The acute effects of nicotine on the subjective and behavioural responses to denicotinized tobacco in dependent smokers

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Both nicotine and various non-nicotine smoking factors are believed to contribute to tobacco addiction but their relative roles remain incompletely understood. This study aimed to help clarify these roles by examining acute interactions between nicotine and denicotinized tobacco (DT). During two randomized blinded sessions, the effects of a quick-release 4 mg nicotine lozenge (NL) versus placebo lozenge (PL) on the subjective and behavioural responses to DT were examined in 27 (14 men) dependent, daily smokers. Participants were administered NL or PL for 30 min before receiving one initial DT cigarette. Participants could then earn additional DT cigarette puffs over the following 60 min. Subjective state was assessed using the Questionnaire of Smoking Urges-Brief and visual analogue scales at baseline, postlozenge and postinitial DT cigarette. Relative to PL, NL was associated with increased alertness as well as with reduced levels of DT self-administration ($P<0.01$). The administration of a single DT cigarette was followed by a reduction in craving under both lozenge conditions ($P<0.001$), an effect that was significantly greater in women ($P<0.01$). Moreover, DT administration was associated with increased ratings of 'pleasant', 'satisfied', 'stimulated' and 'relaxed', as well as with decreased ratings of 'anxious' (P's <0.01), independent of lozenge condition. The findings suggest that both nicotine and non-nicotine smoking factors may make important contributions towards the addictive properties of tobacco. *Behavioural Pharmacology* 23:221–227 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Behavioural Pharmacology 2012, **23**:221–227

Keywords: craving, nicotine, self-administration, smoking, tobacco

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Received 11 May 2011 **Accepted as revised** 2 January 2012

Introduction

The addictive properties of tobacco have often been attributed to a single constituent: nicotine (US Department of Human and Health Services, 1988). However, a growing body of evidence suggests that non-nicotine smoking factors may also be critical to tobacco addiction. In animal models, the range of conditions that support nicotine self-administration (SA) is much more limited than that for other addictive substances (Matta *et al.*, 2007), nicotine administered apart from tobacco has been shown to have distinct behavioural effects from tobacco smoke (Harris *et al.*, 2010), and the combination of nicotine and certain non-nicotine tobacco ingredients is more readily self-administered than nicotine alone (Clemens *et al.*, 2009). Moreover, there is some evidence that nicotine SA may depend on the presence of pharmacological or nonpharmacological conditioned stimuli (Sorge *et al.*, 2009), and that nicotine may exert many of its effects by increasing the positive reinforcing value of such stimuli (Chaudhri *et al.*, 2007) rather than by having strong primary positive reinforcing properties per se. In human studies, the primary reinforcing effects of nicotine in the absence of tobacco have not been demonstrated conclusively (Dar and Frenk, 2004; Fulton and Barrett, 2008), smokers have been found to display a preference for smoked denicotinized tobacco (DT) over intravenous nicotine (Rose *et al.*, 2010), and DT has consistently been found to produce a number of subjective effects that are comparable with those produced by nicotine-containing tobacco (Barrett 2010; Perkins *et al.*, 2010) as well as to acutely suppress many tobacco abstinence symptoms (Donny and Jones, 2009; Barrett 2010; Perkins *et al.*, 2010; Rose *et al.*, 2010), especially in women (Barrett, 2010). However, there are also reports that, relative to DT, nicotine-containing tobacco may produce more pleasant effects (Donny *et al.*, 2006; Kassel *et al.*, 2007) and may more fully suppress subsequent smoking behaviour (Dallery *et al.*, 2003; Barrett 2010), indicating that the combination of nicotine and non-nicotine smoking factors may be essential to tobacco addiction.

Most recent studies that have aimed to compare the relative roles of nicotine and non-nicotine smoking factors have done so by examining the effects of Quest low-nicotine (0.6 mg nicotine) and DT ($\leq$ 0.05 mg nicotine) cigarettes (Perkins *et al.*, 2006, 2010; Attwood *et al.*, 2009; Brody *et al.*, 2009; King *et al.*, 2009; Barrett, 2010). However, because Quest low-nicotine and DT cigarettes are not manufactured using identical tobacco strains (Vector Tobacco) and may differ in their taste and/or other non-nicotine properties, it is not clear to what

0955-8810 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/FBP.0b013e328353431c

extent any similarities and differences observed between them can be attributed to their nicotine contents per se. A second potential difficulty in interpreting much of the existing literature relates to the common practice of using smoking topography equipment to quantify various tobacco puff parameters (Kassel *et al.*, 2007; Donny and Jones, 2009; King *et al.*, 2009; Perkins *et al.*, 2010; Rose *et al.*, 2010). Although the use of such equipment may provide useful information about, and control over, several puff-specific parameters, evidence suggests that both handheld and computerized smoking topography devices can increase perceived smoking difficulty, reduce the level of smoking enjoyment, as well as alter cigarette taste and smoking behaviour (Blank *et al.*, 2009), factors that might be considered critical for understanding the true subjective and reinforcing effects of smoking. The present study aimed to further clarify nicotine–tobacco interactions by examining the effects of acute nicotine administration on the subjective responses to the self-paced administration of a DT cigarette as well as on subsequent DT smoking behaviour.

Methods

Participants

Twenty-seven (14 men) nontreatment-seeking smokers ranging in age from 19 to 54 years (mean = 28.1) completed the study. All participants were medically healthy, free from current or past mental illness and had reached the minimum age to legally consume tobacco in Canada. None intended to quit smoking during the subsequent 30 days and all scored a minimum of 3 (mean = 5.5; SD = 2.2) on the Fagerström Test for Nicotine Dependence (Heatherton *et al.*, 1991). On average, participants reported daily smoking of nonmenthol cigarettes for 11.8 (SD = 11.3) years and smoked 16.8 (SD = 9.2) cigarettes per day. All participants provided informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by a local Research Ethics Board.

Lozenges

In sessions involving acute nicotine administration, a quick-release 4 mg nicotine lozenge (NL) with a mint flavour (NiQuitin Minis 4 mg; Glaxo-Smith-Kline, Marly-le-Roi, France) was used. This product was selected for its rapid onset of action (reported by the manufacturer to be up to three times more rapid than that of nicotine gum; Glaxo-Smith-Kline) and ease of administration relative to other forms of nicotine, as well as its lack of commercial availability in Canada at the time of the study. A breath mint similar in flavour and appearance served as a placebo lozenge (PL).

Tobacco

The DT cigarettes used in the experiments had a manufacturer-reported maximum nicotine yield of 0.05 mg and a tar yield of 10 mg (Quest 3; Vector Tobacco, Mebane, North Carolina, USA). DT cigarettes were presented in plain packaging with all product markings covered. Similar to the NL, the DT cigarettes had never been commercially available in Canada at the time of the study.

Blinding

All sessions were double-blind. Neither the participants nor the research personnel involved in running the sessions had a-priori knowledge of the specific contents of any of the products used during the study. During the consent process, participants were informed that the lozenges and tobacco used in the study might vary in their content of ingredients normally found in cigarettes (e.g. tar, ammonia, carbon monoxide (CO), menthol, nicotine, sucrose, etc.), but not that the lozenges would vary in their nicotine contents specifically or that the tobacco might contain only trace amounts of nicotine. Participants were also informed that there was a small risk that one or more of the products used in the study would produce unpleasant side-effects such as headache, coughing, hiccups, heartburn, flatulence, insomnia, irritation in the mouth and throat or nasal congestion.

Subjective measures

The following subjective measures were administered at baseline and immediately following lozenge administration and initial DT cigarette administration.

Visual analogue scales

The visual analogue scales (VAS) consisted of the following subjective mood descriptors: alert, satisfied, frustrated, sedated, dizzy, head rush, irritable, jittery, high, relaxed, stimulated, pleasant, anxious and trouble concentrating. Items were rated on a 10 cm horizontal line labelled with the integers 1–10 and anchored with the endpoints 'not at all' and 'extremely'. Similar scales have been widely used to collect information about subjective drug effects and have been demonstrated to be a reliable, valid and sensitive method for obtaining information about participants' subjective experiences (Bond and Lader, 1972).

Questionnaire of Smoking Urges-Brief

The 10-item Questionnaire of Smoking Urges-Brief (QSU-Brief) is a psychometrically sound self-report measure that assesses cigarette cravings across two dimensions (factor 1: intention to smoke; factor 2: withdrawal/negative affect relief). Items are rated on a seven-point scale anchored with the endpoints 'strongly disagree' and 'strongly agree'. Five items (I have a desire for a cigarette; if possible I would probably smoke right now; I have an urge for a cigarette; a cigarette would taste good now; I am going to smoke as soon as possible) are summed to determine the factor 1 score and five items (nothing would be better than smoking a cigarette right now; I could control things better right now if I could smoke; all I want right now is a cigarette; I would do almost anything

for a cigarette now; smoking would make me feel less depressed) are summed to determine the factor 2 score. The QSU-Brief has been shown to be sensitive for measuring tobacco craving and abstinence-related effects (Cox *et al.*, 2001).

Design

The research protocol consisted of two double-blind, randomized experimental sessions. Sessions were conducted between 09:00 and 14:00 h, a minimum of 2 and a maximum of 14 days apart, and were identical in procedure, except that participants received NL in one session and PL in the other.

Procedure

Participants arrived for each experimental session having abstained from cigarettes for a minimum of 12 h, alcohol for a minimum of 24 h and food and caffeine for a minimum of 4 h. Abstinence from smoking was confirmed using a breath CO analyzer (Vitalograph, Lenexa, Kansas, USA), using a cutoff of 15 parts per million and a 50% minimum reduction relative to a nonabstinent breath sample that was collected on a regular day of smoking during the screening and consent process. After completing a baseline subjective assessment (VAS, QSU-Brief), participants were administered the lozenge for that session in a quiet, comfortable testing room over a 30-min period. Participants were instructed to place the product between their upper lip and gum line and were told that they could occasionally move it from one side of their mouth to the other. At the end of the 30-min period, participants completed another subjective assessment (VAS, QSU-Brief), and then smoked an entire DT cigarette. Participants were instructed to inhale the smoke and to complete smoking the cigarette to the filter but the pace and duration of their puffs were self-determined. Immediately after finishing the cigarette, participants completed a third subjective assessment (VAS, QSU-Brief). They could then begin using a computerized progressive ratio (PR) task to earn additional DT puffs. For each puff, participants were required to repeatedly press a key on a computer keyboard a predetermined number of times. The first additional puff required 10 key presses and for each subsequent puff the response requirement increased by 30% (i.e. 13, 17, 22, etc.). This task has been previously demonstrated to be sensitive to pharmacological manipulations in human tobacco SA studies (Barrett, 2010; Barrett *et al.*, 2011).

Analyses

The main behavioural measures were the time (s) to self-administer the initial DT cigarette, the latency (s) to initiate the PR task, the maximum number of key presses completed to earn a puff during the PR task (breakpoint) and the total number of puffs earned during each session. After the Kolmogorov–Smirnov method was used to determine whether normality assumptions were fulfilled and it was determined that no transformations were necessary, all behavioural data were analysed using general linear models with the lozenge condition (NL, PL) entered as a repeated-measures factor and sex as a between-subjects factor. The outcomes of interest for the behavioural data were the main effects of condition as well as interactions of condition with sex. Subjective data (VAS, QSU-Brief) were also analysed using general linear models, with time (baseline, postlozenge, postinitial DT cigarette) and lozenge condition entered as repeated-measures factors and sex as a between-subjects factor, and the outcomes of interest were the main effects of time as well as interactions of time with condition and/or sex. All tests of simple main effects were carried out on the linearly independent pairwise comparisons between the estimated marginal means. To account for multiple testing, the threshold for statistical significance for all analyses was set at P value equal to 0.01 and P values between 0.01 and 0.05 were considered trends.

Results

Behavioural data

Mean (± SE) values for each of the behavioural variables are presented in Table 1. Analyses revealed a significant main effect of lozenge condition on the total cigarette puffs earned, $F(1, 25) = 6.9$ ($P < 0.01$), as well as a trend for PR breakpoint values, $F(1, 25) = 5.0$ ($P = 0.04$), reflecting less SA in the NL condition relative to the PL condition. Participants also tended to take longer to complete smoking the initial DT cigarette in the NL condition relative to the PL condition, $F(1, 25) = 5.2$ ($P = 0.03$). There were no significant differences between conditions in latency to initiate the PR task or interactions involving sex for any of the behavioural variables.

Subjective data

Craving

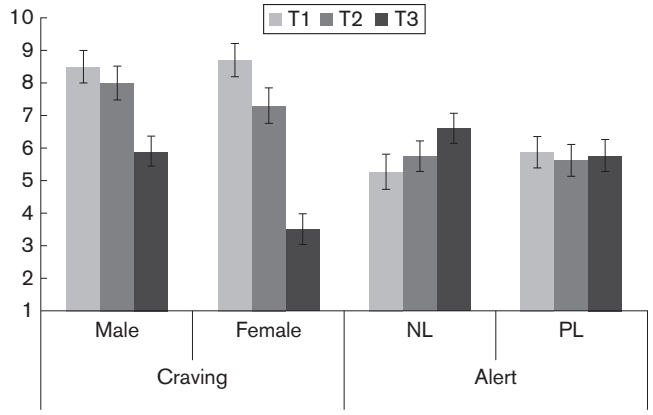
Two craving-related variables were assessed using the QSU-Brief: factor 1 craving (intention to smoke) and factor 2 craving (withdrawal/negative affect relief). For factor 1 craving, there was a significant main effect of time, $F(2, 50) = 71.6$ ($P < 0.001$), reflecting decreased

Table 1 Effects of nicotine (4 mg) and placebo lozenge administration on denicotinized cigarette-smoking behaviour

Variables	Nicotine condition Mean (SE)	Placebo condition Mean (SE)	*F* statistic (*P* value)
Time to complete smoking initial DT cigarette (s)	278.8 (9.9)	261.7 (8.1)	5.2 (0.03)
Latency to initiate PR task (s)	1011.8 (214.1)	870.2 (182.7)	0.4 (0.55)
Breakpoint (maximum number of responses completed in PR task)	556.1 (130.1)	899.2 (201.6)	5.0 (0.04)
Total number of DT cigarette puffs earned in PR task	11.8 (1.3)	14.1 (1.2)	6.9 (0.01)

DT, denicotinized tobacco; PR, progressive ratio.

Fig. 1



Mean (± SE) Questionnaire of Smoking Urges-Brief (QSU-Brief) factor 1 craving scores in men versus women (left) and visual analogue scale ratings of alert in the nicotine lozenge (NL) versus placebo (PL) conditions (right) at baseline (T1), postlozenge (T2) and postinitial denicotinized tobacco cigarette (T3). QSU-Brief scores were adjusted to fit a 10-point scale.

craving following both lozenge ($P < 0.01$) and DT ($P < 0.001$) administration, as well as a significant time × sex interaction, $F(2, 50) = 7.5$ ($P < 0.01$), reflecting a greater post-DT craving reduction in women relative to men ($P < 0.01$) (Fig. 1). For factor 2 craving, there was a significant main effect of time, $F(2, 50) = 42.3$ ($P < 0.001$), reflecting decreased craving following DT administration ($P < 0.01$) (but not postlozenge). There were no further significant interactions of time with condition and/or sex for the craving variables.

Mood

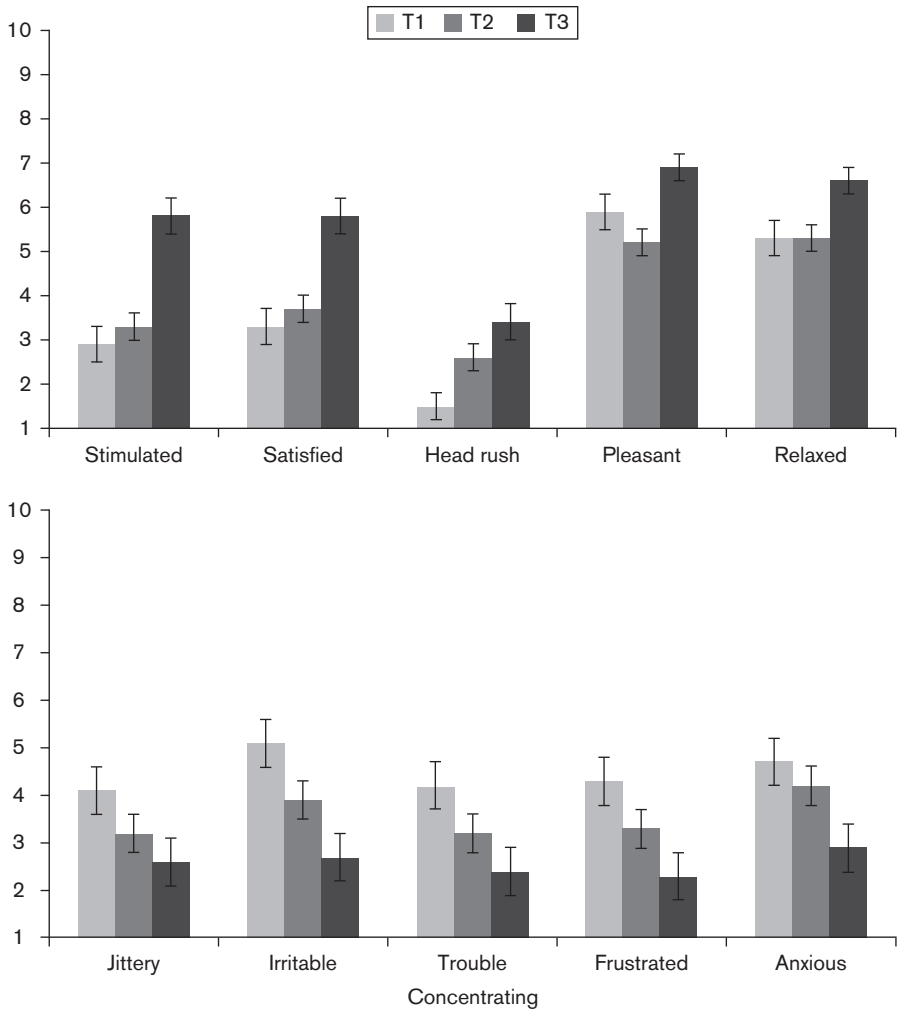
There was a significant condition × time interaction for ratings of 'alert', $F(2, 50) = 7.2$ ($P < 0.01$). In the NL condition, participants' alertness ratings were elevated following DT administration relative to baseline ($P < 0.01$) and to postlozenge ($P = 0.02$). In contrast, in the PL condition, alertness ratings did not significantly change across time (Fig. 1). There were also significant main effects of time for ratings of 'jittery', $F(1, 25) = 6.7$, 'irritable', $F(1, 25) = 17.7$, 'trouble concentrating', $F(1, 25) = 10.8$, and 'frustrated', $F(1, 25) = 22.1$ ($P < 0.01$), reflecting decreased ratings following lozenge administration ($P < 0.01$), as well as for ratings of 'head rush', $F(1, 25) = 15.5$ ($P < 0.001$), reflecting increased ratings following lozenge administration ($P < 0.01$) (Fig. 2). Further significant decreases were observed post-DT for ratings of 'frustrated' and 'irritable' ($P < 0.01$) as well as a trend for 'trouble concentrating' ($P < 0.05$), and there was a further significant increase post-DT for ratings of 'head rush' ($P < 0.01$). There were also significant main effects of time for ratings of 'stimulated', $F(1, 25) = 10.37$, 'satisfied', $F(1, 25) = 16.27$, 'pleasant', $F(1, 25) = 7.1$, and 'relaxed', $F(1, 25) = 7.1$ ($P < 0.01$), reflecting increased ratings post-DT ($P < 0.01$) (but not postlozenge), as well as for ratings of 'anxious', $F(1, 25) = 10.8$ ($P < 0.01$), reflecting decreased ratings post-DT ($P < 0.01$) (but not postlozenge) (Fig. 2). No other significant main effects of time or interactions involving time with condition and/or sex were observed for any of the mood variables.

Discussion

In the present study, the acute administration of an NL was found to decrease the pace of administration of a DT cigarette as well as to attenuate further DT smoking behaviour. These findings are consistent with previous observations indicating that concurrently administered transdermal nicotine (Donny and Jones, 2009) can reduce DT SA, and suggest that the non-nicotine components of tobacco use may become less appealing when a smoker is at least partially satiated with nicotine. In contrast to these findings, Rose *et al.* (2010) recently reported no effect of prior intravenous nicotine administration on subsequent DT smoking behaviour. However, it is possible that this negative finding may relate to the timing and dose of nicotine administration, and that adequate nicotine levels were not maintained to suppress smoking at the time of DT SA (Rose *et al.*, 2010). NL administration was also associated with increased post-DT ratings of alertness, a finding consistent with previous observations that nicotine may be especially important to tobacco's arousing effects (Barrett, 2010), but because there was no comparable NL-related increase in post-DT ratings of subjective stimulation, this result should be interpreted with some caution.

Cigarette cravings were significantly reduced following the acute administration of a single DT cigarette and, consistent with previous findings that non-nicotine smoking factors may be especially important for tobacco addiction in women (Perkins *et al.*, 2001; Barrett, 2010), DT administration was associated with a greater reduction in smoking intentions in women than in men. DT administration was also associated with increased ratings of satisfied, relaxed, stimulated and pleasant as well as with decreased ratings of anxious. Although consistent with previous observations that DT administration is associated with reduced craving as well as with the production of a number of positive subjective effects (e.g. Barrett, 2010; Perkins *et al.*, 2010), these findings should be interpreted with caution in the absence of a high-nicotine cigarette and/or a nonsmoking comparison condition. It is possible that DT affected tobacco craving or other subjective responses through a neuropharmacological action. For example, acetaldehyde has been shown to have independent behavioural and reinforcing effects (Brown *et al.*, 1979; Rodd-Henricks *et al.*, 2002), while monoamine oxidase inhibitors such as harman and norharman also have known effects on central reinforcement mechanisms (Adell and Myers, 1994; Herraiz and Chaparro, 2005). Moreover, CO, a byproduct of tobacco

Fig. 2



Mean (± SE) visual analogue scale ratings of stimulated, satisfied, head rush, pleasant, relaxed (upper) and jittery, irritable, trouble concentrating, frustrated and anxious (lower) at baseline (T1), postlozenge (T2) and postinitial denicotinized tobacco cigarette (T3).

combustion with known physiological effects, has recently been reported to attenuate tobacco craving (Milne *et al.*, 2012). A contribution of these or other pharmacologically active tobacco ingredients, either alone or in combination, cannot be ruled out. Alternatively, the sensory-motor properties of DT administration, independent of any neuropharmacological effect, might, at least in part, account for such effects. For example, past work has shown that blocking smoking-related sensory cues reduces smoking reinforcement (Rose *et al.*, 1984, 1985; Perkins *et al.*, 2001) and it is possible that the replacement of such cues is sufficient to attenuate tobacco craving (Donny and Jones, 2009; Rose *et al.*, 2010). It is also possible that many of the DT effects were related to demand characteristics or expectancy effects associated with smoking and the belief that one received nicotine. Although participants were blind to the contents of the cigarettes, many may have assumed that the cigarettes contained nicotine, especially as DT is not commercially available in the jurisdiction where the study took place. Indeed, several non-nicotine-specific changes in subjective ratings following lozenge administration suggest that expectancy effects likely played a role in at least some of participants' subjective responses. Finally, it is possible that the mere passage of time contributed to many of the DT-related effects. However, because the postlozenge and post-DT assessments occurred in relatively close temporal proximity (within 10 min), and most of the DT-related effects were consistent in both direction and kind with the findings of a previous study that compared the effects of DT with those of a placebo inhaler (Barrett, 2010), this explanation is unlikely.

The present results should be interpreted in light of the following methodological considerations. First, in contrast to many recently published reports investigating the

effects of DT (Kassel *et al.*, 2007; Donny and Jones, 2009; King *et al.*, 2009; Perkins *et al.*, 2010; Rose *et al.*, 2010), the present investigation did not require participants to administer tobacco through a smoking topography device. Although evidence suggests that the use of such devices may impact on smoking behaviour and subjective effects (Blank *et al.*, 2009), it is interesting to note that our observation of NL-related decreases in DT SA and smoking pace mirrors smoking topography findings of an inverse relationship between the level of nicotine exposure and the depth and frequency of cigarette puffing (Herning *et al.*, 1981; Gust and Pickens, 1982; Kassel *et al.*, 2007; Blank *et al.*, 2009). Second, although the NL used in the study was in part selected on the basis of its ability to deliver nicotine more rapidly than other commercially available nicotine products, the pharmacokinetics of nicotine administration through NL were not verified in the present study and likely deviate markedly from those typically achieved through smoking (Russel *et al.*, 1976). It is also possible that nicotine administered through tobacco smoke may exert additional effects both individually and in combination with DT. It is interesting to note, however, that the present findings replicate previous observations made when comparing DT with nicotine-containing tobacco that the combination of nicotine and non-nicotine tobacco ingredients reduced further smoking behaviour and increased the arousing effects of smoking relative to DT (Barrett, 2010). Third, participants were not directly informed during the consent process that they would be receiving nicotine during one of the experimental conditions and their beliefs about the contents of the lozenges and tobacco used in the study were not assessed. A growing body of evidence suggests that the expectation that one is receiving nicotine increases the likeability and clinical efficacy of nicotine replacement products, and that this expectation interacts with pharmacological factors to produce overall subjective and behavioural responses (Hughes *et al.*, 1989; Perkins *et al.*, 2009; Darredeau and Barrett, 2010). Thus, it is possible that certain nonpharmacological aspects of nicotine administration were deemphasized and this may in part account for a lack of nicotine-specific effects on some variables. Alternatively, it is possible that some participants assumed that the lozenges contained nicotine. Evidence suggests that the administration of nicotine (4 mg) and placebo gum can lead to comparable decreases in acute craving when compared with no treatment (Davies *et al.*, 2004) and similar nonspecific treatment effects may have contributed to the present findings. It is also possible that some participants may have correctly guessed on the basis of lozenge stimulus properties that they received nicotine during one condition and an inert substance during the other. However, this seems less likely, given the lack of differences in the ratings of NL and PL across several somatic (e.g. dizzy, jittery), affective (e.g. pleasant, anxious, irritable) and cognitive (e.g. trouble concentrating) effects. Finally, although the sample size was well within the norms for a within-subject design, the sample was relatively homogenous in its level of nicotine dependence and in its lack of psychiatric and medical comorbidity, and further research is required to determine the extent to which the present findings would extend to other subsets of smokers.

In summary, acute nicotine administration was associated with decreased DT SA as well as with increased ratings of alertness, indicating that nicotine may be especially important for some of tobacco's addictive properties such as satiation. However, DT administration itself was associated with decreased intentions to smoke, especially in women, as well as with the production of a number of positive subjective effects. These findings provide further evidence that non-nicotine smoking factors may independently contribute to tobacco addiction.

Acknowledgements

The authors would like to thank Milad Yetka, who ran the experimental sessions, as well as Erin Wagner and Lindsay Peters, who assisted with participant recruitment, screening and blinding procedures.

This work was supported by a Discovery Grant from the Natural Sciences and Engineering Research Council of Canada awarded to S.P.B. The funding source played no role in the study design, in the collection, analysis or interpretation of data, in the writing of the report or in the decision to submit the report for publication.

Conflicts of interest

There are no conflicts of interest.

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