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Dissociating nicotine and nonnicotine components of cigarette smoking

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Abstract

To dissociate the sensorimotor aspects of cigarette smoking from the pharmacologic effects of nicotine, smokers rated the subjective effects of nicotine-containing or denicotinized cigarettes, and intravenous (IV) nicotine or saline infusions. Three groups of participants (n = 20 per group) received either: (1) continuous nicotine, (2) pulsed nicotine, or (3) saline. Each group was exposed to an IV condition once while smoking a denicotinized cigarette and once while not smoking, in a 3 × 2 mixed design. A fourth group (n = 20) received saline while smoking their usual brand of cigarette. The dose and rate of nicotine administration were individualized based on previous measures of ad lib smoke intake. Denicotinized cigarette smoke significantly reduced craving and was rated significantly more satisfying and rewarding than the no-smoking conditions. IV nicotine reduced craving for cigarettes, and increased ratings of lightheadedness and dizziness. However, no significant satisfaction or reward was reported after IV nicotine. The combination of IV nicotine and denicotinized cigarette smoke produced effects similar to those of smoking the usual brand of cigarette. The results suggest that sensorimotor factors are critical in mediating the immediate subjective response to smoking, and that the immediate subjective effects of nicotine administered in doses obtained from cigarette smoking are subtle. Thus, addressing smokers' needs for both for the sensorimotor aspects of smoking as well as for the direct CNS effects of nicotine may be critical in enhancing smoking cessation treatment outcome.

Keywords: Nicotine; Smoking; Euphoria; Addiction; Craving; Substance abuse

1. Introduction

Considerable evidence supports the view that cigarette smoking is maintained by an addiction to nicotine [28]. This view has led to the development of smoking cessation treatment methods that provide nicotine replacement. One of the goals of nicotine replacement therapy is to partially substitute for the rewarding effects of cigarette smoke, reducing the need for tobacco [11]. However, the effects of nicotine, when delivered without cigarette smoke, have generally been found to be much less rewarding than smoking [10,18,19]. Moreover, most people trying to quit smoking eventually relapse even when provided with nicotine in the form of gum, patches, nasal spray, or inhaler [7]. While these alternative forms of nicotine delivery can effectively relieve some smoking withdrawal symptoms [12], craving for cigarettes is only partially alleviated during the initial days of smoking abstinence [1,23].

Why do current methods of nicotine replacement fail to provide adequate substitution for the reinforcing effects of cigarette smoking? Two main explanations have been proposed to account for the relatively low effectiveness of nicotine replacement. The first is that nicotine replacement techniques do not provide an adequate dose or rate of nicotine administration. Not only do many smokers inhale more nicotine per day than is delivered from alternative nicotine delivery systems, but in addition, the inhalation route is more rapid than current nicotine-based treatments. It has been argued that this rapid delivery is critical to the reinforcing potency of cigarette smoking [26]. However, a second explanation is that nicotine replacement methods lack important sensory/behavioral components of cigarette smoking [20]. Indeed, smokers report missing the behavioral aspects as well as the sensory cues of smoking, such as the taste, aroma, and respiratory tract sensations accompanying each puff of smoke [22,23]. In several studies we have shown that these sensations are especially important in

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relieving craving for cigarettes, and they have also been shown to facilitate smoking abstinence [2,29].

To evaluate these contrasting explanations it is important to dissociate nicotine administration from the behavior of cigarette smoking, using a method of nicotine administration that preserves the rapid pharmacokinetic profile of pulmonary delivery. Recently, we reported that the arterial nicotine concentrations measured at 5-s intervals following intravenous (IV) nicotine administration were very similar to those of inhaled nicotine [21]. Thus, IV nicotine delivery offers a feasible approach to duplicating the pharmacologic effects of smoking with minimal sensory/behavioral cues. In a preliminary study [30], we reported that IV nicotine, when administered in conjunction with smoking a denicotinized cigarette, had minimal effects on subjective measures such as satisfaction and craving for cigarettes. In contrast, smoking a denicotinized cigarette had robust effects on these subjective measures, demonstrating the importance of nonnicotine cues in mediating responses to smoking. However, this study had limited statistical power, as it included only six subjects, and a saline control was lacking in the no-smoking conditions, which would have allowed an assessment of the effects of IV nicotine in the absence of smoking.

In the present study, a considerably larger subject sample size was used, and a saline control condition was included in both smoking and no-smoking conditions. Our main goal was to evaluate the hypothesis that presentation of pharmacologic component of smoking using IV nicotine would produce significant rewarding effects. Moreover, individualized tailoring of IV nicotine doses was incorporated into the design to better evaluate the importance of the nicotine component of smoking with realistic dosing parameters. A second goal of this study was to determine with greater precision whether IV bolus nicotine injections are more effective in providing subjective rewarding effects than continuous nicotine infusions. Furthermore, we sought to assess how nicotine dose and sensory/behavioral cues interact in affecting subjective smoking reward. To accomplish this, we measured the immediate subjective responses to the nicotine and nonnicotine components of smoking, individually and in combination. As in the previous study, we assessed the effects of the sensory/behavioral components of smoking using denicotinized tobacco cigarettes, which presented most of the nonnicotine constituents of cigarette smoke with minimal doses of nicotine.

2. Materials and methods

2.1. Design

Eighty subjects were randomly assigned to four groups (see Fig. 1) receiving either: (1) rapid IV injections (boli) of puff-sized doses of nicotine, (2) continuous IV infusions of nicotine, or (3) saline infusions. Subjects in these three groups received two identical IV presentations in the same session, separated by 90 min. During one presentation, subjects smoked a denicotinized cigarette, and during the other presentation no smoke was given (order counterbalanced across subjects); (4) a fourth group also received two saline infusions, during one of which they smoked their usual brand of nicotine-containing cigarette (order counterbalanced). Thus, the first three groups comprised a 3 (nicotine bolus injections vs. nicotine infusions vs. saline) $\times$ 2 (denic cigarette vs. no-smoking) mixed within/between design, with the nicotine factor being a between-subjects factor and smoking being a within-subjects factor. Group 4 (usual brand vs. no smoking) provided a useful benchmark for the rewarding effects of inhaled nicotine delivered in conventional cigarette smoke.

GROUP	CIGARETTE	I.V. CONDITION
1	DENIC (or no smoking)	Continuous Nicotine
2	DENIC (or no smoking)	Pulsed Nicotine
3	DENIC (or no smoking)	Saline
4	USUAL BRAND (or no smoking)	Saline

Fig. 1. Description of conditions for the different experimental groups.

2.2. Subjects

Healthy volunteers were recruited from the community by newspaper advertisements. To facilitate subject recruitment, prospective volunteers were offered two incentives; monetary payment of $75 per session, and after completion of the present study, smoking cessation treatment including a free 6-week course of nicotine skin-patch treatment. Subjects were 18–55 years of age, and smoked at least 20 cigarettes/day of a brand delivering at least 0.7 mg nicotine (by FTC method). Subjects' expired CO concentrations (measured in the afternoon) were >20 ppm (confirming inhalation). Subjects were healthy, based on physical examination, ECG, serum chemistries, CBC, and urinalysis, and were excluded if they had been diagnosed with coronary artery disease, cardiac rhythm disorder, or any serious medical condition, current psychiatric disease (aside from nicotine dependence), hypertension (systolic > 140 mm Hg, diastolic > 90 mm Hg), or hypotension (systolic < 90 mm Hg), or if pregnant or nursing.

2.3. Methods of IV nicotine delivery

Nicotine solutions: pure nicotine base was obtained from Eastman Kodak (Rochester, NY) in accord with our FDA-approved investigational new drug application for IV and inhaled nicotine administration. The Duke University Pharmacy service prepared a solution of 0.01% nicotine (w/w) in saline. The solution, which was basic, was then pH adjusted to 7.0 using acetic acid, sterilized by filtration and autoclaving, and finally was tested for pyrogens.

At least 30 min prior to the first IV infusion, two 22-gauge IV catheters with injection ports were inserted: one catheter

was placed in the antecubital vein of the non-dominant arm for IV infusions (in pilot work we found that bolus injections into the cephalic vein produced pain at the catheter site, extending up the forearm); the second catheter was placed in the antecubital vein or cephalic vein of the dominant arm for blood sampling. The arm was wrapped in polyvinylidine chloride (Saran® wrap) to minimize the risk of contamination of samples from smoke particles in ambient air. Catheters were flushed or maintained with saline infusion per standard technique. IV solutions were administered with an IVAC pump or syringe in double-blind fashion.

Because the arm-to-brain transit time for IV nicotine injections in the bolus condition was expected to be approximately 13–14 s [26], as compared to the 7–8-s lung-to-brain transit time for inhaled nicotine, each bolus injection was administered approximately 3–4 s prior to initiating each puff. Taking a puff and inhaling required 3–4 s and thus the time between actual inhalation of denicotinized smoke and arrival of a nicotine bolus to the brain should have been similar to the usual 7–8 s delay experienced with normal smoking. A partition shielded the IV catheter from view so that subjects did not witness the timing of injections. In the continuous nicotine (or saline) conditions, infusions began with the first puff and ended 1 min after the last puff.

2.4. Methods of cigarette smoke delivery

2.4.1. Denicotinized cigarettes

We obtained denicotinized cigarettes, manufactured by Phillip Morris, which were used in the proposed work. These cigarettes contain tobacco from which the nicotine has been selectively extracted by supercritical carbon dioxide, and have a taste and tar delivery similar to nicotine-containing brands of cigarette. The tar delivery of these cigarettes, when smoked by FTC criteria, is 9 mg. However, the nicotine delivery is extremely low, less than 0.1 mg. Hasenfratz et al. [8] measured smoking behavior and nicotine intake after smoking denicotinized vs. nicotine-containing cigarettes, and found that plasma nicotine levels increased less than 2 ng/ml after smoking the denicotinized cigarette. We have verified that these cigarettes produce less than 2-ng/ml boosts in arterial blood nicotine concentration, and also that they do not increase heart rate, a sensitive index of nicotine delivery in deprived smokers [21].

2.4.2. Controlled puff volume apparatus

Puff volume for both denicotinized and usual-brand cigarettes was controlled with a simple apparatus we validated in previous studies [16]. The device used a glass syringe preloaded with a measured amount of air that was supplied to the burning cigarette with each puff. When subjects took a puff, the syringe barrel slid within the glass housing until the specified volume of air (smoke) had been drawn into the mouth, and no further smoke could be obtained until the device was reset for the next puff. Because subjects had indwelling catheters for nicotine delivery and blood sampling in each arm, the apparatus was held in place with a ring stand situated conveniently in front of the subject, who could take puffs by leaning forward from a semirecumbent position, and drawing from a disposable plastic mouthpiece having a diameter comparable to a cigarette.

2.5. Procedure

The pharmacologic effects of nicotine were delivered without the usual sensory and behavioral cues, using IV nicotine infusions; conversely, the sensory and behavioral components of the smoking habit were conveyed without pharmacologic actions, using denicotinized tobacco smoke. Because there is enormous variability between cigarette smokers in the nicotine dose extracted from cigarettes during ad lib smoking [4], the number of puffs, puff volumes, and interpuff intervals were individualized to match the characteristic topography of each participant. To accomplish this, participants' habitual nicotine intake from cigarette smoking was measured, and then nicotine infusions mimicking the dose and rate of intake were administered. Eighty subjects reported to the laboratory after overnight abstinence for a preliminary baseline session to measure ad lib smoke intake. Self-reported abstinence for this and subsequent sessions was confirmed at the beginning of the session by expired air CO measurement, and subsequently verified by plasma nicotine assay. Usual caffeine consumption was permitted prior to the session.

Ad lib smoking behavior was assessed by measuring the puff volumes, number of puffs taken, and interpuff intervals from subjects' usual brands of cigarettes. To accomplish this, the nicotine intake after ad lib smoking of one cigarette (after overnight abstinence from smoking) was quantified by measuring puff volume, number of puffs, and interpuff intervals, using the smoke delivery apparatus described above. The air-containing syringe was initially filled with 80 cm^3 prior to each puff, and the reading after each puff was recorded, indicating the puff volume inhaled. To calculate the average per-puff dose of nicotine, the smoking pattern was reproduced in the laboratory, and the smoke particulate matter was trapped in Cambridge filters. 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 [25]. Using published values for the nicotine/tar ratio for each brand of cigarette [5], the nicotine delivery per puff could then be estimated. Subsequently, when each subject reported for the infusion session, s(he) received nicotine (or saline) infusions, in double-blind fashion, using the same dose and rate of administration (rate was calculated in terms of mg nicotine per minute for the continuous nicotine infusion condition and mg/injection for the pulsed nicotine condition). As described above, the interinfusion period was 90 min, and infusions were administered either as pulsed

injections, with each injection delivering a nicotine dose equivalent to one puff, or as a continuous infusion. The total duration of the infusions was equal to the duration of ad lib smoking after overnight abstinence. Number of puffs, mean puff volume, and interpuff interval were also set equal to the values measured during each subject's baseline ad lib smoking session.

2.6. Dependent measures

During the infusion session, the following dependent measures were assessed.

2.6.1. Plasma nicotine concentrations

To verify that the IV nicotine infusions produce dose-related increases in systemic nicotine levels comparable to cigarette smoking, 10-cm^3 samples of venous blood samples were collected before and after each infusion. The samples were centrifuged, packed on dry ice, and shipped from Durham, NC, to the Clinical Pharmacology Laboratory at the University of California, San Francisco, for assay by gas chromatography as described by Jacob et al. [13], modified for use of a capillary column. Limits of quantitation of this assay are 1.0 ng/ml (CV 7.8%) and 10 ng/ml (CV 8.7%) for nicotine and cotinine, respectively.

2.6.2. Smoking withdrawal symptom questionnaire

Before and after each infusion we administered a modified Shiffman–Jarvik questionnaire [27] that we have employed previously in several laboratory studies. It has been sensitive in detecting effects of cigarette deprivation and pharmacologic treatments (e.g., Ref. [32]). The items comprise six subscales: craving (craved a cigarette, would have liked a cigarette, thought of cigarettes, missed a cigarette, had urges to smoke, and, scored oppositely, would have refused a cigarette), negative affect (tense, irritable, and, scored oppositely, calm, content), arousal (wide awake, able to concentrate, and unusually sleepy), somatic symptoms (fluttery feelings in chest, heart beat faster than usual, hands shake, headache, cough, mouth sores, sore throat, heartburn, chest tightness, nausea, bad taste in mouth, upset stomach, and dizziness), appetite (have eaten more than usual, hungrier than usual, craved sweets, and craved salty foods), and habit (missed something to do with the hands, and missed having something in the mouth).

2.6.3. Condition evaluation questionnaire

After each infusion condition, subjects completed a questionnaire previously developed [31] to assess the subjective effects of smoking; items assessed Satisfaction ("Was it satisfying?"; "Was there a good taste?"), Psychological reward ("Did it calm you down?"; "Did it make you feel more awake?"; "Did it reduce your hunger for food?"; "Did it make you feel less irritable?"), Nausea/dizziness ("Did you feel nauseated?"; "Did you feel dizzy?"), Craving relief ("Did it immediately reduce your craving for cigarettes?"), and Enjoyment of airway sensations ("Did you enjoy the sensations in your throat and chest?").

2.6.4. Sensory questionnaire

To obtain detailed information about the sensory properties of cigarette smoke and nicotine, we administered, after each infusion, a sensory questionnaire used in several previous studies, which included items assessing: Estimated nicotine delivery, Similarity to usual brand, and perceived Strength on the tongue, nose, back of mouth and throat, windpipe, and chest.

2.6.5. Mood questionnaire

Additionally, a questionnaire designed to detect mood effects of nicotine and smoking was administered after each infusion, consisting of items that were found in factor analyses to load onto two subscales: Euphoria (exhilaration, pleasurable excitement, comfort, relaxation, and well-being); and Dysphoria (dizziness, lightheadedness, nausea, nervousness, and burning or pain at the IV site).

All items of these questionnaires were rated on seven-point scales labeled as follows: 1 ("not at all"), 2 ("very little"), 3 ("a little"), 4 ("moderately"), 5 ("a lot"), 6 ("quite a lot"), or 7 ("extremely").

2.6.6. Cardiovascular measures

Heart rate and blood pressure were monitored at 1-min intervals immediately prior to and during each infusion using an automated sphygmomanometer (Critikon, Tampa, FL).

2.6.7. Smoking behavior

Subjects' expired air CO concentrations were measured before and after each cigarette using a handheld CO monitor (Vitalograph, Lenexa, KS). Expired air CO concentrations were calculated by subtracting the background (ambient) CO from the peak CO reading. The number of puffs taken from each cigarette were also counted by the research technician, and because the puff volume is controlled, this reflected the total volume of smoke taken into the mouth.

2.7. Statistical analyses

Data analysis was performed using SUPERANOVA and STATVIEW (SAS Institute, Cary, NC). For each parametric variable (including questionnaire scales assessing smoking withdrawal symptoms, ratings of smoking satisfaction and reward), a multivariate approach to repeated measures analysis ANOVA was used, which is generally appropriate regardless of the correlation pattern among repeated measurements. For each dependent measure, an analysis was first conducted using data from the 2 (smoke vs. no-smoke) $\times$ 3 (nicotine bolus injections vs. continuous nicotine vs. saline) factorial design. Each subject's rate of smoking and rate of nicotine delivery, as determined from the smoking baseline, was used as a covariate in these analyses. Additionally, in assessing the between-subjects

factor of IV nicotine condition, baseline ratings of the usual brand cigarettes were entered as covariates in the analysis. Any significant interactions between factors were followed-up with an analysis of simple effects. Additionally, planned contrasts compared the nicotine bolus injection conditions with the continuous nicotine infusion condition. In the absence of a difference, a subsequent contrast compared the two IV nicotine conditions with the saline condition.

Finally, contrasts were conducted to compare the combination of IV nicotine + denic cigarette to the usual brand cigarette condition; this analysis determined (within the limits of statistical power) whether the rewarding action of a conventional cigarette could be achieved by the combined presentation of the sensory/behavioral and pharmacologic components of cigarette smoking using separate modes of administration.

3. Results

3.1. Subject characteristics

Table 1 shows the subject characteristics, broken down by infusion condition. There were no significant differences between groups in age, years smoked, gender, FTC nicotine, cigarettes/day, baseline expired air CO, Fagerstrom test for Nicotine Dependence score (FTND) [9], or plasma cotinine levels.

3.2. Effects of denicotinized smoke and IV nicotine

In this section, all effects of smoking refer to the denicotinized cigarette. Comparisons with the usual brand cigarette condition will be described in the next section.

3.2.1. Condition evaluation scales

As shown in Fig. 2, satisfaction ratings were significantly higher in the smoking conditions relative to the no-smoking conditions, $F(1,51)=40.79$, $p < 0.0001$. Similarly, ratings of psychological reward, enjoyment of respiratory tract sensations, and craving reduction were significantly higher in the smoking conditions ($p=0.013$, $p=0.0001$, and $p=0.002$, respectively). In contrast, IV nicotine did not affect ratings of satisfaction, psychological reward or enjoyment of respiratory tract sensations ($ps \geq 0.1$ for the contrasts between saline and the two IV nicotine conditions, which did not differ from each other). However, IV nicotine did reduce craving for cigarettes ($p=0.04$), and did increase ratings of nausea and dizziness relative to saline (mean rating of 1.8, SEM = 0.12 vs. a mean of 1.5, SEM=0.11, $p=0.03$).

3.2.2. Smoking withdrawal symptoms

Precondition ratings as well as prepost change scores were examined. There were precondition differences for several of the scales (craving, negative affect, and habit withdrawal) that indicated some carryover from the prior condition. Therefore, we focused on the analysis of prepost condition change scores (see Fig. 3). An effect of nicotine ($p=0.03$) and trend for smoke administration ($p=0.06$) were detected on the prepost condition change in arousal. However, these effects on arousal were limited to subjects who received the high rate of smoke/nicotine administration ($p=0.01$ for IV condition × rate interaction). Nicotine and smoke administration both increased subjective arousal for subjects in this group ($p=0.06$ and 0.02, respectively). Change in craving showed no significant differences between conditions; however, habit withdrawal ratings showed a significantly greater reduction after smoking relative to no smoking ($p=0.04$). There was also a trend for smoking to reduce negative affect ratings ($p=0.07$). No effect of IV nicotine was detected on either habit withdrawal or negative affect.

3.2.3. Sensory ratings

Ratings of estimated nicotine delivery were no higher for the denicotinized cigarette than for the no-smoking condition, nor were ratings higher in the nicotine than saline infusion conditions. Ratings of similarity to the usual brand cigarette were significantly higher in the denicotinized cigarette condition than the no-smoking condition ($p=0.03$), as shown in Fig. 4. In contrast, IV nicotine had no effect on ratings of similarity. Airway sensations showed a robust effect of smoke condition, with strength ratings higher when smoking the denicotinized cigarette vs. no smoking, for the tongue ($p=0.0001$), nose ($p=0.002$), back of mouth

Table 1

	IV saline (n = 20)		IV NIC (continuous) (n = 20)		IV NIC (pulsed) (n = 20)		Usual brand (n = 20)	
Subject characteristics	mean	SD	mean	SD	mean	SD	mean	SD
Age	42.6	8.04	40.1	2.07	42.2	8.45	43.7	9.08
Gender	10 m, 10 f		12 m, 8 f		10 m, 10 f		10 m, 10 f	
Cigarettes/day	32.0	11.70	29.4	9.10	28.4	10.56	28.0	7.68
FTC nicotine	0.81	0.25	0.84	0.25	0.77	0.21	0.74	0.20
Years smoked	25.3	6.40	21.0	11.24	24.4	8.75	25.3	8.83
Plasma cotinine (screening)	324.5	22.28	272.0	20.74	315.3	38.21	293.1	18.02
FTND	7.1	1.72	7.1	1.60	6.2	1.82	6.4	2.01

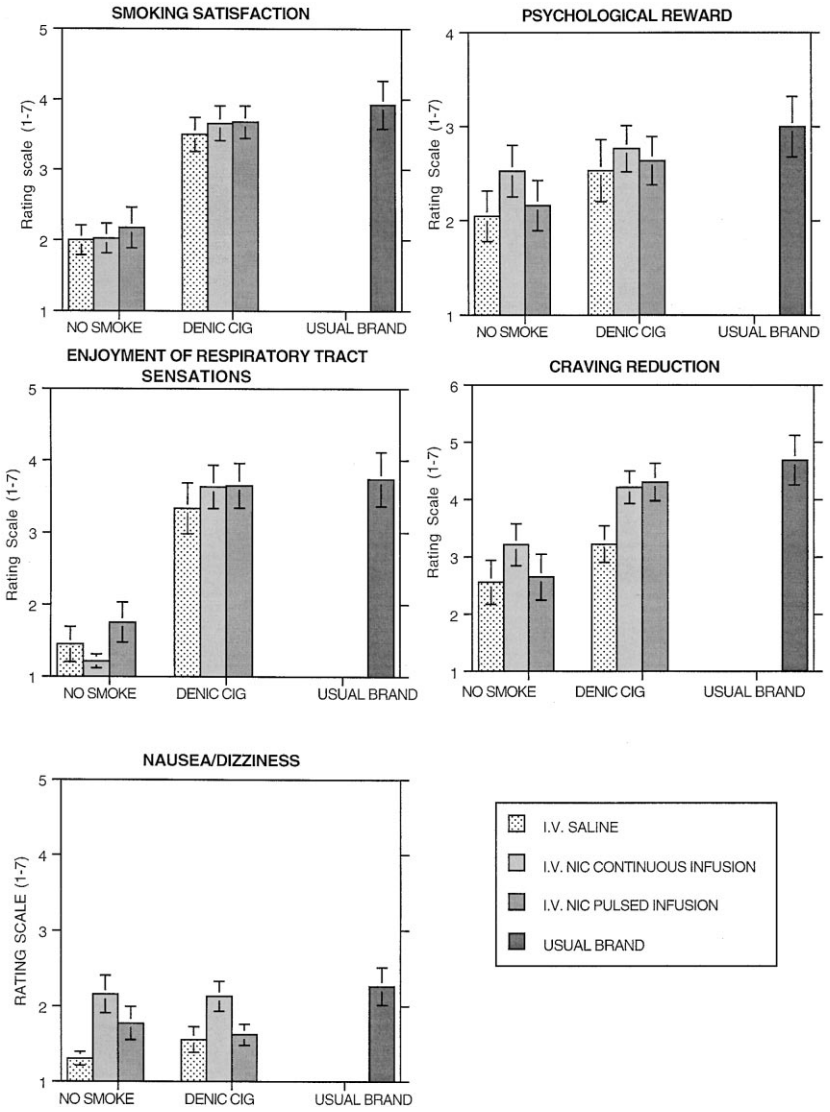

Fig. 2. Mean (± SEM) condition evaluation ratings for the three IV conditions and the different cigarette types.

and throat ($p=0.0001$), windpipe ($p=0.0001$), and chest ($p=0.0001$). Although IV nicotine infusions did not generally produce higher ratings of airway sensations than saline, the pulsed nicotine injections did elicit higher ratings than the continuous infusions, for the nose ($p=0.02$), and there was a similar trend for windpipe sensations ($p=0.07$). For the nose, there was an interaction of IV nicotine × rate of smoke/nicotine delivery ($p=0.04$), such that subjects receiving the more rapid IV nicotine delivery reported stronger sensations, even in the absence of smoking.

3.2.4. Euphoria/dysphoria

The analysis of the euphoria factor showed a significant interaction between IV condition, smoke/nicotine delivery rate, and smoking, $F(2,53)=3.49$, $p=0.04$. An analysis of this interaction in terms of simple effects revealed an effect of smoking that was limited to the saline infusion condition and subjects accustomed to a higher than average rate of nicotine intake during ad lib smoking. In this subgroup, smoking a denicotinized cigarette increased ratings of euphoria. IV nicotine did not significantly influence euphoria ratings, and in fact, the ratings were remarkably similar in nicotine and saline infusion conditions (see Fig. 5). To examine the possibility that the failure to detect an effect of nicotine was due to limited statistical power, the confidence interval of the nicotine–saline difference in euphoria ratings was calculated (averaging the two IV nicotine conditions). The upper limit of the 95% confidence interval (one tailed) for a nicotine–saline difference was +0.7 units on the euphoria scale. Thus, any effect of nicotine that may have gone undetected was not likely to be a large effect.

In contrast, the analysis of dysphoria scores showed a significant main effect of IV condition, ($F(2,53)=5.351$, $p=0.003$. Subsequent contrasts indicated that the two IV nicotine conditions were rated higher in dysphoria than the saline control ($p=0.028$, see Fig. 5).

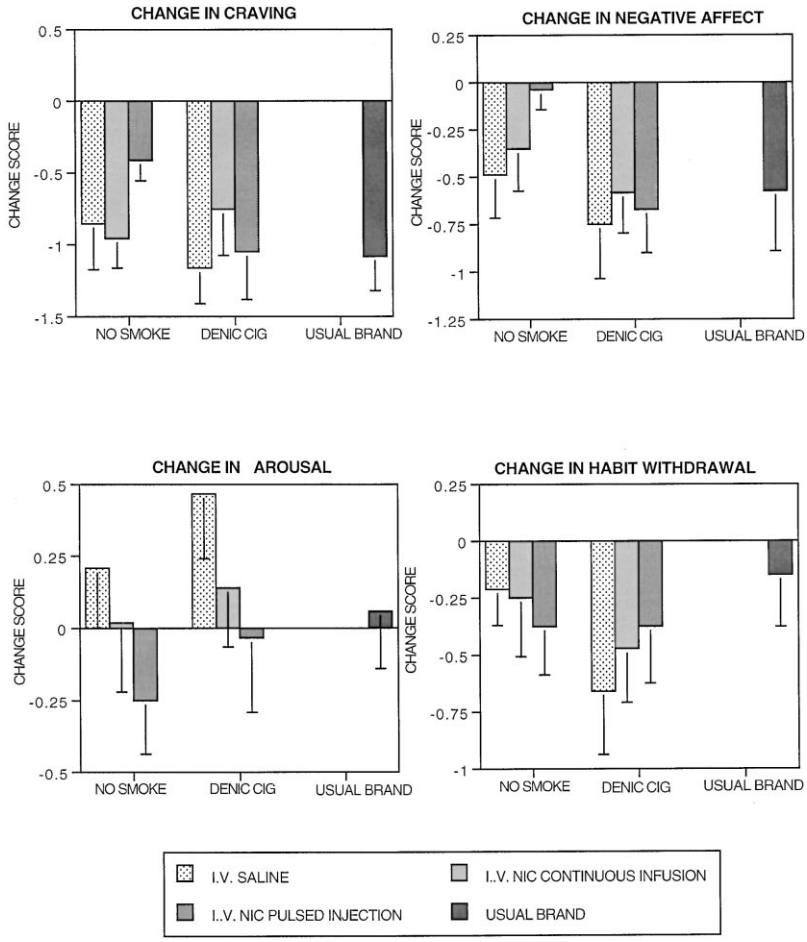

Fig. 3. Mean (± SEM) change in withdrawal symptom ratings (postminus preinfusion) for the three IV conditions and the different cigarette types.

3.2.5. Cardiovascular indices

There was a highly significant effect of nicotine infusion on heart rate boost ($p=0.008$ for the nicotine vs. saline contrast), and a slightly higher boost in the continuous vs. pulsed nicotine condition ($p=0.04$). The mean heart rate boosts were 0.8 bpm (SD=7.35) in the saline condition, 13.1 bpm (SD=10.05) in the continuous nicotine infusion condition, and 8.7 bpm (SD=8.690) in the pulsed IV nicotine condition. Smoking the denicotinized cigarette had no effect on heart rate ($p=0.8$), with a mean heart rate change of 8.1 bpm (SD=9.91) in the smoking conditions vs. 8.4 bpm (SD=10.32) in the no-smoking conditions. There were no significant effects of IV nicotine or smoking on either systolic or diastolic blood pressure.

3.2.6. Smoke/nicotine intake

The prepost infusion boost in expired air CO was, not surprisingly, significantly higher in the smoking conditions ($p=0.0001$); the mean boost was 3.3. ppm (SD=2.51) in the smoking conditions vs. − 0.5 ppm (SD=1.09) in the no-smoking conditions. However, there was also a significantly higher CO boost following smoking in the saline condition than in the two IV nicotine infusions ($p=0.01$ for the interaction of infusion condition × smoke), possibly reflecting differences in the depth of inhalation after each puff; the infusion conditions did not differ significantly from each other ($p=0.4$); the CO boost was 4.3 ppm (SD=3.20) after smoking in the saline condition, 3.1 ppm (SD=2.12) in the continuous IV nicotine condition, and 2.6 ppm (SD=2.01) in the pulsed IV nicotine condition. As expected, the IV nicotine conditions differed from saline in plasma nicotine boost ($p=0.0008$). The two infusion conditions were very similar to each other ($p>0.1$). The mean nicotine boosts were 0.4 ng/ml (SD=0.83) for saline, 12.2 ng/ml (SD=7.51) for the continuous IV nicotine condition, and 10.4 ng/ml (SD=6.61) for the pulsed nicotine condition. Concurrent smoking of the denicotinized cigarette had no measurable influence on the plasma nicotine boost ($p=0.4$).

3.3. Comparisons of usual brand cigarette with denicotinized cigarette + IV nicotine

A set of contrasts was conducted to assess how well the combination of denicotinized cigarette and pulsed injections of IV nicotine matched the subjective qualities of smoking the usual brand cigarette.

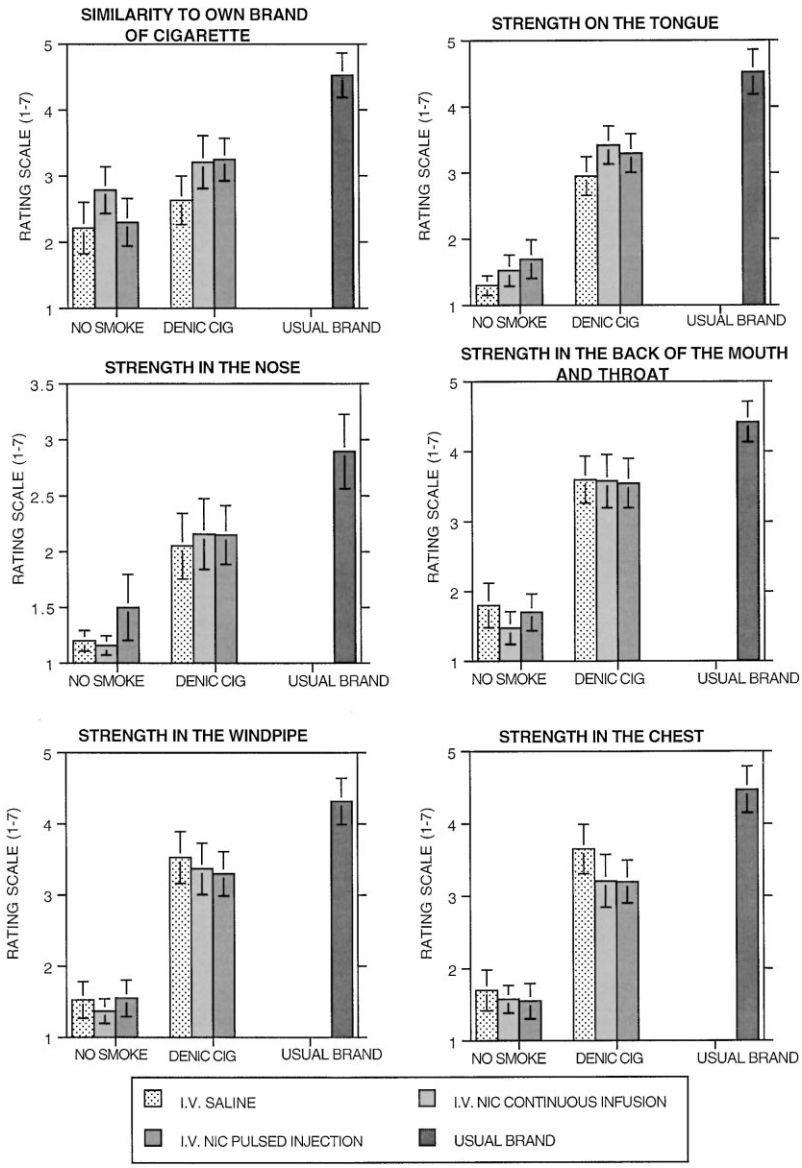

Fig. 4. Mean (± SEM) sensory ratings for the three IV conditions and the different cigarette types.

3.3.1. Condition evaluation scales

None of the differences between the two conditions were significant; the denicotinized cigarette + pulsed IV nicotine condition replicated the ratings of the usual brand cigarette on all of the condition evaluation scales (see Fig. 2).

3.3.2. Smoking withdrawal symptoms

The changes in smoking withdrawal symptoms scales were also very similar in the two conditions ($ps > 0.1$) (see Fig. 3).

3.3.3. Sensory ratings

There was a trend for estimated nicotine ratings to be higher for the usual brand condition ($p = 0.09$); moreover, ratings of similarity to the usual brand were significantly higher in the usual brand cigarette condition ($p = 0.01$). The IV nicotine + denicotinized cigarette received ratings of strength in the respiratory tract similar to those of the usual brand cigarette for the tongue ($p = 0.3$) and nose ($p = 0.8$), but tended to be lower in the back of mouth and throat ($p = 0.06$), and differed significantly in the windpipe ($p = 0.03$) and chest ($p = 0.006$). The usual brand cigarette was rated stronger in the lower respiratory tract regions (see Fig. 4).

3.3.4. Euphoria/dysphoria

Ratings of euphoria and dysphoria also did not differ between the usual brand cigarette condition and the IV nicotine + denicotinized cigarette condition (Fig. 5).

3.3.5. Cardiovascular measures

The heart rate boost following smoking was similar after both conditions (mean boost of 9.8 bpm (SD = 8.8) for the

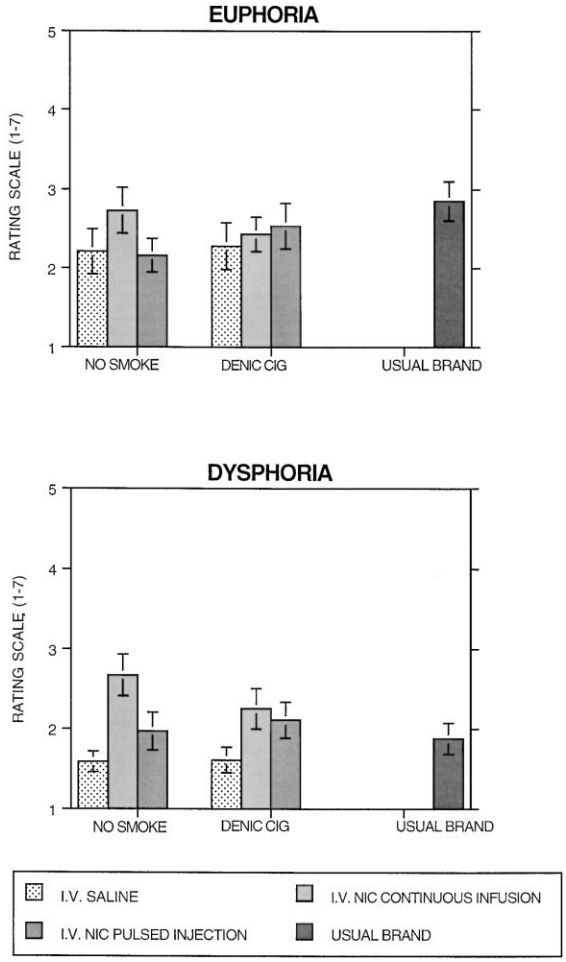

Fig. 5. Mean (±SEM) euphoria/dysphoria ratings for the three IV conditions and cigarette types.

pulsed IV nicotine + denicotinized cigarette condition and 8.1 bpm (SD=7.5) for the usual brand). Similarly, the change in systolic and diastolic blood pressures, though small, did not differ (mean change for the pulsed IV nicotine + denicotinized cigarette condition − 5.0 mm Hg/ − 6.8 mm Hg (SD=9.6/12.1) vs. + 1.0 mm Hg/ − 1.3 mm Hg (SD=14.0/7.6).

3.3.6. Smoke/nicotine intake

Expired air CO boosts were comparable in the two conditions (2.6 ppm (SD=2.0) vs. 3.4 ppm (SD=3.3)). However, plasma nicotine boosts differed somewhat ($p = 0.03$), with the IV nicotine + denicotinized cigarette condition producing higher nicotine boosts [8.2 ng/ml (SD=5.90) vs. 5.6 ng/ml (SD=3.30)].

4. Discussion

The main goal of the study was to determine how the pharmacologic actions of nicotine and the sensory/behavioral aspects of cigarette smoking contribute to the immediate subjective effects of cigarette smoking. Overall, the sensory/behavioral aspects presented by smoking a denicotinized cigarette were marked, and replicated many of the immediate subjective responses evoked by smoking the usual brand of nicotine-containing cigarette. Smoking the denicotinized cigarette produced satisfaction, psychological reward, and craving reduction. Moreover, in some smokers the denicotinized cigarette increased ratings of euphoria. Our results thus underscore the importance of sensory/behavioral factors in smoking reward, and show that these effects can be obtained even using an artificial smoking apparatus. In contrast, the effects of IV nicotine were subtle, and the only subjective variables significantly affected were craving reduction and aversion, with IV nicotine receiving higher ratings for craving reduction than saline and producing some mild nausea and dizziness. Thus, although IV nicotine reduced at least one index of smoking withdrawal, which can be viewed as negative reinforcement, it did not produce a significant pleasurable response. While considerable evidence implicates nicotine addiction as an important determinant of smoking, the immediate subjective effects of nicotine, in doses comparable to those obtained by smoking, appear to be mild. The lack of pleasurable responses to IV nicotine is consistent with our previous results [30] as well as with studies by other investigators who have used similar nicotine dosing parameters [15], or slower nicotine infusions [3,17]. In contrast, some previous studies found that subjects reported intense positive and negative effects of IV nicotine [10,14]. However, in these studies nicotine was rapidly administered in large bolus injections instead of in multiple puff-sized doses. While the latter studies demonstrated that it is possible to elicit large subjective effects, studies using dosing parameters more typical of ad lib smoking suggest that reinforcement mechanisms in tobacco dependence do not appear to depend on intense feelings of subjective pleasure elicited by nicotine. The absence of pleasure associated with IV nicotine was not likely due to the aversive effects of the somewhat higher plasma nicotine concentrations than in the usual brand condition, because even in the usual brand cigarette condition ratings of euphoric effects were modest (between "very little" and "a little" on the seven-point rating scales).

It was somewhat surprising that IV nicotine did not substantially affect other measures of smoking withdrawal, such as a negative affect. The plasma nicotine levels produced in our infusion conditions were similar to those typically achieved by cigarette smoking or alternative nicotine replacement methods [3], and clinically, nicotine replacement has often been shown to reduce negative affect (e.g., Ref. [23]). Possibly, despite overnight deprivation from cigarettes, withdrawal symptoms were limited during the short duration of our study, which was also conducted in a laboratory setting. The mean ratings of negative affect were approximately 4, using the same scale that we have used in several previous smoking cessation trials; in these studies, peak withdrawal ratings often exceed 5 in the absence of

nicotine replacement [2,23]. Alternatively, the within-subjects design was susceptible to carryover effects that could have made it more difficult to detect the effects of nicotine.

The boost in venous nicotine levels was comparable using either continuous or pulsed infusions. However, both IV dosing methods produced somewhat higher venous nicotine boosts than in the usual brand cigarette condition. This was likely due to the absence of any breath-hold requirement, resulting in loss of nicotine in exhaled air. Gilbert et al. [6] has shown that a 5-s breath hold after controlled puffing ensures complete nicotine absorption. However, in this study we wanted to interfere minimally with inhalation topography to preserve the enjoyable aspects of smoking. Although it was practical to measure puff volume at the ad lib smoking baseline session and duplicate this parameter during the subsequent infusion session, it would have been more cumbersome to control inhalation volume in an individualized fashion.

The absence of strict control over inhalation may have also been reflected in the higher CO boost following smoking of the denicotinized cigarette in the saline vs. IV nicotine conditions. The absence of nicotine may have driven compensatory smoking behavior in the saline condition, similar to results we reported in previous studies that examined smoking of denicotinized cigarettes while wearing nicotine vs. placebo transdermal patches [20] or nicotine vs. saline infusions [30]. Thus, receiving systemic nicotine limits smoke intake even when the cigarettes do not deliver nicotine, suggesting that compensatory smoking behavior does not depend on the immediate perception of nicotine in the respiratory tract.

The effects of smoking the usual brand of cigarette were closely matched by the combination of IV nicotine infusions and smoking a denicotinized cigarette. Most of the subjective ratings as well as cardiovascular responses were nearly identical in the two conditions. However, one notable difference was the stronger airway sensations elicited by the usual brand cigarette, due to the local irritant effects of nicotine [24]. Although IV nicotine, when administered rapidly, can elicit lung sensations [11], the sensory effects are subtle using dosing parameters that resemble ad lib smoking.

Generally, the continuous IV nicotine infusion produced similar effects as the pulsed injections. Thus, the immediate effects of each puff-sized nicotine "bolus" may not be critical for duplicating many of the subjective effects of cigarette smoking. This finding is consistent with results from a recent study in which we found that arterial nicotine concentrations produced by nicotine inhalation or injection often show a gradual rise over 30–60 s, not dissimilar from what would be produced by a continuous infusion [21].

Our results may also have implications for smoking cessation treatment development. Current nicotine replacement methods do not adequately address the importance of sensory/habit cues to smokers, which may account in part for the high rates of relapse using current treatments [29]. Therefore, new treatments that provide substitutes for these cues need to be devised and evaluated, alone or in the context of standard nicotine replacement methods.

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