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Pharmacology, Biochemistry and Behavior 76 (2003) 243–250
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Pharmacologic and sensorimotor components of satiation in cigarette smoking

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Received 10 March 2003; received in revised form 7 July 2003; accepted 18 July 2003

Abstract

To examine mechanisms underlying satiation in cigarette smoking, 18 smokers received intravenous (iv) nicotine, alone or in combination with denicotinized cigarette smoke. Nicotine was administered using programmed presentations of either pulsed injections or continuous infusions, with iv saline serving as a control. A high-nicotine cigarette smoke condition (usual brand) was also presented. During each of the six test sessions, subjects were allowed to puff on their usual brands of cigarette ad libitum while the programmed satiation conditions were in force. Administration of iv nicotine caused a small suppression of ad libitum smoking behavior; denicotinized smoke produced a significantly larger reduction, showing that short-term satiation is more dependent on the presentation of smoke than delivery of nicotine per se. However, denicotinized smoke alone did not have as much effect as puffs from the usual brands of cigarettes. The combination of iv nicotine and denicotinized smoke puffs produced equivalent satiation to that of the usual brand. Cigarette craving and negative affect were partially relieved by iv nicotine presentations as well as by denicotinized smoke, and again the combination of iv nicotine and denicotinized smoke approximated the effects of the usual brand. The results of this study underscore the importance of both sensorimotor aspects of smoking and the pharmacologic effects of nicotine in tobacco dependence.

Keywords: Nicotine; Tobacco; Cigarette smoking; Dependence; Satiation

1. Introduction

In designing treatments for smoking reduction or cessation, it may be helpful to identify which aspects of smoking behavior relieve tobacco withdrawal symptoms or produce behavioral satiation, i.e., a short-term suppression in ad libitum smoking following consumption of smoke constituents. Previous studies of tobacco withdrawal have documented the effects of nicotine, administered by a variety of routes, in alleviating withdrawal symptoms (Gross and Stitzer, 1989; Hughes et al., 1984; Perkins et al., 1992; Rose et al., 1984). On the other hand, nonnicotine aspects of smoking have also been shown to relieve craving and other smoking withdrawal symptoms, possibly because of the conditioned effects of smoke cues (Pickworth et al., 1999; Rose and Levin, 1991).

Other studies have focussed on the role of nicotine in regulating ad libitum smoking behavior, and manipulations of cigarette nicotine delivery have indeed been shown to modulate the rate of smoking. Increasing nicotine delivery tends to reduce smoke intake, and conversely, lowering nicotine delivery tends to increase smoking behavior (McMorrow and Foxx, 1983). The phenomenon of ''titration'' of nicotine intake is imprecise, however, and smokers only crudely regulate their nicotine levels within wide bounds (Kozlowski and Herman, 1984). Studies of titration, while showing some role for nicotine, leave unanswered the question of what components of cigarette smoke might be sufficient to completely satisfy the desire to engage in further smoking behavior, i.e., induce satiation.

Previous studies in our laboratory have suggested that sensorimotor cues involved in the act of smoking play a significant role in providing satisfaction and modulating smoking behavior. For example, in one study, a low-nicotine smoking condition presenting relatively high intensity sensory cues did not elicit compensatory increases in smoking that were observed with low-sensory, low-nicotine smoke

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0091-3057/$ – see front matter © 2003 Published by Elsevier Inc.
doi:10.1016/j.pbb.2003.07.002

(Rose et al., 1993). In other studies in which the nicotine and sensorimotor components of cigarette smoking were dissociated, using iv nicotine and denicotinized smoke presentations, iv nicotine was rated as much less satisfying than denicotinized cigarette smoke, highlighting the importance of sensorimotor aspects for smoking satisfaction (Rose et al., 2000; Westman et al., 1996). However, these studies did not measure how the rate of smoking a preferred brand of cigarette might be affected by different satiation manipulations. This shortcoming posed an interpretational problem because the type of smoke used to provide satiation was the same as that used to measure ad libitum smoking. Thus, a reduction in ad libitum smoking might have reflected not only satiation but a reduction in the palatability of the smoke tested in a given condition. In the current study, the test cigarette used for ad libitum smoking was held constant across conditions, and the relative efficacy of the different satiation manipulations could be ascertained.

We examined the ability of a variety of manipulations to satiate smokers. At one extreme, we presented programmed puffing of the usual brand of cigarette in an amount equal to that which each subject normally smoked in the same length of time (assessed during a baseline session). We expected that this satiation manipulation would nearly completely suppress concurrent ad libitum smoking. At the opposite extreme, subjects received saline infusions without any programmed puffing; the expectation was that ad libitum consumption of their usual-brand cigarettes would be maximal in this condition. Between these extremes, there were four other satiation conditions designed to provide one or another component of smoke and yield information about the efficacy of different smoke components in reducing ad libitum smoking. Three of these conditions presented iv nicotine, administered in puff-sized ‘‘bolus’’ injections or as a continuous infusion, and in one of these conditions, the iv nicotine pulses were accompanied by programmed puffing on a denicotinized cigarette. In a different condition, puffs of a denicotinized cigarette were presented accompanied by saline infusion. We expected partial satiation with presentations of the nicotine alone or with denicotinized smoke alone, but we predicted that the combination of denicotinized smoke with iv nicotine would recapture the full satiating potency of presentations of smoke from the usual-brand cigarettes.

2. Methods

The research was approved by the Duke University Medical Center Institutional Review Board, and written informed consent was obtained from all participants.

2.1. Subject recruitment

Eighteen smokers, both sexes included, were recruited from the community by newspaper and radio advertisements and by word-of-mouth. Subjects were required to be between the ages of 18 and 55, smoke at least 20 cigarettes each day [or self-administer 10 mg nicotine per day based on Federal Trade Commission (FTC) nicotine yield of their preferred brand of cigarette], and score ≥ 5 on the Fagerström Test for Nicotine Dependence questionnaire (FTND), indicating at least a moderate dependence on nicotine. Based upon physical examination, ECG, serum chemistries, CBC, and urinalysis, respondents were excluded if they had hypertension (systolic >140 mm Hg, diastolic >90 mm Hg), hypotension (systolic < 90 mm Hg, diastolic < 60 mm Hg), coronary artery disease, cardiac rhythm disorder, any other major medical condition, current psychiatric disorder other than nicotine dependence (DSM-IV criteria), were pregnant or nursing mothers, or reported current smokeless tobacco use. Volunteers were compensated at the rate of US$25 per hour for participation in the seven laboratory visits.

2.2. Cigarettes

To present the denicotinized cigarette satiation conditions, we used cigarettes that contained tobacco from which the nicotine had been selectively extracted by high-pressure CO_2 (Philip Morris). Tar and CO delivery for these cigarettes, when smoked by FTC criteria, was approximately 9–10 mg, while their nicotine delivery was extremely low, less than 0.1 mg.

2.3. Intravenous nicotine delivery

A solution of 0.05% nicotine in saline was prepared by the Duke University Pharmacy Services. The solution was pH-adjusted to 7.0 using acetic acid, sterilized by filtration and autoclaving, and finally tested for bacterial growth and pyrogens. The nicotine solution was diluted to a concentration based on each subject’s per-puff nicotine dose when smoking ad libitum. A syringe pump (Harvard Apparatus Model 22, Holliston, MA) was used to deliver nicotine infusions or pulsed 2-s injections. Several safety features were incorporated into the device and associated computer program, including an automatic shutoff in case of power failure, a programmed limit on the rate of dosing (once per 15 s) and a limit on the total cumulative dose in a session (no more than twice that during ad libitum smoking). Additionally, the total dose of nicotine contained in the syringes at any time was less than 6 mg.

The doses of nicotine administered in each pulsed iv injection were set equal to the per-puff nicotine dose each subject obtained from their habitual brands of cigarettes. This dose was calculated by manually taking cigarette puffs from the same type of cigarettes using a syringe, replicating the same average puff volume and interpuff intervals previously measured in an ad libitum smoking baseline session. The smoke particulate matter was trapped in Cambridge filters (Federal Trade Commission, 1976), and after extraction with ethanol, a spectrophotometer was used to measure the absorbance of the solution at a wavelength of 400 nm,

which is an accurate measure of "tar" concentration (Rose et al., 1987). Using published values for the nicotine/tar ratio for each brand of cigarette (Federal Trade Commission, 2000), the nicotine delivery per puff could then be estimated.

For the pulsed iv nicotine condition, each 2-s injection contained the per-puff dose in a 2-ml volume. In the slow, continuous iv nicotine infusion condition, the rate of administration was set equal to the total nicotine dose divided by total session time (4 h).

2.4. Procedure

Subjects participated in seven sessions of approximately 4-h duration, conducted after overnight abstinence (12 h) from smoking. In a baseline session, subjects smoked their usual brands of cigarettes ad libitum, and puffing topography was measured (see below). To minimize variability in nicotine absorption from variations in inhalation, subjects were instructed to hold their breath for 5 s after each puff (Gilbert et al., 1989).

Data from this ad libitum smoking baseline session were used to individualize the doses of smoke and nicotine presented during the programmed satiation conditions. Cigarettes were provided at the same times during the subsequent sessions as in the baseline session. Controlled puffs from each cigarette were presented using a spirometric apparatus validated in previous studies (Levin et al., 1989). The device contained a glass syringe preloaded with a measured amount of air that was supplied with each puff to a burning cigarette enclosed within a glass chamber. The puff volume and interpuff interval used were equal to the average values from the baseline ad libitum smoking session.

In the subsequent six sessions, participants were exposed, in a crossover design, to the satiation manipulations shown in Table 1 (order counterbalanced using digram-balanced Latin squares (Keppel et al., 1982). After 1 h of exposure to each satiation manipulation, subjects were then allowed to smoke their preferred brand of cigarette ad libitum for the remaining 3 h of the session, while continuing to receive the programmed satiation puffs and iv nicotine or saline (each pulsed iv administration coincided with a programmed puff). However, ad libitum smoking was not permitted during the time periods when programmed puffs were administered, nor was it allowed during the corresponding periods in conditions that did not present controlled puffs as part of the satiation manipulation. Thus, the actual time available for ad libitum smoking was held constant across all conditions. Subjects were also allowed to listen to the radio and read magazines during the ad libitum smoking period. All sessions took place with an iv line infusing either nicotine or saline.

Table 1
Description of experimental conditions

Condition	Controlled smoke	iv
A	usual brand	saline
B	denicotinized	saline
C	denicotinized	nicotine (pulsed)
D	no smoke	nicotine (pulsed)
E	no smoke	nicotine (slow infusion)
F	no smoke	saline

2.5. Dependent measures

Smoking topography, including the number of puffs taken and puff volume, was measured during the ad libitum smoking period of all sessions using the Clinical Research Support System (CReSS; Plowshare Technologies, Baltimore, MD). Subjects smoked cigarettes through a mouthpiece that was attached to a laptop computer via a data collection interface box. Puff volumes measured in Session 1 were used to set the parameters for controlled smoke presentations and for iv nicotine dosing during the satiation procedures, as described above. Cumulative puff volume taken from the usual-brand cigarettes during the 3-h ad libitum smoking periods in subsequent sessions was the main dependent measure of satiation.

Expired air CO concentrations were measured hourly to verify compliance with the overnight abstinence requirement and to measure ad libitum smoke intake, using a portable CO monitor (Vitalograph, Lenexa, KS). Heart rate and blood pressure were measured with an automated sphygmomanometer every 5 min.

Venous blood samples (5 cc) were collected every hour, centrifuged to separate the plasma, packed on dry ice, and shipped from Durham, NC, to the Clinical Pharmacology Laboratory at the University of California, San Francisco, for assay of nicotine and cotinine concentrations.

Subjective measures of mood and smoking withdrawal were taken every 30 min, using an abbreviated version of the Shiffman–Jarvik questionnaire (Shiffman and Jarvik, 1976) to assess craving, negative affect, and arousal. A cigarette evaluation questionnaire (Westman et al., 1992) was also administered immediately after each cigarette to measure subjective effects; a composite measure of satisfaction, psychological effects, craving relief, and enjoyment of airway sensations was calculated. All items of these questionnaires were rated on seven-point scales ranging from 1 ("not at all") to 7 ("extremely").

2.6. Statistical analysis

All statistical analyses were performed using SUPERANOVA and STATVIEW (SAS Institute, Cary, NC). A multivariate approach to repeated-measures ANOVA was used, which appropriately took into account the correlation pattern among repeated measurements (Maxwell and Delaney, 1990).

Several planned comparisons were carried out to assess the satiating effects of nicotine and nonnicotine smoke components. To assess the role of nonnicotine components,

Table 2
Subject characteristics

Demographic information ($n = 18$)		
Sex	8 males/10 females	
Race	12 white/6 black	
	Mean	(S.D.)
Age (year)	35.9	(11.8)
No. of cigarettes/day	26.2	(15.3)
FTC nicotine (mg)	0.9	(0.2)
Years smoked	17.9	(12.0)
FTND score	6.3	(2.1)
Baseline CO (ppm)	29.1	(17.9)

the dependent measures of ad libitum smoking (of the usual-brand cigarettes) in the denicotinized smoke/saline iv satiation condition were compared with those in the no smoke/saline condition. To assess the influence of nicotine per se, the two no-smoking, iv nicotine conditions (pulsed and slow infusion) were compared with the no-smoking, saline condition, and to the denicotinized smoke/saline condition. To assess the role of rapid vs. slow nicotine administration, the no-smoking, pulsed iv nicotine condition was compared with the no-smoking, slow iv nicotine infusion condition. Finally, to assess the extent to which the combination of denicotinized smoke plus iv nicotine (pulsed injections) recaptured the effects of controlled puffs of the usual-brand cigarettes, those two satiation conditions were compared with each other. In most cases, contrasts between conditions were calculated using a pooled error term that included all six conditions. However, in analyzing nicotine or cotinine, where there were several missing data points, only the conditions pertaining to a given contrast were included in the comparison.

3. Results

3.1. Subject characteristics

Table 2 summarizes the demographic characteristics and smoking habits of the participants in the study.

3.2. Compliance with overnight abstinence

Baseline plasma nicotine and CO levels did not differ across conditions, and the values were consistent with overnight abstinence. Mean baseline plasma nicotine concentration was 4 ng/ml (S.D. = 2.4) and expired air CO concentrations averaged 12 ppm (S.D. = 4.9). The mean baseline cotinine level was 245 ng/ml (S.D. = 106.7).

3.3. Validation of nicotine and smoke administration procedures

Because only one iv catheter was inserted for each participant, blood samples collected during conditions presenting iv nicotine could not be assayed meaningfully for nicotine because of direct contamination. Instead, in these conditions, cotinine served as a marker of nicotine intake. During the first hour of programmed administration, before the ad libitum smoking period, the iv nicotine conditions showed an increase in plasma cotinine levels that, on average, was comparable to that of the usual-brand satiation condition. Increases in cotinine level from baseline to Hour 1, calculated relative to the saline control condition, averaged 33 ng/ml (S.D. = 35.0) in the iv nicotine conditions vs. 26 ng/ml (S.D. = 18.1) in the usual-brand satiation condition [$F(1,26) = 12.98$, $P = .003$ for the comparison of all nicotine conditions against saline; $F(1,13) = .37$, $P > .5$ for the compar-

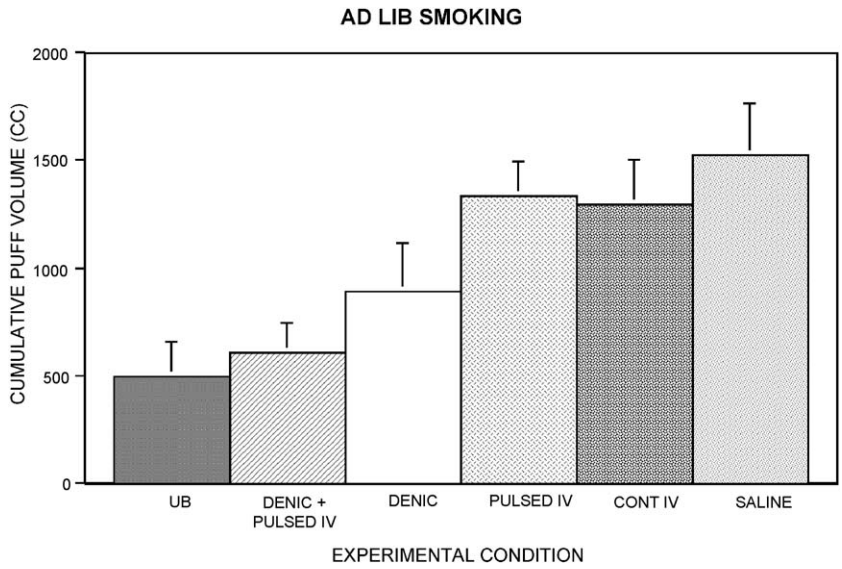

Fig. 1. Cumulative smoke volume (mean ± S.E.M.) taken during the 3-h ad libitum smoking period in each of the seven satiation conditions.

ison of usual brand/iv saline to the iv nicotine satiation conditions]. In the denicotinized smoke/iv saline condition, the cotinine level at the end of the first hour did not differ from that of the no-smoking/saline condition [$F(1,28) = 0.00$, $P = .99$], but there was a very small increase in plasma nicotine (0.2 ng/ml (S.D. = 0.73) vs. a change of − 0.7 ng/ml (S.D. = 0.99) [$F(1,10) = 9.20$, $P = .01$]. Expired air CO in the denicotinized cigarette conditions increased during the first hour by an average of 4.8 ppm (S.D. = 3.07) vs. 6.1 ppm (S.D. = 3.38) in the usual-brand satiation condition [$F(1,34) = 3.01$, $P = .09$], and a change of − 0.9 ppm (S.D. = 0.98) in the no-smoking conditions [$F(1,34) = 51.97$, $P < .0001$ for the contrast with the denicotinized smoke conditions].

3.4. Effects of satiation conditions on ad libitum smoking

As shown in Fig. 1, there was a powerful satiating effect of programmed puffs of the usual-brand cigarette; as expected, subjects took less additional smoke volume ad libitum in the usual brand/iv saline satiation condition than in the no smoking/iv saline control condition [$F(1,85) = 51.89$, $P < .0001$]. More interesting was the significant satiating effect of programmed puffs of denicotinized ciga-

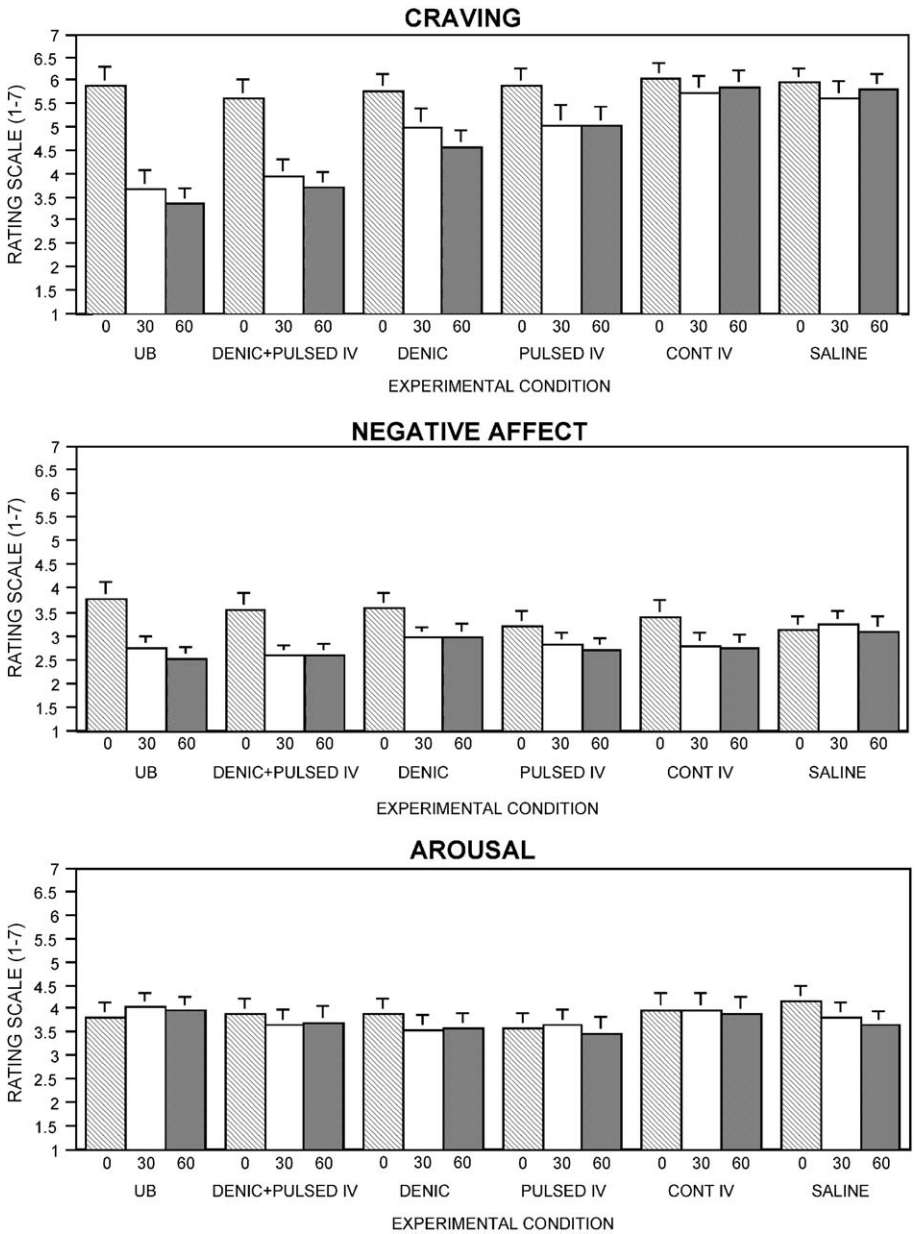

Fig. 2. Mean (± S.E.M.) self-reported craving for cigarettes (upper panel), negative affect (middle panel), and arousal (lower panel) during the first 60 min of each satiation condition (before the initiation of the ad libitum smoking period). Ratings were made at 0, 30, and 60 min, using seven-point rating scales.

rettes, with subjects taking less smoke volume from the usual-brand cigarettes in the denicotinized cigarette/iv saline condition than in the no-smoke/iv saline condition [$F(1,85) = 19.35$, $P < .0001$]. Additional evidence of satiation from the programmed denicotinized puffs was shown by the significant reduction in nicotine boost (from Hours 1 to 4) as well as in cotinine boost during the denicotinized cigarette/iv saline satiation condition relative to the no-smoke/iv saline condition. These results indicated that less nicotine was obtained from ad libitum smoking of the usual-brand cigarettes when receiving programmed presentations of denicotinized cigarettes. The change in nicotine concentration was 17 ng/ml (S.D. = 12.1) in the saline condition vs. 6 ng/ml in the denicotinized cigarette/iv saline condition [$F(1,9) = 6.91$, P=.03], and the changes in cotinine concentrations were 9 ng/ml (S.D. = 20.4) and −9 ng/ml (S.D. = 22.6), respectively [$F(1,13) = 10.55$, P=.006]. Expired air CO boost could not accurately be compared between these conditions because of the difficulty in separating the CO boost due to ad libitum smoking from that due to the programmed puffs of denicotinized smoke.

In contrast to the strong satiating effect of denicotinized cigarette smoke, there was a less robust satiation apparent in the iv nicotine conditions (which did not differ significantly from each other). Cumulative puff volume did show a trend to be lower in the iv nicotine conditions than in the saline condition [$F(1,85) = 2.86$, P=.09], and there was a marginally significant effect on CO boost (CO boost during ad libitum smoking of 9 ppm in the iv nicotine conditions vs. 12 ppm in the saline condition, $F(1,18) = 4.44$, P=.05]. However, in a direct comparison of cumulative puff volume between the denicotinized smoke/iv saline condition and the no-smoking/iv nicotine conditions, the satiating effect of the denicotinized smoke was found to be greater [$F(1,85) = 11.49$, P=.001]. The usual-brand satiation condition also showed a larger effect on ad libitum puff volume than denicotinized smoke alone [$F(1,85) = 7.86$, P=.006], but the combination of iv nicotine and denicotinized cigarette smoke was as satiating as the usual-brand cigarettes [$F(1,85)$=.67, P=.41].

3.5. Withdrawal symptoms

A similar pattern of results emerged when examining the effects of the different satiation conditions on withdrawal symptoms during the first hour of each session (before ad libitum smoking commenced). Here, it was apparent that both denicotinized smoke and iv nicotine had similar effects in relieving craving (see Fig. 2). In terms of decreasing craving from the baseline level, the denicotinized cigarette/iv saline condition was more effective than the no-smoking/iv saline control [$F(1,80) = 6.94$ P=.01]. In addition, there was a trend for pulsed iv nicotine to have a greater effect than the continuous iv nicotine infusion [$F(1,80) = 2.81$, P=.1]. The combination of denicotinized smoke and iv nicotine nearly matched the effect of the usual-brand satiation condition [$F(1,160) = 2.06$, P=.16], whereas neither the denicotinized smoke alone nor the pulsed iv nicotine alone relieved craving to the extent of the usual brand [$F(1,160) = 9.98$, P=.002 and $F(1,160) = 31.49$, $P < .0001$, respectively].

There were nonsignificant trends for denicotinized smoke alone, as well as iv nicotine alone, to decrease negative affect ratings (see Fig. 2). The usual brand was more effective in relieving negative affect than denicotinized smoke alone [$F(1,80) = 5.74$, P=.02], but, as with craving, was not significantly different from the combination of the denicotinized cigarette plus iv nicotine [$F(1,80)$= .87, P=.35].

Subjective arousal was higher in the usual brand satiation condition than in the no-smoking/saline control condition [$F(1,80) = 5.42$, P=.02], but no other effects reached statistical significance.

3.6. Subjective effects

Ratings of the first usual-brand cigarette smoked during the ad libitum period were compared across conditions, and there were no significant effects of any of the satiation manipulations.

4. Discussion

The main result of this study was that a considerable degree of satiation, measured by a reduction in ad libitum smoking of the usual-brand cigarettes, was obtained when subjects were provided with the sensorimotor components of smoking, delivered by puffs of denicotinized cigarettes. The finding that denicotinized smoke produced a large satiation effect is consistent with our previous studies and with those from other laboratories showing that sensorimotor cues provide an important component of immediate smoking satisfaction (Butschky et al., 1995; Gross et al., 1997; Pickworth et al., 1999; Rose, 1988; Rose et al., 1985, 1993, 2000). The fact that the satiation conditions in the present study did not acutely interfere with the subjective enjoyment of ad libitum smoking renders the conclusions less susceptible to the objection that reduced ad libitum smoking represented aversion rather than satiation.

Intravenous nicotine, administered either as a continuous infusion or as puff-sized bolus doses, had a smaller, but measurable, effect on ad libitum smoking. Previous studies on the effects of iv nicotine on ad libitum smoking have yielded mixed results; Kumar et al. (1976), for instance, reported that iv nicotine administration did not suppress ad libitum smoking behavior. Lucchesi et al. (1967), however, did find a ‘‘small but significant’’ reduction in ad libitum smoking when subjects received iv nicotine infusions. Benowitz and Jacob (1990), using an elegant method in which iv administration of deuterium-labeled nicotine allowed the separate measurement of nicotine taken in from ad libitum smoking, also found that a 14-h iv infusion of

nicotine (in the same dose normally self-administered by subjects during ad libitum smoking) caused about a 25% reduction of nicotine intake from ad libitum smoking. Taken together with the present results, there indeed seems to be an effect of nicotine levels in the short-term regulation of ad libitum smoking, but it is not a large effect, at least when modest doses of nicotine are administered (cf. (Benowitz et al., 1998)).

It might be argued that a larger effect of iv nicotine was not seen because even the pulsed nicotine injections did not adequately replicate the effects of pulmonary delivery of nicotine from inhaled cigarette smoke. However, findings from studies in our laboratory argue against this hypothesis. In one study, arterial nicotine concentrations during cigarette smoking and during pulsed iv nicotine delivery showed similar profiles and peak levels (Rose et al., 1999a). In addition, in a number of studies, we have shown that manipulations of the intensity of sensory impact, including local anesthesia of the airways and administration of a peripherally acting nicotinic acetylcholine receptor antagonist, attenuate smoking satisfaction even though nicotine is administered via the pulmonary route (Rose et al., 1985, 1999b).

The fact that iv nicotine, even administered in rapid injections, has only a subtle effect on ad libitum smoking behavior does not negate the widely accepted theory that inhaled nicotine reinforces smoking behavior. Indeed, our view is that the behavior of smoking is strengthened as a result of numerous reinforcing doses of nicotine. However, the history of reinforcement establishes the conditioned reinforcing value of associated sensorimotor cues; thus, smokers experience a craving to engage in the actual behavior of smoking and require more than nicotine for satiation to occur.

In contrast to the small effect of iv nicotine on ad libitum smoking, craving for cigarettes and negative affect during the first hour showed more sensitivity to iv nicotine administration, and pulsed injections appeared to be more effective than the continuous infusion in relieving craving. This result provides some support for the bolus hypothesis, which holds that smokers are dependent in part on rapid absorption of nicotine in cigarette smoke (Russell and Feyerabend, 1978). However, both continuous and pulsed nicotine administration equivalently alleviated negative affect symptoms. These results are reminiscent of the findings from smoking cessation treatment studies using nicotine skin patches (analogous to continuous iv nicotine infusion), which generally show more robust relief of negative affect symptoms than craving for cigarettes (Abelin et al., 1989; Rose et al., 1990).

The denicotinized cigarettes did not alleviate withdrawal symptoms to as great an extent as did nicotine-containing cigarettes. This finding is in agreement with some previous studies (e.g. Pritchard et al., 1996) but contrasts with the results of other studies that have reported equivalent withdrawal suppression from denicotinized and nicotine-containing cigarettes (e.g. Butschky et al., 1995; Gross et al., 1997; Pickworth et al., 1999). One notable difference across studies that might account for the different results is the degree of tobacco dependence of the subject samples. Studies finding no difference in withdrawal symptoms after smoking nicotine-containing and denicotinized cigarettes have generally recruited subjects with higher levels of dependence. According to a review by Brauer et al. (2001), more highly dependent smokers respond more similarly to denicotinized and nicotine-containing cigarettes, possibly because of greater conditioning of the stimulus cues in smoke or to a greater tolerance to the pharmacologic effects of nicotine. Thus, subjects in the present study, having moderate dependence (based on the FTND questionnaire), would have been expected to show more sensitivity to the effects of nicotine. Procedural differences might also contribute to the different results obtained across studies; for example, Gross et al. (1997) examined smokers using denicotinized or nicotine-containing cigarettes during an afternoon session after they had smoked nicotine-containing cigarettes all morning. Measured plasma nicotine levels were relatively high in all test conditions, possibly masking some of the effects of the different cigarette conditions on craving or other withdrawal symptoms. In summary, subject characteristics, deprivation state, and smoke-dosing procedures may alter the relative influences of nicotine and nonnicotine factors on withdrawal symptoms.

In the present study, programmed puffs of the usual-brand cigarettes produced considerable, but not complete satiation, as subjects still took in approximately 25% of their baseline ad libitum intake in addition to the controlled puffs provided by that satiation condition. This is not surprising inasmuch as day-to-day variations in smoking pattern in some cases may have resulted in an urge to smoke occurring before the scheduled delivery of satiation puffs. Also, it is possible that puffing from the controlled delivery apparatus did not fully satiate the desire to hold a cigarette and puff freely.

The combination of iv nicotine and denicotinized smoke recaptured most of the subjective and behavioral effects of smoking the usual-brand cigarettes, replicating and extending our previous finding that the combination of a nicotine skin patch and denicotinized cigarettes duplicated the reduction in craving seen with usual-brand cigarettes (Rose et al., 2000). Following the analytic/synthetic method of "putting Humpty Dumpty together again" allows us to better understand the role of various components of smoking in the overall maintenance of cigarette addiction.

In conclusion, neither the nicotine component nor the sensorimotor component alone was sufficient to duplicate the effects of the usual brand. The nonnicotine components of smoking partially relieved withdrawal symptoms and produced some satiation, indexed by the short-term decrease in ad libitum smoking when cigarettes were freely available. The pharmacologic effects of nicotine also partially relieved craving and contributed to satiation. Together, receiving pulsed iv nicotine administrations plus smoking a denicoti-

nized cigarette recaptured most of the subjective and behavioral effects of smoking the usual-brand cigarette. Our results strongly suggest that in designing treatments to aid in smoking reduction or cessation efforts, both the pharmacologic and sensorimotor aspects of cigarette smoking must be addressed.

Acknowledgements

This work was supported by Grant DA 02665 from the National Institute on Drug Abuse.

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