrawal symptom (Hughes, Gust, Skoog, Keenan, & Fenwick, 1991; Shiffman & Jarvik, 1976). In contrast, Pickworth et al. (1999) and Butschky, Bailey, Henningfield, and Pickworth (1995) reported equivalent reductions in withdrawal symptoms when subjects smoked denicotinized and standard nicotine-containing cigarettes; however, a separate analysis of withdrawal symptoms apart from craving was not provided. Moreover, in the Pickworth et al. study, denicotinized cigarettes did not produce the electroencephalographic changes associated with smoking standard nicotine-containing cigarettes.

In the present study, we did not observe a reduction in withdrawal symptoms apart from craving when subjects used the low nicotine content cigarettes (although ratings were not high). In addition, cigarette ratings indicated that little psychological reward was obtained from the low nicotine content cigarettes. The fact that nicotine withdrawal symptoms may occur upon abrupt switching to low nicotine content cigarettes suggests that compliance with use of these cigarettes in longer-term studies might be enhanced by introducing them gradually. Alternatively, nicotine replacement therapy might be provided concurrently with use of low nicotine content cigarettes; in a previous study, we showed that compliance with the use of low nicotine content cigarettes was facilitated by having subjects wear nicotine patches (Rose et al., 2001).

The results of the present study have potential clinical implications for use of low nicotine content cigarettes as a means to combat nicotine dependence or as an approach to harm reduction. With respect to the prevention or treatment of nicotine dependence, analyses of plasma nicotine and cardiovascular variables suggested that the levels of nicotine achieved when smoking these cigarettes are insignificant from a pharmacological standpoint. One also would expect that use of these cigarettes would provide insufficient nicotine to establish nicotine dependency in smoking-naïve individuals, if tobacco regulation could effectively prevent access to high-nicotine cigarettes. Arguments in support of the regulation of tobacco nicotine content to reduce nicotine exposure have been

presented by Benowitz & Henningfield (1994) and Henningfield et al. (1998). However, factors establishing tobacco dependency are not well understood. Processes may exist whereby dependency on cigarettes could be generated even with extremely low intake of nicotine, for example, through receptor desensitization, which can occur with chronic exposure to even very low levels of nicotine (Grady, Marks, & Collins, 1994) or through intake of nonnicotine constituents of tobacco (e.g., monoamine oxidase inhibitors; Fowler et al., 1996). Additionally, the extent to which a product marketed as "nonaddictive" might appeal to youth is unknown. Such a marketing approach could lead to more initiation of smoking among teenagers, with the risk that they would progress to nicotine-containing products; by contrast, smoking low nicotine content tobacco cigarettes might divert young smokers from nicotine addiction and ultimately reduce their risk of lifetime smoking. Surveillance studies should be conducted to assess both of these possibilities as products having selective reductions in nicotine delivery are introduced into the marketplace.

A final clinical relevance of our findings pertains to whether low nicotine content cigarettes might be useful in a harm-reduction approach for smokers who may be unwilling or unable to achieve total abstinence. Although total abstinence is preferable in terms of reduced toxin exposure, the question has been posed as to whether smoking tobacco products with reductions in the delivery of various toxins could result in a significant reduction in health risks (Hughes, 1998). The low nicotine content cigarettes studied here were presumably low in nicotine-derived nitrosamines, which could potentially affect the risk of users developing tobacco-related cancers. However, the relative roles of nitrosamines vs. polycyclic aromatic hydrocarbons in tobacco-related carcinogenesis have yet to be determined (Hoffman, Djordjevic, & Hoffman, 1997). Aside from a potential reduction in carcinogen exposure, another potential benefit that may be considered is the reduction in nicotine intake per se. The role of nicotine in tobacco-related disease has been controversial, and although some authorities have argued that it is of minor health concern, significant doubts remain. Nicotine causes vasoconstriction, may promote thrombosis and atherosclerosis, and impairs insulin sensitivity, which in turn may lead to cardiovascular disease (Assali, Beigel, Schreibman, Shafer, & Fainaru, 1999; Benowitz, 1988). Recently published studies using laboratory models have shown that nicotine, at physiologically relevant concentrations, may promote arteriogenesis (Heeschen, Weis, & Cooke, 2003), which conceivably could increase the blood supply to tumors and may inhibit apoptosis (Suzuki, Bayna, Molle, & Lew, 2003), which might prevent cancerous cells from self-destructing. These results (a) raise the possibility that nicotine may interact with other mutagenic smoke constituents to promote carcinogenesis and (b) call into question the often-made assertion that nicotine plays little or no role in smoking-related disease. However, even if a real reduction in toxin exposure were achieved through reductions in nicotine delivery, any assessment of harm reduction from use of a low-nicotine tobacco product would need to take into account whether smokers' beliefs about its safety would deter efforts to achieve abstinence from smoking.

Further studies of low nicotine content cigarettes are needed to more fully evaluate their potential application in reducing tobacco-related disease, through their use either as smoking cessation or prevention tools or as reduced-harm products for smokers who do not quit.

Acknowledgments

This research was supported by an unrestricted donation from Vector Tobacco Co. to Duke University Medical Center. The authors appreciate the assistance of James Bates, Tyler Buckner, Benjamin Isbell, and Francis Kim in conducting this study.

References

Assali, A. R., Beigel, Y., Schreibman, R., Shafer, Z., & Fainaru, M. (1999). Weight gain and insulin resistance during nicotine replacement therapy. *Clinical Cardiology, 22,* 357–360.

Benowitz, N. L. (1988). Toxicity of nicotine: Implications with regard to nicotine replacement therapy. In O. F. Pomerleau, & C. S. Pomerleau (Eds.), *Nicotine replacement: A critical evaluation* (pp. 187–218). New York: Liss.

Benowitz, N. L. (2003, February). *Denicotinized or nicotine-free cigarettes as research and treatment tools.* Abstract of presentation at the ninth annual meeting of the Society for Research on Nicotine and Tobacco, New Orleans, LA.

Benowitz, N. L., Hall, S. M., Hernining, R. I., Jacob, P. I., Jones, R. T., & Osman, A.-L. (1983). Smokers of low-yield cigarettes do not consume less nicotine. *The New England Journal of Medicine, 309,* 139–142.

Benowitz, N. L., & Henningfield, J. E. (1994). Establishing a nicotine threshold for addiction. *The New England Journal of Medicine, 331,* 123–125.

Buchhalter, A. R., & Eissenberg, T. (2000). Preliminary evaluation of a novel smoking system: Effects on subjective and physiological measures and on smoking behavior. *Nicotine & Tobacco Research, 2,* 39–43.

Butschky, M. F., Bailey, D., Henningfield, J. E., & Pickworth, W. B. (1995). Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers. *Pharmacology, Biochemistry, and Behavior, 50,* 91–96.

Conkling, M. A., Song, W., & Mendu, N. (2002). *U.S. Patent No. 6,423,520.* Washington, DC: U.S. Patent and Trademark Office.

Fowler, J. S., Volkow, N. D., Wang, G.-J., Pappas, N., Logan, J., Shea, C., Alexoff, D., MacGregor, R. R., Schlyer, D. J., Zezulkova, I., & Wolf, A. P. (1996). Brain monoamine oxidase A inhibition in cigarette smokers. *Proceedings of the National Academy of Sciences of the United States of America, 93,* 14 065–14 069.

Ginzel, K. H., & Eldred, E. (1977). Reflex depression of somatic motor activity from heart, lungs and carotid sinus. In A. S. Paintal & P. Gill-Kumar (Eds.), *Krogh Centenary symposium on respiratory adaptation, capillary exchange and reflex mechanisms* (pp. 358–395). Delhi, India: Vallabhbai Patel Chest Institute, University of Delhi.

Grady, S. R., Marks, M. J., & Collins, A. C. (1994). Desensitization of nicotine-stimulated [^{3}H]-dopamine release from mouse striatal synaptosomes. *Journal of Neurochemistry, 62,* 1390–1398.

Gullotta, F. P., Kuhn, M., von Holt, K., & Heintze, G. (2000, November). *The electrophysiological and subjective effects of smoking cigarettes with equal tar but different nicotine levels.*

Poster session at the 10th Neuropharmacology Conference, New Orleans, LA.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerström, K.-O. (1991). The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction, 86,* 1119–1127.

Heeschen, C., Weis, M., & Cooke, J. P. (2003). Nicotine promotes arteriogenesis. *Journal of the American College of Cardiology, 41,* 489–496.

Henningfield, J. E., Benowitz, N. L., Slade, J., Houston, T. P., Davis, R. M., & Deitchman, S. D. (1998). Reducing the addictiveness of cigarettes. *Tobacco Control, 7,* 281–293.

Herning, R. I., Jones, R. T., Bachman, J., & Mines, A. H. (1981). Puff volume increases when low-nicotine cigarettes are smoked. *British Medical Journal, 283,* 187–189.

Hoffman, D., Djordjevic, M. V., & Hoffman, I. (1997). The changing cigarette. *Preventive Medicine, 26,* 427–434.

Hoffmann, D., Rivenson, A., & Hecht, S. S. (1996). The biological significance of tobacco-specific nitrosamines: Smoking and adenocarcinoma of the lung. *Critical Reviews in Toxicology, 26,* 199–211.

Hughes, J. R. (1998). Harm-reduction approaches to smoking. The need for data. *American Journal of Preventive Medicine, 15,* 78–79.

Hughes, J. R., Gust, S. W., Skoog, K., Keenan, R. M., & Fenwick, J. W. (1991). Symptoms of tobacco withdrawal: A replication and extension. *Archives of General Psychiatry, 48,* 52–59.

Jones, S., Lo, H., & Simon, S. A. (2002). Nicotinic receptors in the periphery. In E. D. Levin (Ed.), *Nicotinic receptors in the nervous system* (pp. 81–109). Boca Raton, FL: CRC Press.

Keppel, G. (1982). *Design and analysis: A researcher's handbook* (2nd ed.). Englewood Cliffs, NJ: Prentice-Hall.

Kozlowski, L. T., Pope, M. A., & Lux, J. E. (1988). Prevalence of the misuse of ultra-low-tar cigarettes by blocking filter vents. *American Journal of Public Health, 78,* 694–695.

Nil, R., & Battig, K. (1989). Separate effects of cigarette smoke yield and smoke taste on smoking behavior. *Psychopharmacology, 99,* 54–59.

Pickworth, W. B., Fant, R. V., Nelson, R. A., Rohrer, M. S., & Henningfield, J. E. (1999). Pharmacodynamic effects of new denicotinized cigarettes. *Nicotine & Tobacco Research, 1,* 357–364.

Pritchard, W. S., Robinson, J. H., Guy, T. D., Davis, R. A., & Stiles, M. E. (1996). Assessing the sensory role of nicotine in cigarette smoking. *Psychopharmacology, 127,* 55–62.

Robinson, J. H., Pritchard, W. S., & Davis, R. A. (1992). Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine. *Psychopharmacology, 108,* 466–472.

Robinson, M. L., Houtsmuller, E. J., Moolchan, E. T., & Pickworth, W. B. (2000). Placebo cigarettes in smoking research. *Experimental and Clinical Psychopharmacology, 3,* 326–332.

Rose, J. E. (2003, February). Denicotinized or nicotine-free cigarettes as research and treatment tools. Presentation at the ninth annual meeting of the Society for Research on Nicotine and Tobacco, New Orleans, LA.

Rose, J. E., Behm, F. M., & Levin, E. D. (1993). The role of nicotine dose and sensory cues in the regulation of smoke intake. *Pharmacology, Biochemistry, and Behavior, 44,* 891–900.

Rose, J. E., Behm, F. M., & Westman, E. C. (1998). Nicotine/mecamylamine treatment for smoking cessation: The role of precessation therapy. *Experimental and Clinical Psychopharmacology, 6,* 331–343.

Rose, J. E., & Levin, E. D. (1991). Inter-relationships between primary and conditioned reinforcement in the maintenance of cigarette smoking. *British Journal of Addiction, 86,* 605–609.

Rose, J. E., Westman, E. C., & Behm, F. M. (2001). *The use of denicotinized cigarettes to reduce tobacco dependence.* Poster presentation at the annual meeting of the Society for Research on Nicotine and Tobacco, Seattle, WA.

Rose, J. E., Westman, E. C., Behm, F. M., Johnson, M. P., & Goldberg, J. S. (1999). Blockade of smoking satisfaction using the peripheral nicotinic antagonist trimethaphan. *Pharmacology, Biochemistry, and Behavior, 62,* 165–172.

Russell, M. A. H., Sutton, S. R., Iyer, I., Feyerabend, C., & Vesey, C. J. (1982). Long-term switching to low-tar low-nicotine cigarettes. *British Journal of Addiction, 77,* 145–158.

Shiffman, S. M., & Jarvik, M. E. (1976). Smoking withdrawal symptoms in two weeks of abstinence. *Psychopharmacology, 50,* 35–39.

Suzuki, J., Bayna, E., Molle, E. D., & Lew, W. Y. W. (2003). Nicotine inhibits cardiac apoptosis induced by lipospolysaccharide in rats. *Journal of the American College of Cardiology, 41,* 482–488.

Wang, Y., Pereira, E. F., Maus, A. D., Ostlie, N. S., Navaneetham, D., Lei, S., Albuquerque, E. X., & Conti-Fine, B. M. (2001). Human bronchial epithelial and endothelial cells express alpha 7 nicotinic acetylcholine receptors. *Molecular Pharmacology, 60,* 1201–1209.

Westman, E. C., Levin, E. D., & Rose, J. E. (1992). Smoking while wearing the nicotine patch: Is smoking satisfying or harmful? *Clinical Research, 40,* 871A.