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Placebo cigarettes in a spaced smoking paradigm

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Abstract

Existing evidence supports the notion that nicotine delivery and recentness of smoking mediate the effects of smoking, including decreases in tobacco craving. However, smoking placebo (denicotinized) cigarettes decreases tobacco craving after overnight abstinence. The present study tested whether the recentness of smoking was an important determinant in the ability of a placebo cigarette to reduce tobacco craving. Placebo (0.07 mg nicotine) and conventional (1.1 mg nicotine) cigarettes were used in a spaced smoking paradigm. In six experimental sessions lasting 240 min, subjects smoked either a placebo or conventional nicotine cigarette in intervals of either 30, 60, or 240 min. Heart rate (HR), exhaled carbon monoxide (CO) levels, and subjective (Schuh–Stitzer, QSU) measures of tobacco craving were obtained throughout the spaced smoking paradigm. HR and CO levels increased after smoking both types of cigarettes. Increasing the interval since the last cigarette significantly ($p<0.001$) increased the baseline values of tobacco craving. Smoking either the placebo or the conventional cigarette caused a significant ($p<0.01$) reduction in the craving score after smoking. However, the nicotine yield of the cigarette did not influence these patterns. It is concluded that acute tobacco cravings can be repeatedly diminished with cigarettes that do not deliver nicotine.

Keywords: Smoking; Cigarettes; Tobacco craving; Withdrawal; Spaced smoking; Placebo cigarettes; Denicotinized cigarettes

1. Introduction

Several lines of evidence support the view that nicotine delivery is an important determinant of smoking behavior (review: Russell, 1990). Smoking typically decreases when plasma nicotine levels are increased by urinary alkalization (Benowitz and Jacob, 1985) or administration of exogenous nicotine from intravenous administration (Lucchesi et al., 1967), nicotine chewing gum (Kozlowski et al., 1975), nicotine patch (Pickworth et al., 1996) or the administration of high yield cigarettes (Ashton and Watson, 1970; Frith, 1971; Pickworth et al., 2002). On the other hand, acidification of the urine (Schachter et al., 1977) and the administration of the centrally acting nicotine antagonist mecamylamine (Nemeth-Coslett et al., 1986), manipulations that diminish plasma nicotine levels or its actions at receptors, increase smoking.

Another determinant of the effect of smoking is the time interval since the last cigarette. Most smokers state the hardest cigarette to give up would be the first one in the morning (after overnight abstinence) (Fagerström, 1978) because the effects of this cigarette are greater than those subsequently smoked. The spaced smoking paradigm is an experimental design that has been used to parametrically vary the interval between cigarettes. Using a spaced smoking paradigm, where participants smoked every 30, 60 or 360 min during a 6-h period, cigarette craving increased throughout the abstinence interval (Schuh and Stitzer, 1995; Fant et al., 1995). Smoking topography of the last cigarette of the 6-h session was influenced by pretreat-

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ment smoking interval. Specifically, the number of puffs drawn from the cigarette, heart rate (HR) increase, and measures of cigarette liking and satisfaction were inversely related to recentness of smoking.

Recently, the availability of placebo cigarettes that deliver components of tobacco smoke such as carbon monoxide (CO) and tar, but do not deliver nicotine, have advanced smoking research. These denicotinized placebo cigarettes have been used in clinical studies to distinguish the effects of smoke-delivered nicotine from the behavior of smoking and the delivery of other components of tobacco smoke (Robinson et al., 2000). For example, in tobacco-deprived smokers, a single placebo cigarette (Next®, Philip Morris, Richmond, VA) diminished tobacco withdrawal without increasing plasma nicotine levels or producing cardiovascular effects (Butschky et al., 1995). Other studies have consistently demonstrated that smoking a single placebo cigarette diminished tobacco craving (Baldinger et al., 1995; Gross et al., 1997; Rose et al., 2000; Pickworth et al., 1999). These findings support the notion that sensory factors are important in the acute alleviation of tobacco craving (Rose and Behm, 1991; Rose et al., 1993; Robinson et al., 2000; Pritchard et al., 1996). However, these findings were limited because participants only smoked a single placebo cigarette.

In the present research, placebo cigarettes were used in a spaced smoking paradigm to test the importance of recentness of smoking and nicotine delivery on subjective and physiologic responses to cigarette smoking. This study extends previous results in that placebo cigarettes were smoked on several occasions in a single experimental session. Furthermore, by using both conventional and placebo cigarettes, the effects of nicotine delivery on acute responses to cigarette smoking could be distinguished from the delivery of other components of tobacco smoke, the stimulus properties of tobacco smoke and the behavior of smoking.

2. Methods

2.1. Participants

Eight adult (average age=35.8 years; range: 25–49) volunteers (four men, four women) were recruited from the community through newspaper advertisements and word of mouth. Five participants were African American, and three were Caucasian. All participants were current menthol cigarette smokers. They smoked an average of 30.6 cigarettes/day (17–40); the FTC yield of their usual brand of cigarettes averaged 1.2 mg nicotine (range 1.1–1.3). Their score on a test of nicotine dependence (Fagerström, 1978) averaged 7.0 (6–10); scores above 5 indicate a high level of tobacco dependence. All of the participants underwent a medical examination to verify their general good health for safe participation in the study. Each participant signed a consent form describing the study, and its risks and benefits that had been approved by the NIDA Institutional Review Board.

2.2. Experimental cigarettes

The Ultratech Corporation (Lafayette Hills, PA) prepared the research cigarettes under a contract with NIDA, Intramural Research Program. Two types of experimental cigarettes were prepared—a conventional cigarette that delivered nicotine (1.1 mg) and tar (15.9 mg) and a placebo cigarette that delivered virtually no nicotine (0.07 mg) and similar amounts of tar (17.3 mg) (Pickworth et al., 1999). The cigarettes were filtered and appeared identical. In a previous study smoking these denicotinized cigarettes did not increase plasma levels of nicotine (Pickworth et al., 1999). The participants who ordinarily smoked menthol cigarettes were given experimental cigarettes that had been placed in a test tube with 1 g of menthol crystals overnight.

2.3. Dependent measures

2.3.1. Physiologic measures

HR was collected before and within 1 min after smoking using an automated blood pressure monitor (DataScope; Paramus, NJ). Exhaled CO was measured using a Vitalograph monitor (Lenexa, KS). CO measures were collected within 5 min after smoking. Participants took two deep breaths, held a third inhalation for 20 s and exhaled through the CO monitor. HR and CO measures were collected before and after the participants' own cigarette and before and after the last experimental cigarette.

2.3.2. Subjective measures

At 15-min intervals throughout the session, participants completed the four-item Schuh–Stitzer (1995) visual analog questionnaire on cigarette craving. The average of the responses to four questions which queried wanting, urging, needing a cigarette and how pleasant a cigarette would be was used. The short form (10 items) of the Questionnaire on Smoking Urges (QSU) (Cox et al., 2001) assesses strong desire and intention to smoke and perceived positive effects of smoking (Factor 1) and relief of negative affect and an urgent desire to smoke (Factor 2).

2.4. Procedure

The study was performed on an outpatient basis in the clinical ward of the NIDA Intramural Research Program. Before beginning the study, the participants attended a 2-h orientation session where they signed the consent form and were instructed in the procedure of the experiment. Participants reported for the six experimental sessions in the morning. There were no restrictions on smoking prior to the experimental sessions. Baseline physiologic, subjective

and performance measures were collected. The subject then smoked a single cigarette of their own brand. The 240 min experimental session began at the end of smoking this cigarette. Participants smoked the research cigarettes every 30, 60 or 240 min. Thus, in an experimental session the subject smoked 1, 4 or 8 experimental cigarettes. All participants smoked both the placebo and conventional cigarette at 30, 60 and 240 min intervals. The type of cigarette and interval were randomized among participants.

2.5. Data analysis

Measures obtained before and after the last experimental cigarette of each session were analyzed by means of analysis of variance techniques (Winer et al., 1991). A $2 \times 2 \times 3$ ANOVA was employed with cigarette type (two levels: placebo and conventional) time (two levels: pre- and post-smoking) and interval (three levels: 30, 60, 240 min) as within subject factors. When the ANOVA revealed differences in the main factors or their interactions, paired *t*-tests were used to identify significant contrasts.

3. Results

As described below, both intervals since the last cigarette and nicotine content significantly affected physiologic consequences of smoking. However, decreased tobacco craving was affected by the interval since the last cigarette, but not by their nicotine content.

3.1. Subjective measures of tobacco craving

As illustrated in Fig. 1A, tobacco craving measured by the Schuh–Stitzer scale increased as the interval since the last cigarette increased. For example, there were orderly and significant ($F=37.2$, $p<0.001$) increases in the baseline (pre-smoking) values on the Schuh–Stitzer scale, which increased from 17 (30 min) to 35 (60 min) and 83 (240 min). After smoking there were significant reductions in the score ($F=11.1$, $p<0.01$). However, both the nicotine and placebo cigarettes decreased scores on the Schuh–Stitzer scale such that the main effect of cigarette type and the interactions between cigarette and interval and cigarette and time were not significant. Tobacco craving measured by the QSU illustrated in Fig. 1B, C, and D followed a similar pattern to the Schuh–Stitzer measure. As the interval since the last cigarette increased, the pre-smoking scores increased. For example, QSU Total pre-smoking scores increased from 2.7 (30 min), to 4.7 (60 min) and 8.4 (240 min). After smoking there were significant reductions in the scores as a function of interval ($F=35.3$, $p<0.001$) and time ($F=10.9$, $p<0.01$), but not for cigarette ($F=2.02$, ns), nor the interaction between cigarette and time, nor cigarette and interval. Both Factors 1 and 2 of the QSU followed this pattern.

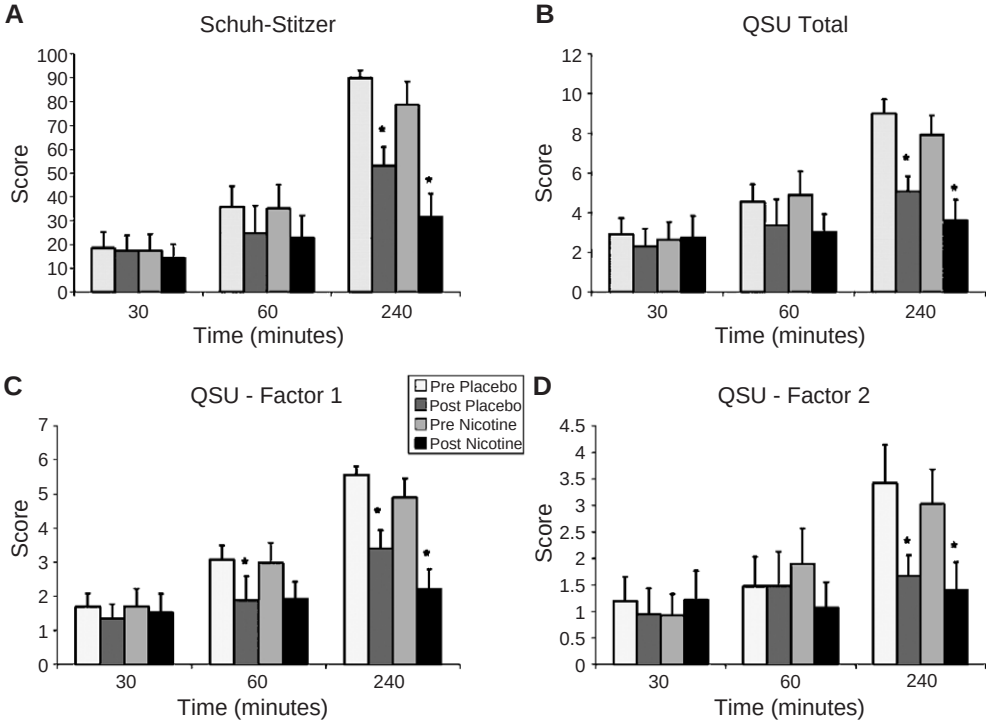

Fig. 1. Mean scores (SEM) on two scales of tobacco craving (A) Schuh–Stitzer (1995) and (B, C, D) the short form of the Questionnaire on Smoking Urges (QSU) (Cox et al., 2001). Questionnaires were completed before (pre) and after (post) smoking the last experimental cigarette (nicotine or placebo) in the experimental session. The interval is the time since the previous cigarette was smoked. (*) Indicates that the post smoking score differed significantly from the pre-smoking score ($p<0.05$).

3.2. Physiologic measures

As illustrated in Fig. 2A, smoking either the conventional or the placebo cigarette increased HR. Averaged across all conditions, the smoking-induced increase averaged 8.6 beats per minute. There was a significant effect of cigarette type ($F=6.15$, $p<0.05$) and time (pre vs. post) ($F=44.4$, $p<0.001$), but there was no significant main effect of interval. Post hoc tests indicated that the nicotine (conventional) cigarette significantly increased heart rate at all three intervals, whereas the placebo cigarette increased heart rate only in the 30 and 240 min interval conditions.

Exhaled CO levels before and after smoking are illustrated in the lower panel of Fig. 2. Averaged across all of the conditions, smoking-induced increases in exhaled CO averaged 4.5 ppm and the increase was greater at the 240 min interval (average 6 ppm) than at the 30 min interval (average 3 ppm). There was no significant effect of cigarette type ($F=0.1$, ns), but there was a significant effect of time ($F=11.4$, $p<0.01$) and interval ($F=20.2$, $p<0.001$). Post hoc tests indicated that the placebo cigarette significantly increased CO at all intervals and the nicotine (conventional) cigarette increased CO at the 60 and 240 min intervals.

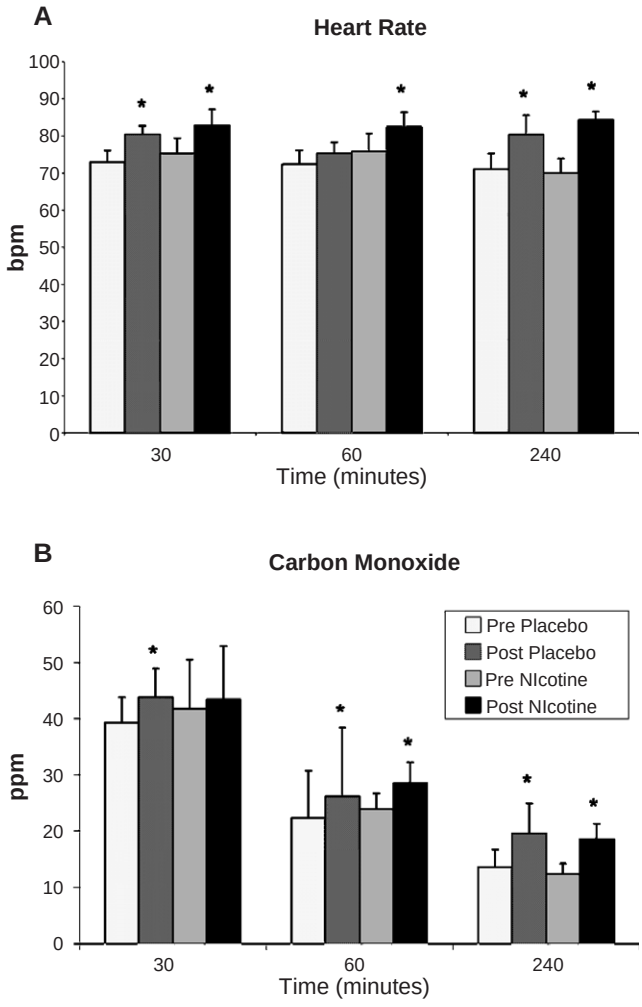

Fig. 2. Mean heart rate (A) in beats per minute (bpm) and exhaled carbon monoxide (CO) in parts per million (ppm) (B) before (pre) and after (post) smoking the last experimental cigarette (nicotine or placebo) in the experimental session. The interval is the time since the previous cigarette was smoked. (*) Indicates that the post-smoking value differed significantly from the pre-smoking score ($p<0.05$).

4. Discussion

In this study we compared the effects of placebo and conventional cigarettes in a spaced smoking paradigm. One purpose of the present study was to determine the effects of repeated administration of the placebo cigarette. In previous studies, single administrations of placebo and conventional cigarettes were compared (Butschky et al., 1995; Gross et al., 1997; Rose et al., 1993; Pickworth et al., 1999; Robinson et al., 1992). The general finding from this research was that a single placebo cigarette could temporarily decrease acute tobacco cravings and symptoms of tobacco withdrawal. The results of the present study indicate that over a 4-h session, repeated administration of the placebo and conventional cigarettes significantly reduced tobacco craving and the reduction increased as the interval since the last cigarette increased.

The spaced smoking paradigm was used in previous studies of conventional cigarettes (Fant et al., 1995; Schuh and Stitzer, 1995) where tobacco craving increased at 15 min intervals and reached maximal levels within 3 h of the last cigarette. Cigarette smoking immediately decreased tobacco craving, but craving increased within minutes after smoking. Similar results were observed after smoking the placebo and the conventional cigarettes in the present study. Within 30 min of smoking tobacco cravings increased, demonstrating that tobacco craving occurs relatively quickly. Furthermore, the tobacco craving measured before the last experimental cigarette was much lower in the 30 min smoking interval condition than in the 60 or 240 min conditions, regardless of the type of cigarette smoked. Recentness of smoking, more than delivery of nicotine–in the short intervals of this study–determined the effects of cigarette smoking on tobacco craving. Similarly, both factors of the short form of the QSU (Cox et al., 2001) increased as a function of abstinence and decreased after smoking either the conventional or placebo cigarette. The placebo cigarette was effective in reducing the two components of tobacco craving indexed by the QSU-perceived pleasure of smoking (Factor 1) and withdrawal relief (Factor 2).

In previous studies, smoking a placebo cigarette significantly decreased tobacco cravings (Butschky et al., 1995; Pickworth et al., 1999; Gross et al., 1997). The results of the present experiment indicate that repeated administrations of the placebo cigarette retain their ability to reduce acute tobacco cravings. In a study comparing the effects of conventional and placebo cigarettes in both a normal paced

and a rapid smoking paradigm (Dallery et al., 2003), sensory cues associated with smoking suppressed tobacco cravings regardless of the pace of smoking or the nicotine content of the cigarettes. Rose et al. (2000) combined smoking (placebo or conventional) cigarettes with intravenous administration of nicotine or saline. This study reported that smoking (placebo or conventional) cigarettes was more effective than intravenous nicotine administration in reducing nicotine craving. Furthermore, the placebo cigarette was as effective as a conventional cigarette in craving reduction. Hutchison et al. (2004) used placebo cigarettes in an investigation of cue-induced cigarette craving in abstinent smokers exposed to smoking cues. The placebo (and the conventional) cigarettes decreased tobacco cravings, even after pre-treatment with the atypical antipsychotic drug, olanzapine—a manipulation that decreased cue-induced craving. Taken together, these studies emphasize the complex interactions of sensory cues (i.e. taste, smell, mouth feel), the delivery of tar, CO and other components of tobacco smoke, and smoking behavior (lighting the cigarette, puffing, inhaling) in the immediate subjective response to cigarette smoking.

In the present study, both the placebo and the conventional cigarette significantly increased HR. In some previous studies, the increase in HR after the placebo cigarettes was not significant (Pickworth et al., 1999). Similarly another placebo cigarette (Next) did not significantly increase HR (Butschky et al., 1995; Gross et al., 1997); however, Pritchard et al. (1999) reported small but significant increases in HR after smoking placebo cigarettes. The results of the present study could not eliminate the possibility that other components of tobacco smoke (e.g., CO) may influence HR.

Some of the variability in the results of this study and others in the literature could be due to differences in the degree of tobacco abstinence before smoking. In the present study and others (e.g. Pritchard et al., 1999) tobacco deprivation was not required, whereas in some (e.g. Butschky et al., 1995) overnight abstinence was enforced. The explanation for the increase in HR after the placebo cigarette is not clear; it is possible that small amounts of nicotine delivered by the placebo cigarettes (Pickworth et al., 1999) might accumulate, or that other smoke components increase the HR. Unlike the HR response, the brain's electrical activity after smoking placebo cigarettes is opposite to changes seen after smoking a conventional cigarette. Whereas conventional cigarettes activate the EEG (Ulett and Itil, 1969; Knott and Venables, 1977; Pickworth et al., 1989), placebo cigarettes cause EEG slowing (Pickworth et al., 1999, 2003). Thus, smoking a placebo cigarette causes some effects (e.g. HR increase) qualitatively similar to, but usually smaller than, conventional smoking and other effects (e.g. EEG) opposite to those of conventional smoking. These findings further suggest that components of tobacco smoke, other than nicotine, may be biologically active. For example, non-nicotine components of tobacco smoke decrease brain levels of monoamine oxidase A (MAO A) (Fowler et al., 1996) and MAO B (Fowler et al., 1998), and these changes are thought to change sensitivity to the actions of nicotine or exert behavioral effects independently (review: Berlin and Anthenelli, 2001; Fowler et al., 2003).

Exhaled CO levels indicate that participants smoked the placebo and the conventional cigarette similarly. As the interval since the last cigarette increased, the CO boost (difference between pre- and post-smoking CO) also increased, indicating that in the more deprived conditions the participants smoked more intensely. These results are similar to those of other studies (Butschky et al., 1995; Pickworth et al., 1999) in which the smoking of the placebo cigarette resulted in equal increases in exhaled CO. Smoking intensity increased in situations where the smoking experience is experimentally changed, for example, by tobacco deprivation (Zacny and Stitzer, 1985), by shortening the cigarette (Woodson and Griffiths, 1992), or increasing or decreasing air vent blocking (Sweeney et al., 1999; Zacny et al., 1986). Most investigators have attributed changes in smoking behavior to differences in nicotine delivery, but others have suggested that the delivery of tar influences cigarette taste and smoking behavior (Hasenfratz et al., 1993; Schuh et al., 2001).

Although the data from the present study support the notion that sensory cues and the behavior of smoking acutely diminish tobacco craving, there are a number of limitations that must be acknowledged. The data were collected from a small number of heavily tobacco dependent smokers who were not tobacco deprived and were not trying to quit smoking. Tobacco deprivation is known to influence the subjective effects of smoking (Zacny and Stitzer, 1985) and abstinence may lead to increase cigarette liking. To the extent that cigarette liking influences smoking behavior, the difference between the placebo and conventional cigarettes may have been exaggerated by the abstinence interval.

All of the smokers were menthol smokers and although we tried to "mentholize" the cigarettes, their taste could have had an effect on their smoking. Some evidence suggests that menthol may have the ability to produce its own reinforcing effects (Ahijevych and Garrett, 2004; Rose and Behm, 2004). Rose and Behm (2004) found that removing menthol from the cigarettes of usual menthol cigarette smokers led to a decrease in reward, further supporting the notion that sensory cues, such as mentholation, may influence subjective responses to cigarette smoking. However, in a study comparing menthol and nonmenthol smokers given high, medium, and very low yield nicotine cigarettes, mentholation was not a significant factor in subjective ratings of cigarette strength, liking and craving relief (Pickworth et al., 2002). In addition, the effects of the highly structured laboratory environment may have also influenced the effects of their smoking. Mucha et al. (1996) demonstrated that smoking in the natural environment caused a smaller increase in heart rate

than smoking in the laboratory. In spite of these limitations, our results indicate that placebo cigarettes retain the ability to diminish tobacco craving during repeated administration. The findings of this study emphasize the importance of placebo cigarettes in smoking research (Robinson et al., 2000).

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