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Nicotine-Containing Versus De-Nicotinized Cigarettes: Effects on Craving and Withdrawal

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GROSS, J., J. LEE AND M. L. STITZER. *Nicotine-containing versus de-nicotinized cigarettes: Effects on craving and withdrawal.* PHARMACOL BIOCHEM BEHAV **57**(1/2) 159–165, 1997.—Nicotine exposure levels and subjective effects from smoking a de-nicotinized cigarette (Next) were examined under controlled conditions. Ten tobacco smokers smoked 20 puffs from their own brand (1.1 mg nicotine delivery, commercial cigarettes), a 0.7 mg nicotine "light" cigarette, or the Next de-nicotinized cigarette (< 0.1 mg nicotine) during independent experimental test sessions. The Next cigarette did not deliver any appreciable nicotine, did not elevate heart rate during smoking, and was rated as less satisfying than the smokers' own brand. Subjective ratings of cigarette craving and tobacco withdrawal symptoms increased during a 90 min post-smoking abstinence period. However, there were no measurable differences on these subjective ratings across the three cigarette test brands. It is concluded that nicotine can be removed from cigarettes without affecting the onset time course or intensity of cigarette cravings and other tobacco withdrawal symptoms in an acute abstinence model. Further studies to determine the subjective and physiological effects of nicotine-free cigarettes would contribute to a greater understanding of tobacco withdrawal and the processes involved in smoking maintenance. © 1997 Elsevier Science Inc.

De-nicotinized cigarettes   Withdrawal effects   Craving   Light cigarettes   Next cigarette   Subjective effects

IT is generally accepted that nicotine is the primary active ingredient that supports addictive patterns of tobacco cigarette smoking (16). While the direct effects of nicotine have been fairly well documented when nicotine is delivered in uncontaminated forms, for example, by IV infusion (8), nicotine gum (10), and nicotine nasal spray (11), the complex pharmacological and sensory factors associated with tobacco cigarette smoking need to be better understood in order to develop more effective smoking cessation strategies. Studies which have examined nicotine outside the smoking context do not allow for the interpretation of the very important non-nicotine aspects of cigarette smoking such as sensory and gustatory effects as well as the complex contextual and behavioral factors which are thought to maintain much of the smoking habit (13,7). However, research has shown that smokers will report enjoyment from and can achieve withdrawal relief from smoking de-nicotinized cigarettes (4). Without a tool such as the de-nicotinized cigarette, it has been difficult to understand the role that nicotine *per se* plays in the acute effects of tobacco smoking and abstinence.

De-nicotinized cigarettes, once marketed in the US as Next (machine yield < 0.1 mg nicotine), have been used to examine the role of non-nicotine factors in producing the subjective and biobehavioral effects of smoking (2) and in suppressing withdrawal symptoms (4). Baldinger et al. (2), for example, took a variety of measures during 24 h periods when subjects smoked cigarettes delivering 0.95 mg on average versus 0.08 mg nicotine. They detected differences in pulse rates but found no differences in cigarette consumption or craving ratings. Butschky et al. (4) manipulated nicotine dose during laboratory test sessions both by varying the number of cigarettes smoked (0–5) and the nicotine delivery characteristics of test cigarettes (1.1 versus 0.09 mg) using Next as the nicotine-free cigarette. Subjective ratings of liking and satisfaction differed for the nicotine-containing and denicotinized cigarettes. However, these produced strikingly similar reductions in craving and withdrawal measures immediately post-smoking.

The purpose of this study was to replicate findings from Baldinger et al. (2) and Butschky et al. (4) concerning rated

sensory and reinforcing characteristics of de-nicotinized versus nicotine containing cigarettes. In addition, the study was intended to extend the observations of Butschky et al. (4) by determining whether more intense withdrawal ratings (i.e. craving and distress symptoms) would be detected during a more extended post-smoking observation period after subjects smoked a de-nicotinized cigarette compared to nicotine-containing cigarettes. The experimental model utilized detailed measures of subjective effects both during and after cigarette smoking in order to examine the onset time course of cigarette cravings following the smoking of cigarettes with differing nicotine delivery characteristics including denicotinized cigarettes.

METHOD

Subjects

Smokers were recruited using community-based advertising for a 3 day laboratory study of cigarette smoking. Participants included 7 males and 3 females with a mean age of 38.2 years who were not interested in quitting smoking. These subjects smoked between 23–45 nonmenthol cigarettes per day (mean = 28.25) with an average nicotine yield of 1.07 (range = 0.9–1.1). Subjects had been smoking regularly from 15–30 years (mean = 22.1). The mean Fagerstrom (5) score of 8.3 (s.d. = 1.7) was evidence of the high degree of dependence for all subjects. Prior to participation in the study, volunteers signed an informed consent that had been approved by this institution's human subject review board. On average, subjects earned $85 for their participation.

Materials

Three different brands of cigarettes were used during the experimental sessions. The test cigarette, against which the other two brands served as comparisons, was the brand "Next" manufactured by Philip Morris, Inc. (Richmond, VA, USA). Next is a de-nicotinized cigarette with a machine nicotine yield of < 0.1 mg and a tar yield of 10.8 mg (4). The first comparison cigarette was the subjects' own preferred brand (Own). All subjects smoked cigarettes with rated nicotine yields between 0.9 and 1.1 mg. The average nicotine yield of the Own condition was 1.07 and average tar yield was 15.8. The second comparison cigarette selected was Winston Lights king size (Light; FTC rated machine yield of 0.7 mg nicotine and 10 mg tar). The tar yield of Light is similar to the Next while still providing a substantial contrast with Next on nicotine delivery.

Procedures

Each subject participated in three laboratory smoking sessions. Each session included a morning standardized exposure period (0930–1200) followed by an afternoon experimental testing period (1201–1400). Procedure for both morning and afternoon sessions were identical except for the cigarettes that were smoked. During all morning standardized exposure periods, subjects smoked their own preferred brand cigarettes while during the afternoon experimental period, subjects smoked the experimental cigarettes provided by research staff. A randomized counter-balanced design determined which of the three experimental smoking conditions, Own, Next, or Light brand, was assigned each afternoon.

The format of the daily sessions was as follows. The first step was to obtain baseline data utilizing a core battery of measures that included expired air carbon monoxide (CO),

heart rate, craving ratings, and a withdrawal symptom questionnaire (measures are described more fully below). The subject then smoked the designated cigarettes under monitored conditions. Specifically, subjects smoked 20 puffs of the assigned cigarette through a plastic mouthpiece attached to monitoring equipment that recorded puff durations and interpuff intervals. In order to account for any differences in burn characteristics across cigarettes, subjects smoked a fixed number of puffs (four) from each of 5 cigarettes during test periods rather than smoking the entire cigarette. During the afternoon testing period, cigarette brand names were not visible and subjects were uninformed concerning the identity of the current test cigarette. Puff spacing and intensity was not controlled.

During each smoking bout, craving and satisfaction ratings were completed after each puff. At the end of the smoking bout, the core battery and questions about cigarette characteristics were administered. Following this, there was a 90 min deprivation period during which the subject sat quietly in the lab and completed a craving report every 15 min. At the end of the 90 min deprivation period, subjects completed the core battery once again.

Blood was drawn twice each day for the purpose of determining plasma nicotine. The first blood draw was at the end of the morning standardized exposure period (i.e., just prior to experimental smoking). This represents the pre-experimental smoking nicotine exposure level (hereafter referred to as "before smoking"). The second draw was immediately following puff 20 of the afternoon experimental smoking period.

Measures

Physiologic measures. Expired breath carbon monoxide was obtained by asking subjects to first exhale, and then inhale and hold their breath for 15 s. Subjects then exhaled into a mouthpiece attached to a Vitalograph EC50 CO monitor which provided immediate CO analysis in parts per million (ppm; Vitalograph Incorporated, Lenexa, KS). Heart rate was taken manually by the research assistant at the radial pulse for 10 s and converted to beats per min. Blood was drawn in a standard fashion from a forearm vein and analyzed by an outside lab (Labstat, Ontario) for nicotine using gas chromatography.

Subjective report measures. A 3-item craving/satisfaction measure was used during smoking bouts. Questions were presented on the computer screen using a 100 mm VAS. Subjects rated the following after each cigarette puff: 1) "How much did you like or enjoy the puff you just took?"; 2) "How much do you want to smoke right now?"; and 3) "How satisfying was your last puff?" Ratings ranged from "not at all" to "very much." An 8-item cigarette characteristics measure was used to rate the sensory and reinforcing properties of the cigarettes. At the end of the smoking bout, subjects were asked to rate the cigarettes as follows: "How strong was the cigarette?; "How hot was the cigarette?"; "How hard was it to draw smoke from the cigarette?"; "How harsh was the cigarette?"; "How much taste did you get from the cigarette?"; "How satisfying was the cigarette?"; "How much tobacco vs. 'just air' did you get from the cigarette?"; and "What is the likelihood that you would buy cigarettes like these?" Anchor points (eg: "no taste" = 0 to "a lot of taste" = 100) appropriately reflected extreme responses to each question.

During the 90 min deprivation periods (at 0, 15, 30, 45, 60, 75 and 90 min), subjects were asked to rate their craving or

urge for a cigarette using a 4-item measure. Items included: 1) "How pleasant would a puff be right now?"; 2) "How much of an urge or desire do you have to smoke right now, just for the pleasure of smoking?"; 3) "How much do you need to smoke right now, for relief?"; and 4) "How much do you want to smoke right now?" Responses ranged from "not at all" to "very much."

The tobacco withdrawal scale, administered at the start and end of each 90 min smoking deprivation interval, was based on the measure developed by Hughes and Hatsukami (9) but was modified for use with a 100 mm VAS. Subjects rated their subjective distress based on the following items: 1) Urges to smoke; 2) Irritability/frustration/anger; 3) Anxious; 4) Difficulty concentrating; 5) Restlessness; 6) Hunger; 7) Impatient; 8) Craving cigarettes/nicotine; 9) Drowsiness; 10) Depression/Feeling blue; and 11) Desire for sweets. Anchor points at the ends of the VAS line were "none" and "severe."

Statistical Analyses

Because all subjects underwent all three experimental smoking conditions, this constituted a within-subject repeated measures study. Multivariate repeated measures ANOVA (experimental cigarette condition × measurement time point) was used to assess changes in dependent variables (CO, nicotine, heart rate, craving scores) measured before and after the 20 puff smoking bout. Effects of the 90 min smoking abstinence period were also assessed using repeated measures ANOVA for the 4-item craving scale administered at 15 min intervals throughout and for the withdrawal symptoms measure administered at the start and end of this interval. Analyses were conducted using SPSS for the Macintosh. Huynh-Feldt corrected p-values are presented to correct for any violations of the sphericity assumption. When post hoc analyses were relevant, Tukey's honestly significant difference test was conducted to ascertain differences between means.

RESULTS

Physiological Effects of Smoking

A multivariate repeated measures ANOVA was used to examine equivalency of pre-smoking measures across conditions and changes produced by smoking the three types of test cigarettes. Mean nicotine levels before smoking Own, Light, and Next brands were 11.3, 12.2 and 10.8 ng/ml respectively. Mean CO values were 29.9, 29.1, and 28.2 ppm while mean heart rates were 70, 75.4, and 73.8 bpm (Fig. 1). Heart rates for Own versus Light differed across conditions prior to smoking ($q = 6.14$, $p < 0.01$).

For nicotine, as shown in Fig. 1, there was a significant main effect of time ($F(2,18) = 6.87$, $p < 0.03$) with nicotine levels greater, on average, after smoking the experimental cigarette than before. There was also a significant main effect of cigarette brand ($F(1,9) = 9.12$, $p < 0.002$) with the Own brand having the highest nicotine level overall, and a significant interaction ($F(2,18) = 9.65$, $p < 0.001$). Post hoc analysis revealed that pre-to-post smoking increase in nicotine was significant only for Own brand (6.0 ng/ml; $q = 7.89$, $p < 0.01$) with no significant differences in pre-to-post smoking nicotine levels for either the Light (1.4 ng/ml) or Next (−0.5 ng/ml) brands. Post hoc analyses also revealed that absolute after smoking nicotine levels were significantly higher for Own brand versus Light ($q = 4.85$, $p < 0.05$) and Own versus Next ($q = 9.11$, $p < 0.01$).
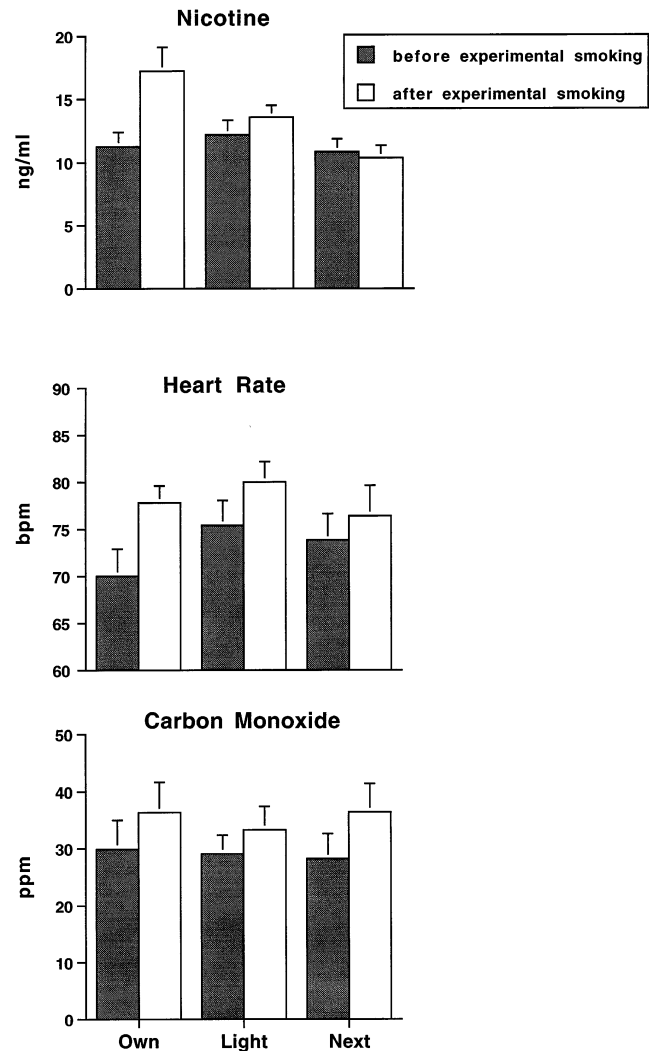

FIG. 1. Mean plasma nicotine, heart rate, and carbon monoxide levels before and after smoking the experimental cigarettes. Nicotine boost was significant for Own brand ($p < 0.01$) but not for Light or Next. For heart rate, Own ($p < 0.01$) and Light ($p < 0.05$) showed significant heart rate boosts. CO boost was significant for all three cigarette brands; Own and Light (p's < 0.001), Next ($p < 0.05$). Shaded bars reflect before smoking while open bars reflect after smoking periods. SEMs are shown.

Also shown in Fig. 1, there was a significant time effect ($F(2,18) = 12.1$, $p < 0.007$) and brand × time interaction ($F(2,18) = 4.45$, $p < 0.03$) for heart rate. Post hoc analyses found that the heart rate increase from before to after smoking was significant for the Own ($q = 8.87$, $p < 0.01$) and the Light ($q = 5.23$, $p < 0.05$) brand conditions but not for the Next brand. Heart rates rose 7.8 bpm for Own, 4.6 for Light, and 2.6 for Next. Also shown in Figure 1 is CO for each brand before and after smoking, which was not expected to be influenced by the varying nicotine content of the three brands. Consistent with the prediction, there was only a significant main effect of time ($F(2,18) = 29.7$, $p < 0.0001$). Post hoc analyses showed that CO levels after smoking were significantly higher than before smoking for each of the three brands

(Own $p < 0.01$, Light $p < 0.05$, Next $p < 0.01$). CO values rose, on average, 6.3 ppm following smoking of 20 puffs.

Craving and Satisfaction Ratings During Smoking

The three-item craving/satisfaction measure was administered after each of the 20 puffs during the experimental smoking session to assess craving and satisfaction during smoking as a function of nicotine content of the cigarette. Using a repeated measures ANOVA for cigarette brand (3 brands) × time (20 puffs), there was a significant main effect of cigarette brand for each of the two items: "How much did you like or enjoy the puff you just took?" (enjoyable); ($F(2,18) = 5.05$, $p < 0.02$) and "How satisfying was your last puff?" (satisfying); ($F(2,18) = 4.19$, $p < 0.04$). Subjects rated the Own brand as significantly more "enjoyable" than the Next or Light brands (mean rating over 20 puffs was 65.5 for Own, 38.1 for Light and 33.9 for Next). Similarly for the "satisfying" question, mean ratings were 59.8 for Own, 35.9 for Light, and 33.9 for Next. For neither of these questions was there a significant effect of time or a significant brand × time interaction. For the question "How much do you want to smoke right now?", there was no brand main effect or brand × time interaction; "want to smoke" ratings were 72.1, 59.9, and 62.6 for Own, Light and Next brands, respectively. There was, however, a significant main effect for time, reflecting a decrease in ratings for successive puffs across all brands ($F(19,171) = 5.22$, $p < 0.001$). Ratings decreased from a mean of 70.9 following puff number 1 to 56.1 following puff number 20.

Cigarette Characteristic Ratings

To assess the sensory effects of cigarettes at the end of the experimental smoking bout, ratings on eight items were analyzed independently using a one-way (test cigarette condition) repeated measures ANOVA. Table 1 shows the means for each of the cigarette brands and the F and p values. Overall, these scores suggest that the subjects could differentiate among the three test cigarettes based on their sensory characteristics. Particularly on the two items with statistically significant condition effects (strong, $p < 0.009$, and more smoke than air, $p < 0.01$), there was a graded response with highest ratings given to Own brand, lowest to Next brand, and intermediate ratings observed for Light. A similar although statistically nonsignificant pattern was seen for the item harsh. On items that were more reflective of cigarette "liking" (satisfy, taste, buy), subjects tended to give high ratings to the Own brand with lower and approximately equivalent ratings observed for Light and Next brands; these effects achieved borderline statistical significance.

Craving and Withdrawal Effects During the Deprivation Period

The 4-item craving measure was administered immediately after smoking and every 15 min throughout the 90 min deprivation period to compare the urge to smoke following exposure to each brand. In addition, this measure allowed us to assess the comparative suppression of craving by each brand. The items reflecting "urge or desire to smoke for pleasure" and "need to smoke for relief" are shown as representative items in Fig. 2, as all four questions showed similar patterns of responding. A cigarette brand (3 brands) × time point (pre, 0, 15, 30, 45, 60, 75, 90 min) repeated measures ANOVA was used. The time point designated "pre" is the 90 min post-smoking data point from the morning standardized exposure

TABLE 1

MEAN VALUES BY BRAND FOR THE EIGHT CIGARETTE CHARACTERISTIC VARIABLES

	Own Mean	Light Mean	Next Mean	F	p Value
Strong	57.3[a]	40.9	25.8[b]	6.15	0.009
Smoke than air	63.5[a]	40.2	26.3[b]	6.89	0.01
Harsh	52.7	44.1	28.5	2.59	ns
Satisfy	56.1	35.4	31.6	3.66	0.05
Buy	53.6	33.3	22.9	3.33	0.07
Taste	63.6	42.7	38.8	3.17	0.07
Hot	22.9	29.3	13.5	2.90	0.08
Draw	36.1	53.0	59.8	1.78	ns

[a,b]Means with different superscripts indicate significantly different values based on post hoc tests.

session and is used as a pre-experimental smoking comparison point to illustrate suppression of craving. For each of the four deprivation period craving questions, ratings increased significantly over time and there was a significant time main effect (all p's < 0.0001). There was no significant main effect nor a significant brand × time point interaction for any of the questions, as illustrated in Fig. 2. The "relief" question (lower panel, Fig. 2) was the only craving item on which scores after smoking the Next brand appeared consistently higher, albeit not significantly so, than scores for the other two brands. Comparison of data point "pre" versus the "0 min post-smoking" scores demonstrates that the three test cigarettes produced equivalent craving suppression.

The withdrawal scale was administered at the beginning and at the end of the 90 min deprivation period to determine the acute withdrawal effects for each of the cigarette brands. A cigarette brand (3 brands) × time (before, after) repeated measures ANOVA was used to analyze each item and the total score. There were no significant brand effects, nor any brand × time interactions. As seen in Table 2, there were significant increases over time during the deprivation period for 8 of the 11 individual items: urge to smoke ($p < 0.002$), irritable/frustrated/angry ($p < 0.022$), anxious ($p < 0.004$), difficulty concentrating ($p < 0.011$), restlessness ($p < 0.021$), hunger ($p < 0.002$), impatient ($p < 0.035$), and craving cigarettes/nicotine ($p < 0.003$). The total withdrawal score also showed a significant main effect for time ($p < 0.007$). The only items which did not change over time were drowsiness, depression/feeling blue, and desire for sweets; these three items were uniformly low at all assessment intervals.

DISCUSSION

This laboratory study examined the subjective effects of nicotine-containing versus denicotinized cigarettes before, during, and after smoking a cigarette. Objective measures of nicotine exposure and heart rate changes (Fig. 1) confirmed that no appreciable nicotine was delivered by the denicotinized Next cigarettes, while expired breath CO measures supported the conclusion that similar amounts of smoke were inhaled from the three test cigarettes. Light cigarettes, rated as delivering 0.7 mg nicotine, were selected as a comparison for the Next brand on tar delivery (10.0 mg v. 10.8 mg) while theoretically producing a substantially greater nicotine boost. However, the magnitude of nicotine boost actually observed
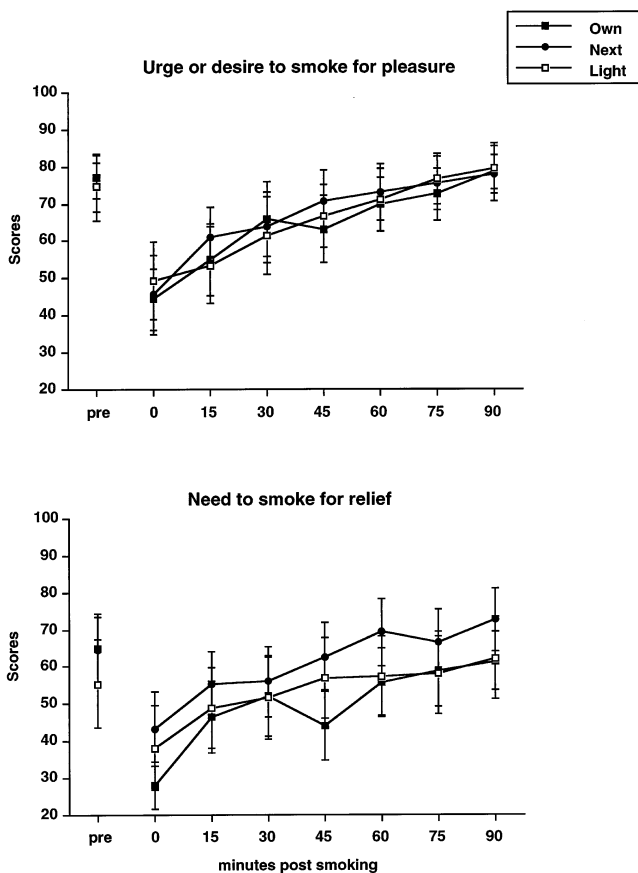
Craving during the deprivation period

FIG. 2. Mean craving scores during the 90 min deprivation period is shown for two of the four craving questions. Time main effects are significant while there are no brand or interaction effects. The "pre" data point reflects the craving scores at the 90 min post-smoking time point from the morning standardized exposure period.

after smoking the light cigarettes (1.4 ng/ml), was less than expected and less than previously reported in studies which employed similar smoking protocols using cigarettes delivering 0.6–0.8 mg nicotine (12,18). In these previous studies, nicotine increases ranging from 14 to 26.4 ng/ml were observed. One possible explanation for the low nicotine boost with the light cigarette could be that in the present study, only 4 puffs were drawn from each cigarette, while in comparable studies, such as Zachny & Stitzer (18) and Robinson et al. (12) the entire cigarette was smoked. The implication is that our subjects would not have been exposed to the higher concentrations of nicotine which develop in the proximal portion of the cigarette as it is smoked. This argument could also be applied to the lack of nicotine increase detected after smoking Next cigarettes (Fig. 1). However, previous studies have independently verified the lack of nicotine delivery from the Next cigarettes (4).

Cigarette sensory characteristic ratings from the present study (particularly strength ratings) suggested that subjects could discriminate differences among the test cigarettes. This is consistent with recent data reported by Baldinger et al. (2).

Subjects rated both Next and Light comparison cigarettes as less satisfying than their own brand (Table 1). These findings replicate those of Butschky et al. (4), who also found lower ratings of the Next cigarette compared to a regular brand on measures of liking, good effects, and satisfaction. Based on the unexpectedly low nicotine boost produced by smoking of "light" cigarettes in the present study, it would be predicted that these and Next would be rated similarly on measures that reflect smoking satisfaction and liking, a prediction that was generally upheld in the data (Table 1). However, neither this nor the previously published studies allow for any conclusions regarding the bases for these discriminations (i.e. nicotine delivery, tar delivery, filtration characteristics, etc.). In fact, previous observations suggest that subjects tend to rate unfamiliar cigarettes as less satisfying even if these deliver amounts of nicotine and tar comparable to their own brand (18). Thus, these acute ratings may not be very useful for determining long-term acceptance of cigarettes with altered delivery characteristics.

The present study extended previous findings regarding postsmoking withdrawal suppression by determining whether the nicotine delivery characteristics of cigarettes influence the onset time course of cigarette craving during a brief period of smoking abstinence (Fig. 2). Consistent with previous data from this laboratory (14), we observed a post-smoking suppression of craving ratings followed by an orderly rise in cigarette craving scores during the 90 mins following smoking of test cigarettes. In addition, several typical tobacco withdrawal symptom scores were elevated following as little as 90 mins of smoke deprivation; these included ratings of irritable, anxious, difficulty concentrating, restlessness, hunger and impatience. However, neither the magnitude nor the time course of these ratings was influenced by the nicotine delivery or other characteristics of cigarettes smoked during the session. The observation that nicotine-free cigarettes can suppress craving ratings in a manner similar to nicotine-containing cigarettes is consistent with data reported by Hasenfrantz et al. (7) and by Butschky et al. (4).

The ability of nicotine-free cigarettes to suppress withdrawal and craving ratings can most likely be attributed to conditioned sensory characteristics of smoking. Rose and colleagues (13,3) have strongly argued for the importance of these sensory effects in smoking and have demonstrated experimentally that lownicotine aerosols and citric inhalers produce airway stimulation which can influence satisfaction and craving ratings. It has also been suggested that the particulate constituents ("tars") delivered by cigarettes may have pharmacological reinforcing properties beyond the sensory effects they produce when inhaled (7). On the other hand, there is also evidence that pure nicotine delivered by methods other than tobacco cigarettes can suppress withdrawal and craving ratings. For example, Perkins and colleagues (11) showed that desire to smoke was suppressed with repeated administrations of nicotine nasal spray. Similar findings have been reported by Hajek and colleagues with the use of a smoke-free cigarette nicotine vaporizer (6). There is also some support for reduction in craving with the use of nicotine gum and nicotine patch although this effect is not very robust (1,15).

One of the most interesting questions that can be addressed with the nicotine-free cigarettes concerns the longer-term effects of removing nicotine both on cigarette satisfaction ratings and on the emergence of tobacco withdrawal symptoms. Baldinger and co-workers (2) have recently shown that no excess withdrawal symptoms or cravings could be detected when denicotinized cigarettes were smoked for a full 24 h. Similarly,

TABLE 2

MEAN VALUES FOR WITHDRAWAL SYMPTOM SCALE ITEMS DURING THE DEPRIVATION PERIOD

	Time	Cigarette Brand			
		Own (Mean)	Light (Mean)	Next (Mean)	Time Main Effect p-value
Urge to smoke	0 min post-smoking	41.6	48.6	47.6	
	90 min post-smoking	71.4	74.9	73.6	0.002
Irritable/Frustrated/Angry	0 min post-smoking	12.7	18.4	9.5	
	90 min post-smoking	27.4	27.2	18.0	0.002
Anxious	0 min post-smoking	13.6	17.3	11.1	
	90 min post-smoking	25.5	28.5	24.4	0.004
Difficulty concentrating	0 min post-smoking	9.1	15.3	12.7	
	90 min post-smoking	13.9	23.0	19.9	0.010
Restlessness	0 min post-smoking	15.3	12.2	13.7	
	90 min post-smoking	23.3	25.7	25.1	0.020
Hunger	0 min post-smoking	27.6	31.1	25.8	
	90 min post-smoking	34.4	43.6	43.2	0.002
Impatient	0 min post-smoking	13.9	15.8	14.4	
	90 min post-smoking	17.5	25.9	23.2	0.040
Craving cigarettes/nicotine	0 min post-smoking	27.0	36.7	38.1	
	90 min post-smoking	62.1	60.4	59.5	0.003
Drowsiness	0 min post-smoking	16.1	11.9	23.6	ns
	90 min post-smoking	20.9	18.5	21.6	
Depression/Feeling blue	0 min post-smoking	7.4	5.6	7.4	ns
	90 min post-smoking	7.0	10.3	9.7	
Desire for sweets	0 min post-smoking	12.5	6.3	18.9	ns
	90 min post-smoking	17.2	13.8	15.8	
Composite score	0 min post-smoking	16.8	18.0	18.9	
	90 min post-smoking	26.2	29.1	27.9	0.007

West et al. (17) found that smoking an ultra-low yielding cigarette (0.1 mg nicotine) for 10 days also did not lead to excess withdrawal symptom reporting or significantly increased craving for a higher nicotine cigarette. It is possible that switching to very low or nicotine-free cigarettes prior to a cessation attempt could be a potentially useful prerequisite to the quit attempt if post-cessation withdrawal symptoms were less severe as a result of removing the influence of nicotine. The fact that post-smoking withdrawal and craving ratings were elevated to the same extent after nicotine-containing versus denicotinized cigarettes in the present study argues against the clinical efficacy of such a maneuver. However, the single 20 puff smoking test employed here would not provide sufficient exposure to stabilize a nicotine-free state in the smoker. Thus, withdrawal effects after longer-term exposure to nicotine-free cigarettes should be evaluated.

Although nicotine has been clearly identified as the primary active alkaloid in tobacco smoke that sustains addiction (16), its specific role in the complex pharmacology of tobacco ciga-

rette smoking remains to be clearly delineated. This study has supported previous observations that removal of nicotine from a medium tar tobacco cigarette produces reduced ratings of satisfaction as compared to the subjects' usual brand, but has little impact on immediate post-smoking ratings of craving or other tobacco withdrawal symptoms. The availability of nicotine-free filtered cigarettes with characteristics otherwise similar to marketed brands would be a great benefit to researchers wishing to disentangle the role of the various cigarette smoke constituents. Such research tools would also allow a better understanding of the role of tar delivery, upper airway stimulation and other sensory effects of smoking that may support continued smoking behavior via conditioned reinforcing effects.

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