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Modulating tobacco smoking rates by dopaminergic stimulation and blockade

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Modulating tobacco smoking rates by dopaminergic stimulation and blockade

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This study was designed to demonstrate that dopaminergic stimulation would result in decreased smoking behavior and nicotine intake, whereas dopaminergic blockade would result in increased smoking behavior and nicotine intake, in the same subjects. In prior human studies, a dopaminergic antagonist, haloperidol, increased smoking and/or nicotine intake, and a dopamine agonist, bromocriptine, decreased smoking. The smoking behavior of 20 heavy smokers was observed on two separate visits in a randomized, double-blind, repeated-measures-within-subject design. In the drug-reversal design, either bromocriptine (2.5 mg) or haloperidol (2.0 mg) was administered at each 5-h session, during which subjects smoked their own cigarettes *ad libitum*. Smoking topography was measured using a thermistor flow detector apparatus. Subjects smoked their cigarettes faster ($p < 0.05$) and total puffing time was greater ($p < 0.05$) with haloperidol than with bromocriptine. There was a trend for both a shorter latency to smoke ($p < 0.10$, one-tailed) during time of expected peak drug concentration and for a shorter inter-cigarette interval with haloperidol than with bromocriptine ($p < 0.10$, one-tailed). Shiffman–Jarvik Withdrawal Scale craving subscale scores increased significantly more with haloperidol than with bromocriptine ($p < 0.05$). Mean Profile of Mood States (POMS) scores differed significantly for only one subscale (Confusion: bromocriptine > haloperidol; $p < 0.05$). These data support the hypothesis that nicotine mediates reinforcement from smoking via dopamine, and that smoking behavior can be manipulated within the same subjects in opposite directions by alternately stimulating and blocking dopamine.

Introduction

There have been many animal studies showing that nicotine causes dopamine release (Mifsud, Hernandez, & Hoebel, 1989; Nisell, Nomikos, & Svensson, 1994a, 1994b; Pontieri, Tanda, Orzi, & Di Chiara, 1996) and

others that show animals will self-administer intravenous nicotine (Rose & Corrigall, 1997). These animal studies suggest that dopamine is likely involved in mediating nicotine intake and response in animals. There are very few human studies testing the hypothesis that smoking behavior is mediated by dopaminergic mechanisms.

McEvoy, Freudenreich, Levin and Rose (1995) reported increased smoking in schizophrenics when they were given haloperidol, a dopamine antagonist, compared with periods when they were taking no anti-psychotic medications. The effect of haloperidol on smoking has also been tested in non-psychiatric subjects. Dawe, Gerada, Russell, and Gray (1995) found increased nicotine intake from post-prandial smoking when subjects were pretreated with 5 mg haloperidol in comparison to placebo. Caskey, Jarvik and Wirshing (1999) also

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demonstrated increased rates of smoking with single-dose administration of haloperidol vs. placebo (1.0 mg and 2.0 mg vs. placebo) and a dose–response effect (1.0 vs. 0.5 mg).

Data from our own laboratory (Caskey *et al.*, 1999) also indicated that acute administration of bromocriptine, a dopamine agonist, to a small sample of non-psychiatric subjects ($n = 5$) resulted in a significantly slower rate of smoking than a placebo (2.5 mg vs. placebo). Bromocriptine, a specific agonist at the D2 receptor, is an ergot alkaloid currently used for the treatment of amenorrhea, galactorrhea, prolactin-secreting adenomas and Parkinson's disease. Bromocriptine exerts its therapeutic action through its potent stimulation of post-synaptic D2 receptors (Rascol, 1999; Vance, Evans, & Thorner, 1984), thereby mimicking endogenous dopamine. Bromocriptine has less activity at the D1 subfamily of dopaminergic receptors (Rascol, 1999). Bromocriptine has a half-life of 7+5 h (Hardman, Limbird, Molinoff, Ruddon, & Gilman, 1996) and a T_{\max} of 3 h (Gilman, Goodman, Rall, & Murad, 1985). Haloperidol, primarily a competitive D2 antagonist, has a half-life of 18+5 h (Hardman *et al.*, 1996) and a T_{\max} of 2.5 h (Moore, 1977, 1979).

In a larger ($n = 18$) study of the effects of acute administration of bromocriptine (placebo vs. 2.5 mg and 3.75 mg) on smoking in non-psychiatric smokers, Jarvik *et al.* (2000a) found a significant monotonic decreasing dose–response for several topographical measures of smoking behavior. Subjects smoked fewer cigarettes, took fewer puffs, had shorter total puffing time and shorter mean puff duration with increasing bromocriptine doses during a 5-h period of *ad lib* smoking. Additionally, significant monotonic decreasing dose–response effects were observed for both plasma nicotine and cotinine, with decreased levels of both markers of nicotine intake with increasing bromocriptine. Subjects had significantly lower measures of craving in the 3.75-mg condition compared with placebo when measured by the Shiffman–Jarvik Withdrawal Scale (SJWS) craving subscale.

The current study was designed to test whether we could manipulate smoking behavior within the same subjects in opposite directions by alternately administering bromocriptine and haloperidol on separate occasions. We hypothesized that the subjects' smoking behavior and nicotine intake would be lower when administered bromocriptine and higher when the same subjects were administered haloperidol. In our previous experiments subjects received either bromocriptine or haloperidol but never both.

Methods

Subjects

Subjects were recruited via advertisements in local newspapers and were then screened using a brief telephone interview. Exclusion criteria included cardiac

or respiratory/pulmonary illness or disease; endocrine or metabolic disorders; seizure disorders; treatment with any anti-psychotic, anti-depressant, or other psychotropic medication; and/or the taking of any medication that could interact with bromocriptine or haloperidol. The inclusion criterion was smoking a minimum of 15 cigarettes per day for at least 2 years. Twenty heavy smokers (14 males, six females) were recruited from the greater Los Angeles community. Their mean age (\pm SD) was 30.0 ± 9.2 years; range = 18–45 years) and mean level of education in years was 13.7 ± 1.5 ; range = 11–17 years). Subjects had smoked for an average of 12.5 ± 7.6 years; range = 3–26 years) and were currently smoking an average of 20.1 ± 6.3 cigarettes per day (range = 12.5–40). Two subjects retained in the study initially had reported smoking at least 15 cigarettes per day during the telephone screening and then reported smoking 10–15 cigarettes per day on a questionnaire administered subsequently. During the baseline visit to the laboratory, expired carbon monoxide (CO) for one of these two subjects was 24 ppm, 50 min after completing the last cigarette, and the other subject's CO was 30 ppm, 15 min after completing the last cigarette, indicating regular smoking for both subjects. Baseline visits (and CO assays) were conducted in the late afternoon and early evening. The mean FTC-rated nicotine level (Federal Trade Commission, 1994) for subjects' preferred brand of cigarettes was 1.0 ± 0.3 mg (range = 0.7–1.8 mg). One of 20 subjects regularly smoked mentholated cigarettes. The mean Fagerström Test for Nicotine Dependence (FTND, Heatherton, Kozlowski, Frecker, & Fagerström, 1991) was 4.9 ± 1.6 , range = 2–8.

Design and procedure

This study utilized repeated-measures design with two conditions. Subjects were randomized to order of conditions, and the study was run double-blind. Subjects came to the laboratory for one screening baseline visit and two experimental sessions spaced approximately 1 week apart. Sessions were conducted at the Greater Los Angeles Veterans Affairs Healthcare System. Subjects were paid for participating in the baseline visit (\$20) and two experimental sessions (\$50 each).

Baseline visit

An initial laboratory visit was conducted to provide in-depth health screening and to familiarize potential subjects with the experimental procedures; this was done in groups of 5–15 people. At the baseline visit subjects gave written informed consent, had a physical examination (including an ECG), and completed background questionnaires. Health screening included a medical history and physical examination (including blood pressure, heart rate and weight). Smoking status was verified by CO (>20 ppm). Subjects smoked a cigarette through an experimental smoking apparatus to acquaint them with the experimental procedure. The apparatus

(described below) was designed to measure smoking topography (e.g., puff duration). Subjects also completed both the Profile of Mood States (POMS) and the SJWS to familiarize them with these questionnaires, which were to be used repeatedly throughout the experimental sessions.

Experimental sessions

Experimental sessions began at 08.30 h. (At the baseline session, subjects were instructed not to eat anything or drink any caffeinated beverages prior to coming to the experimental sessions in order to facilitate drug absorption. Subjects who reported having had food or caffeinated beverages after midnight were rescheduled.) Blood pressure was then measured. Subjects then completed a baseline questionnaire battery (including POMS and SJWS; see below). Next, subjects provided a baseline expired-air CO sample. At this time subjects smoked a 'loading cigarette' to start the experimental session. Subjects were instructed to smoke as much or as little of one of their own cigarettes as they pleased. Subjects were asked when they had finished their most recent cigarette prior to smoking the loading cigarette. The mean interval between completion of the most recent pre-experimental cigarette and the loading cigarette was 35.4 ± 19.6 min (range = 1–60 min). Blood was drawn exactly 2 min after completion of the loading cigarette. The drug (2.5 mg bromocriptine or 2.0 mg haloperidol) was administered after the blood draw. The two specific dose levels were selected on the basis of our previous experiments (Caskey *et al.*, 1999; Jarvik *et al.*, 2000a). In the earlier experiments, the doses yielded the predicted experimental effects and were generally well tolerated by subjects with a minimum of side-effects. In contrast, a higher dose of bromocriptine (3.75 mg) did produce a noticeable increase in side-effects, primarily nausea (Jarvik *et al.*, 2000a). Another CO measurement, taken 20 min after the loading cigarette, was used as the baseline measurement for subsequent experimental analyses of CO changes. Breakfast was served 45 min after drug ingestion. Breakfast items included a 12-ounce bowl of corn flakes, 16 ounces of low-fat milk, 16 ounces of orange juice, 6 ounces of low-fat mixed fruit yogurt, and three small cinnamon rolls, though subjects were not required to consume any of the food offered.

Experimental sessions lasted a minimum of 5 h and typically lasted 6 h. Subjects were instructed to smoke freely (*ad libitum*) using the smoking topography apparatus during the experimental sessions. Subjects smoked their own brand of cigarettes. Subjects watched videotaped movies for the remainder of the session by themselves. The movies were light-hearted comedies (MPAA ratings of PG or PG-13), which did not include any scenes of actors smoking. The questionnaire battery (POMS, SJWS, additional measures of desire to smoke and two nausea measures) was given 30 min after completion of the loading cigarette. Before each successive cigarette, subjects were required to notify the

experimenter via wireless intercom when they wanted to smoke another cigarette. CO and repeated-questionnaire measures were taken before every cigarette. The time at which the cigarette was lit, the number of puffs, the duration per puff and the time that the cigarette was extinguished were recorded. Immediately after each cigarette, the subjects completed the two nausea scales. CO levels were measured again 20 min after each cigarette. Hourly CO samples were also collected. Subjects completed the repeated-measures questionnaire battery 30 min after each cigarette. In cases where subjects desired to smoke again prior to the repeated-measures battery (i.e., less than 30 min), they first completed the battery and then were allowed to smoke. This procedure was repeated for each cigarette. Blood was again drawn precisely 2 min after the first cigarette smoked after 3 h post-drug ingestion (time of expected C_{max}). Subjects' blood pressure and heart rate were measured to ensure that they were within normal limits before subjects were released (5–6 h post-drug ingestion).

Equipment

A thermistor puff-detecting device was used to measure cigarette smoking topography (puff duration). This device consists of a thermistor (Victory Engineering) embedded in a commercially available cigarette holder (Aqua Filter). The thermistor is heated to 200°C by electrical current. Cigarette smoke passing over the thermistor causes a drop in the thermistor's temperature, causing a change in the thermistor's electrical resistance. Changes in the thermistor's resistance are converted into a voltage signal. The cigarette holder and the telephone handset cord (which attached to a small box with electronics configured to measure the changes in electrical resistance) weighed 62 g. Combining the thermistor apparatus with an electronic timing device enabled us to measure the time of onset and completion for each cigarette, puff duration, number of puffs per cigarette, inter-puff interval and inter-cigarette interval. A Bedfont II Microsmokerlyzer was used to measure expired-air CO.

Measures

Questionnaires

One-time-only background questionnaires included a measure of smoking history and demographic information (Smoker's Profile), the FTND (Heatherton *et al.*, 1991), the Smoking Motivation Questionnaire (ARU; Russell, Peto, & Patel, 1974), and the Smoker's Beliefs Questionnaire (Olmstead, unpublished data).

Repeated-measure questionnaires included: (1) the Urge to Smoke questionnaire (UTS; Jarvik *et al.*, 2000b); (2) Schuh and Stitzer's craving index, a four-item visual analog scale (SSI; Schuh & Stitzer, 1995); (3) the complete SJWS (Shiffman & Jarvik, 1976); (4) the POMS questionnaire; (5) a 100-mm Visual Analog

Table 1. Mean smoking topography measures for bromocriptine and haloperidol (standard deviations in parentheses)

	Number of subjects	Mean for bromocriptine	Mean for haloperidol	Significance of difference	p values for adjusted means (nausea boost ANCOVA: Likert scale p , VAS p)
Total puffing time (seconds)	20	52.0 (28.8)	77.6 (48.4)	$p = 0.025$	$p = 0.09$, $p = 0.04$
Total number of puffs	20	31.1 (18.3)	44.8 (31.2)	$p = 0.035$	$p = 0.07$, $p = 0.06$
Mean puff duration (seconds)	20	1.9 (0.7)	1.9 (0.6)	$p = \text{ns}$	$p = \text{ns}$, $p = \text{ns}$
Total number of cigarettes	20	2.3 (0.9)	3.0 (1.3)	$p = 0.044$	$p = 0.12$, $p = 0.10$
Smoking rate (cigarettes/hour)	20	0.5 (0.2)	0.6 (0.3)	$p = 0.044$	$p = 0.12$, $p = 0.10$
Mean inter-cigarette interval	20	41.2 (24.9)	32.1 (16.8)	$p = 0.187$	$p = 0.16$, $p = 0.05$

VAS, visual analog scale.

nausea scale; (6) a four-point Likert nausea scale; and (7) a single-item Strength of the Urge to Smoke (SUTS; Jarvik *et al.*, 2000b). The UTS, SSI, SJWS and the SUTS were administered 30 min after the completion of each cigarette. The two nausea scales were administered immediately after completion of each cigarette and then again 20 min after cigarette completion. The nausea measures were included for use as covariates in order to partial out the possible effect of nausea from the effects of the drugs on smoking topography. The decision to include the nausea measures was based on a prior study of the effects of bromocriptine on smoking topography (Jarvik *et al.*, 2000a). In that experiment, subjects were given placebo and 2.5 and 3.75 mg bromocriptine, and there was a near-significant positive linear trend for increasing nausea with increasing doses of bromocriptine. Nausea is a common side-effect with bromocriptine. Based on the lack of side-effects from acute low doses of haloperidol observed in our previous experiments (Caskey *et al.*, 1999), no additional questionnaires were included to assess possible side-effects of haloperidol. In those experiments, no effects for haloperidol were observed on the Barnes Akathisia Scale, the Unified Parkinson's Disease Rating Scale or two subscales of the Addiction Research Center Inventory.

Bioassays

Blood samples (10 ml) were assayed for nicotine and cotinine concentrations. Breath samples were assessed for CO content.

Data analysis

Since subjects were allowed to smoke *ad lib*, and most measures were taken in relation to each cigarette smoked, the number and timing of measures could vary dramatically across subjects. These included the topography measures and subjective and mood effects. For these variables, the values were aggregated over the post-loading cigarette observation period (approximately 6 h) yielding one summary measure per drug condition. The two drug conditions were compared using paired *t*-tests for the topography measures (given no appropriate baseline values) and repeated measures analysis of

covariance (rANCOVA) with session baseline values as covariates for subjective effect variables. For those measures that were assessed at set time points (expired CO, plasma nicotine, plasma cotinine), repeated measures analysis of variance (rANOVA) or rANCOVA were used with session baseline values set as covariates. The importance of baseline subject characteristics (e.g., FTND scores and FTC-rated nicotine yields of the participants' cigarettes) were also examined as potential covariates. Effect sizes (Cohen, 1988) are reported.

Results

Smoking behavior

A variety of measures showed that subjects smoked more under haloperidol than under bromocriptine (see Table 1). Subjects' total puffing time was significantly higher in the haloperidol than in the bromocriptine condition ($t_{(19)} = 2.44$, $p < 0.05$, $d = 0.55$). Subjects also took significantly more puffs from their cigarettes with haloperidol than with bromocriptine ($t_{(19)} = 2.27$, $p < 0.05$, $d = 0.44$). Subjects smoked significantly more cigarettes in the haloperidol condition than in the bromocriptine condition ($t_{(19)} = 2.15$, $p < 0.05$, $d = 0.48$). Subjects' smoking rate (cigarettes per hour) was significantly faster with haloperidol than with bromocriptine ($t_{(19)} = 2.15$, $p < 0.05$, $d = 0.47$). As seen in Table 1, the mean puff duration (total puffing time/total number of puffs) was nearly identical in the two drug conditions. There were non-significant trends ($p = 0.09$, one-tailed, $d = 0.17$) for shorter inter-cigarette intervals in the haloperidol condition than in the bromocriptine condition (see Table 1) and for a shorter latency to smoke with haloperidol than with bromocriptine during time of expected peak drug concentration ($p = 0.10$, one-tailed, $d = 0.25$).

CO

As would be expected with *ad lib* smoking, using rANOVA, there was a significant effect for Time ($F_{(3)} = 5.11$, $p < 0.05$, $\eta^2 = 0.25$), with CO levels increasing from baseline over time in both drug conditions. There was a non-significant trend for the Drug by Time interaction effect ($F_{(3)} = 1.89$, $p = 0.14$, $\eta^2 = 0.11$) (see Figure 1)

Figure 1
Carbon Monoxide Means
N = 16

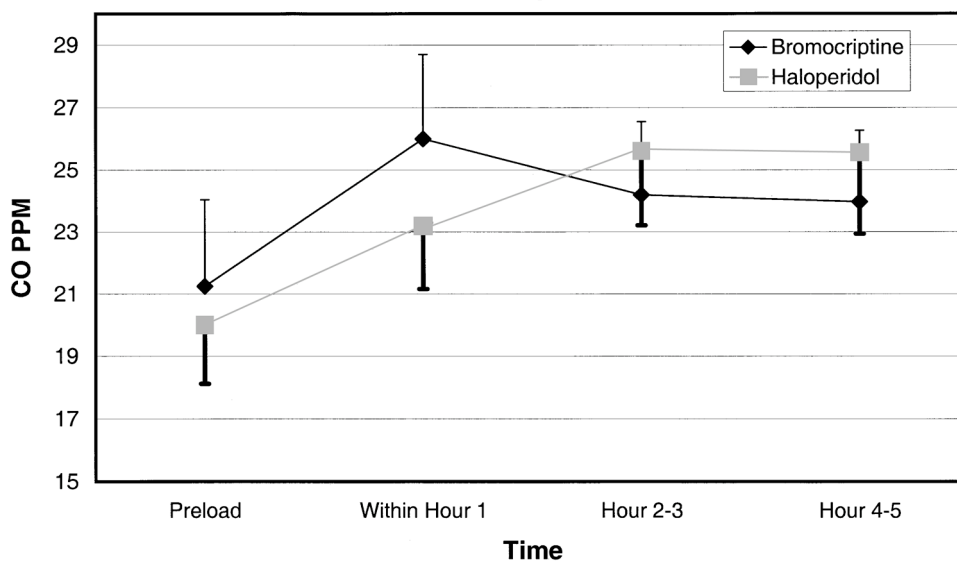


Figure 1. Carbon monoxide means, $n = 16$.

with CO levels increasing with haloperidol over the entire duration of the experimental session and decreasing (after the first hour) with bromocriptine. Though this effect did not achieve statistical significance, the effect size (η^2) is noteworthy. Sixteen subjects were used in this analysis. Four subjects with incomplete sets of CO measurements were excluded: two subjects were missing preloading cigarette baseline assays, and two other subjects were too nauseated to give at least one of the subsequent hourly breath samples.

Nicotine

No significant effects were detected in the analyses of nicotine levels.

Cotinine

Baseline cotinine levels did not differ (haloperidol: mean = 245.5 ± 123.0 ng/ml; bromocriptine: mean = 258.7 ± 141.9 ng/ml). A significant Drug by Time interaction effect was obtained ($F_{(1)} = 8.02$, $p = 0.015$, $\eta^2 = 0.40$) (see Figure 2), which is primarily accounted for by a decrease in cotinine levels in the bromocriptine condition from baseline to the second measurement. One subject was missing from this analysis ($n = 19$) because of a specimen loss due to sample handling error.

Nausea ratings

Two nausea ratings (four-point and visual analog) were taken at baseline (prior to smoking the 'loading' cigarette) and then again immediately and 20 min after subjects completed each cigarette. There were no initial differences in nausea ratings between the two drug

conditions. A series of repeated-measures ANOVAs were conducted to test for Drug and Drug by Time interactions for the two types of measures and for the two measuring time points (immediately and 20 min after cigarette completion). There was only one significant effect in all these analyses: a Drug by Time interaction ($F_{(1)} = 4.41$, $p = 0.05$, $\eta^2 = 0.20$) with the Likert scale comparing baseline ratings with ratings taken immediately after cigarette completion (averaged across all cigarettes smoked). The averaged ratings increased 0.35 points from baseline with bromocriptine and decreased 0.07 points with haloperidol (possible scale range: 0–3 points). It should be noted that the mean nausea levels in both drug conditions were generally quite low. The mean four-point nausea ratings for all such ratings in the bromocriptine condition were 0.5 both immediately and 20 min after cigarette completion (SD = 0.6 for both measures). The mean four-point nausea ratings for haloperidol were also quite low both immediately (mean = 0.2 ± 0.5) and 20 min after cigarette completion (mean = 0.1 ± 0.5). The mean visual analog scale (VAS) nausea ratings in the bromocriptine condition were also low immediately after cigarette completion (mean = 16.6 ± 23.5 mm out of 100 mm) and 20 min after cigarette completion (mean = 12.9 ± 15.4 mm). Similarly, the overall mean of all VAS nausea ratings in the haloperidol condition were also quite low both immediately after cigarette completion (mean = 6.5 ± 14.0 mm) and 20 min after cigarette completion (mean = 5.6 ± 14.2 mm).

Smoking behavior as a function of nausea ratings

A series of analyses of covariance (ANCOVA) were conducted in order to test whether the differences in

Figure 2
Unadjusted Means for Cotinine, $N=19$

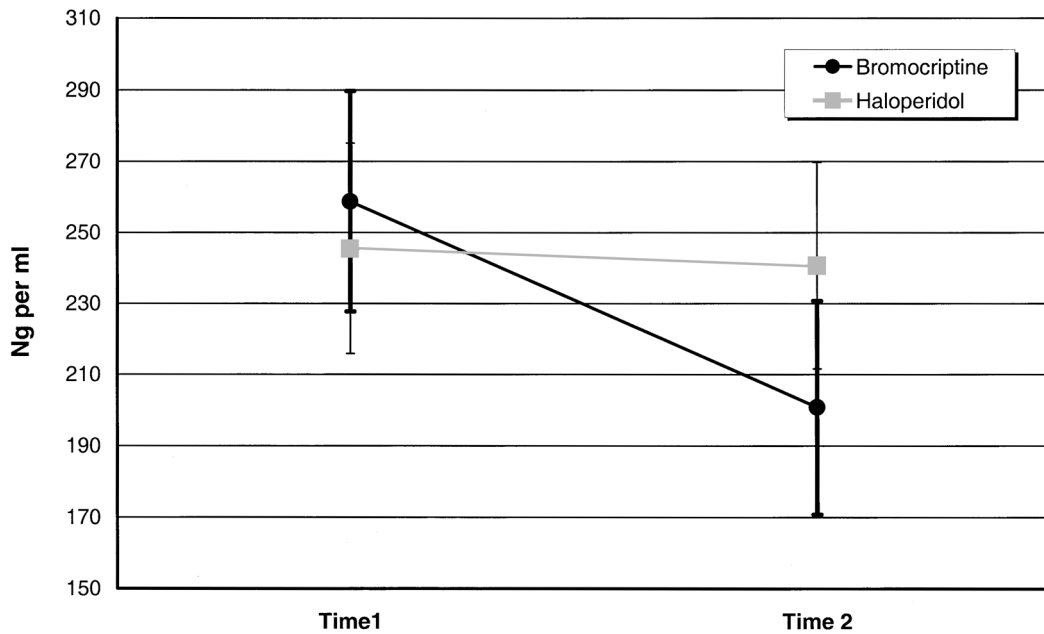


Figure 2. Unadjusted means for cotinine, $n = 19$.

smoking behavior between the bromocriptine and haloperidol drug conditions were attributable to the higher levels of nausea in the bromocriptine condition. Three different nausea 'boost' measures were calculated for each of the two nausea measurements (VAS and Likert). The first 'boost' measure was calculated as the change score from the nausea measurement immediately after the 'loading' cigarette to the nausea measurement immediately after the subjects' last cigarette. The second 'boost' measure was calculated as a change score from the baseline nausea measurement (prior to the 'loading' cigarette) to the nausea measurement immediately after

the last cigarette that subjects smoked. The third boost measure was calculated as the change score from the nausea measurement 20 min after the loading cigarette to the measurement 20 min after the last cigarette that subjects smoked. These six variables were used as covariates in separate ANCOVAs, and the resulting patterns of F , p and η^2 statistics were similar for all six sets of ANCOVAs. The F , p , and η^2 statistics for the first set of nausea boost scores (nausea measured immediately after completion of the 'loading' cigarette and immediately after each subject's last cigarette) are presented in Table 2.

Table 2. Topography variable drug effects (F value, p value, η^2) after covarying for change in nausea ratings (post-loading to post-final cigarette)

Topography variable	Nausea covariate comparison of bromocriptine vs. haloperidol			
	Nausea scale type	F value	p value	η^2
Total puffing time	Likert	3.23	0.09	0.19
	VAS	5.47	0.04	0.28
Mean puff duration	Likert	0.12	ns	0.01
	VAS	0.47	ns	0.03
Total number of puffs	Likert	3.88	0.07	0.22
	VAS	4.11	0.06	0.23
Total number of cigarettes	Likert	2.81	0.12	0.17
	VAS	3.03	0.10	0.18
Smoking rate	Likert	2.81	0.12	0.17
	VAS	1.91	0.10	0.18
Inter-cigarette interval	Likert	2.25	0.16	0.14
	VAS	4.69	0.05	0.25

VAS, visual analog scale.

For a number of the topography variables, the p values for the drug effect obtained with the ANCOVAs were no longer statistically significant (i.e., $p > 0.05$). However, examination of the η^2 values shows a range from 0.13 to 0.28 (with the exception of mean puff duration). Those η^2 values are associated with large effect sizes, such that, despite the lack of statistical significance for the drug effect in a number of the ANCOVAs, the obtained effect sizes for the differences in smoking topography between haloperidol and bromocriptine are quite substantial.

Craving measures

Over the course of 5-h experimental sessions, subjects reported significantly higher craving levels in the haloperidol condition (mean = 4.5 ± 1.2) than in the bromocriptine condition (mean = 3.8 ± 1.3) on the SJWS craving subscale ($p < 0.05$, one-tailed). With the other three measures, the results were in the expected direction (higher craving with haloperidol) but did not attain significance.

Mood measures

Subjects' mean scores on the POMS differed significantly ($p = 0.05$, two-tailed) on only one subscale, with subjects reporting higher levels of confusion with bromocriptine (mean = 1.6 ± 0.9) than with haloperidol (mean = 1.5 ± 1.0).

Discussion

The results from this study are consistent with the hypothesis that dopamine agonism (via bromocriptine) would result in less smoking behavior than dopamine antagonism (via haloperidol) and are consistent with the results of previous experiments examining the effects of dopamine antagonism and agonism on smoking behavior (Caskey *et al.*, 1999; Dawe *et al.*, 1995; Jarvik, 2000a). Overall, these results imply that smoking behavior can be manipulated within the same subjects in opposite directions by alternately stimulating and blocking dopamine, which strongly suggests the importance of dopamine in reinforcement from cigarette smoking.

The ANCOVA results suggest that nausea played some role in the differential response in smoking behavior to the two drugs but also clearly indicate that there is a substantial drug effect independent of nausea. Although the p value for only one of the smoking topography ANCOVAs is less than 0.05, the effect sizes for all the topography variables (excepting mean puff duration) were large ($\eta^2 > 0.14$ for all variables except mean puff duration). Cohen's (1988) criterion for a large effect size is $F = 0.40$ (which equals $\eta^2 = 0.14$) (Cohen, 1988, pp. 283, 287). In light of the effect size calculations, it appears that this experiment was under-

powered and the small sample size has likely affected the p values.

These analyses are somewhat compromised by the design used in the current study in that nausea measurements were specifically tied to cigarette smoking. Because all subjects did not smoke the same number of cigarettes (two different subjects in each drug condition smoked only one cigarette per session), the nausea measurements were taken at varying times across subjects. Additionally, the design could also have been improved if we had included both hourly measures of nausea level and had measured nausea levels immediately prior to smoking.

As in a previous study on the effects of bromocriptine on smoking behavior (Jarvik *et al.*, 2000a), only the SJWS craving subscale yielded near significant ($p = 0.07$, two-tailed, $p < 0.05$, one-tailed) differences between the two drug conditions (though the mean differences on the other three measures were in the expected directions).

The differences between the drug conditions on the POMS confusion subscale (higher scores with bromocriptine) are intriguing. However, the confusion subscale scores are low for both drug conditions.

Animal research has pointed to the possibility that nicotine reinforcement may be controlled by dopaminergic pathways (Clarke, 1990, 1992; Corrigan, 1991; Corrigan & Coen, 1991; Corrigan, Franklin, Coen, & Clarke, 1992; Rose & Corrigan, 1997). Dopamine has been previously hypothesized to play a central role in mediating the reinforcing effects of other stimulant drugs, e.g., cocaine and amphetamines (Koob & Bloom, 1988; Wise & Rompre, 1989). Several animal studies have clearly shown that dopamine is released by nicotine in brain areas associated with reward, e.g., the nucleus accumbens and the ventral tegmental area (Brazell, Mitchell, & Gray, 1991; Clarke, 1992; Mifsud *et al.*, 1989; Nisell *et al.*, 1994a; Svensson, Granhoff, & Englerg, 1990). Further, administration of dopamine antagonists has been shown to reduce nicotine self-administration in animals (Corrigan & Coen, 1991). The specific antagonists used in that study were haloperidol, the D1-selective antagonist SCH23390, and spiperone, a D2-selective antagonist. The decreases in nicotine self-administration were dose dependent. The decreases in self-administration of nicotine were interpreted as an indication of the role of dopamine in nicotine reinforcement.

In summary, this study has demonstrated differences between the effects of bromocriptine and haloperidol on a variety of measures of tobacco cigarette smoking over a 5-h period with reduced levels of smoking with bromocriptine and increased levels of smoking with haloperidol. We assume that since bromocriptine is a drug that specifically stimulates dopamine D2 receptors and haloperidol somewhat less specifically blocks these same D2 receptors, dopamine appears to mediate the reinforcing effects of inhaled tobacco cigarette smoke.

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