Original investigation

Oxytocin Reduces Cigarette Consumption in Daily Smokers

Kathryne Van Hedger PhD, Meredith J. Kushner BA, Royce Lee MD, Harriet de Wit PhD

Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL

Corresponding Author: Harriet de Wit, PhD, 5841 South Maryland Avenue MC3077, Chicago, IL 60637, USA. E-mail: hdew@uchicago.edu

Abstract

Introduction: Despite widespread knowledge of the dangers of cigarette consumption, smoking continues to be a public health concern. One compound that has shown potential for treatment in preclinical models is the neuropeptide oxytocin (OT). The purpose of the present study was to examine the effects of intranasal oxytocin on cigarette craving, behavioral economic demand for cigarettes, and cigarette consumption, in regular smokers after 18 hours of abstinence.

Method: Otherwise healthy daily smokers ($n = 35$) completed two sessions where they received OT (40 IU intranasal) or placebo (PBO) and completed measures of craving and cigarette demand, and they were given six opportunities to smoke partial cigarettes in exchange for money.

Results: On average participants smoked few cigarettes after receiving OT than after receiving PBO, and they reported less desire for additional cigarettes during the smoking period. OT did not affect cigarette demand or standardized measures of cigarette craving.

Conclusions: This study suggests that OT decreases some indices of smoking desire and consumption, providing modest support for the idea that OT might be effective for reducing cigarette smoking.

Implications: This study provides new evidence that oxytocin might have clinical value in the treatment of addictive disorders, in this case tobacco addiction. The study adds to a growing literature suggesting that this neuropeptide, which is mainly known for its role in social bonding and attachment, may also affect mood and motivational states relevant to addiction.

Introduction

Smoking remains the number one cause of preventable death in the United States.¹ Despite the availability of both pharmacological and behavioral treatments for smoking cessation, relapse rates are as high as 92.6%.² Thus there is a need to develop novel treatments. One promising candidate for treating drug abuse including nicotine dependence is the neuropeptide oxytocin (OT).^{3,4}

OT may reduce craving to smoke through direct effects on motivational states, or by decreasing negative affect or anxiety symptomatic of withdrawal states. OT has anxiolytic effects in measures of social interaction, emotion recognition, and trust,⁵ which might be beneficial in substance abuse treatment. In preclinical studies, exogenous administration

of OT reduced self-administration of methamphetamine and heroin in drug-dependent rats.^{6,7} In humans, several studies have reported that intranasal OT reduces both craving for drugs and negative affect states experienced during withdrawal. For example, OT reduced craving for marijuana induced by acute social stress in marijuana-dependent individuals.⁸ In cigarette smokers, OT relieves negative affect, a cardinal symptom of nicotine withdrawal,^{9,10} and also reduces craving for cigarettes induced by smoking-related cues.¹¹ To date, human studies have included self-report measures of affect or craving, but not cigarette consumption (smoking). Although subjective cravings for drugs are closely tied to use of the drugs,¹² they are not invariable predictors of drug consumption. In the present study, we examined the effect of OT measures of craving, behavioral indices of demand, and consumption of cigarettes.

We assessed cigarette demand using the Cigarette Purchase Task (CPT),¹³ and assessed consumption by giving participants choices between money and smoking. The CPT assesses demand for cigarettes based on behavioral economic principles, by asking individuals to report the number of cigarettes they would consume at various prices. It has been shown to be sensitive to increased demand for cigarettes during smoking abstinence and also in response to smoking-related cues.¹⁴ Although it consists of hypothetical choices, responses on the CPT are highly similar to responses in real purchasing situations.¹⁵ Greater demand for cigarettes has also been shown to partially predict successful abstinence in smokers who are trying to quit.¹⁶ Consumption was measured by providing participants with six opportunities to smoke or receive money during a 60-min smoking period. The amount of money was based on an estimated equivalent to the purchase price of a cigarette.

Thus, the purpose of the present study was to test the effect of intranasal OT on cigarette craving, demand, and consumption in daily cigarette smokers, after 18 hours of abstinence. We hypothesized that OT would reduce craving and withdrawal-related anxiety, and therefore reduce the subjective motivation to smoke cigarettes. We also hypothesized that OT would dampen the reward value of cigarettes, and thus reduce demand for cigarettes on the CPT. Finally, we hypothesized that OT would reduce the objective measure of the number of cigarettes smoked. The effects of OT were tested during acute abstinence under double-blind conditions, and compared to placebo in a within subjects design.

Methods

Study Design

This study used a within-subject, placebo-controlled design to examine the desire for cigarettes after a single dose of OT (40 IU) or placebo (PBO). Daily smokers abstained from cigarette use for 18 hours before each of two study sessions. During the sessions, they received either OT or PBO in a nasal spray, in counterbalanced order, followed 30 min later by a cigarette purchase task (CPT), and a 60-min self-administration smoking period. Self-reported craving was assessed before and after the sprays. The primary outcome measures were cigarette craving, demand for cigarettes on the CPT, and number of partial cigarettes smoked in the choice period. This study was approved by the University of Chicago Biological Sciences Division Institutional Review Board. Participants provided written consent and were paid for their participation in this study.

Participants

Healthy daily cigarette smokers ($n = 35$, 17 women) aged 18–35 years were recruited from the University of Chicago and surrounding area. They completed an initial in-person screening consisting of a physical exam, clinical interview, and current and lifetime nonmedical drug use history. Exclusion criteria included Major Axis I psychiatric disorders,¹⁷ serious medical condition, regular medication (except hormonal birth control), current or past year substance dependence (except nicotine dependence), and contraindication for intranasal drug administration (eg, prior nasal surgery). Additionally, women who were pregnant, planning to become pregnant, or lactating were excluded. Further requirements were a minimum of a high school education and English fluency.

Procedure

Orientation

Participants completed a 45-min orientation session before the first session to explain the study and obtain informed consent. They were told that the purpose of the study was to investigate the effects of the hormone oxytocin on mood and that they would receive a nasal spray containing either OT or PBO, followed by the opportunity to smoke. Participants were asked to bring a pack of their preferred brand of cigarettes to the orientation session, which was purchased by the research team for use during the sessions. Participants agreed to abstain from alcohol for 24 hours, recreational drugs for 48 hours, marijuana for 7 days, and cigarettes for 18 hours prior to the start of each session. Normal caffeine intake was permitted. Participants were informed that compliance with the drug abstinence requirements would be confirmed at each session. Finally, participants completed the Fagerström Test for Nicotine Dependence (FTND).¹⁸

Experimental Sessions

Participants completed two 4-hour experimental sessions during which they received OT (40 IU) or PBO under double-blind conditions. Drug order was counterbalanced. Sessions began at 1 pm and took place at least 72 hours apart. Upon arrival at each session, compliance with drug use restrictions was assessed using a breathalyzer (Alco-sensorIII, Intoximeters, St Louis, MO), urine drug test (ToxCup, Branan Medical Corporation, Irvine CA), expired air CO level (Bedfont Scientific piCO+ Smokerlyzer, coVita, Santa Barbara, CA), and women were tested for pregnancy (AimStickPBD, hCG professional, Craig Medical Distribution, Vista, CA). Positive tests resulted in rescheduling or dismissal. Participants completed baseline mood and cigarette craving questionnaires, and, at 1:50 pm, they received the nasal spray containing OT or PBO. This was followed 30 min later by additional mood and craving questionnaires, and the cigarette purchase task. At 3:00 pm, participants completed the 60-min smoking period, which was followed by mood and craving questionnaires at 20-min intervals until 5:00 pm. At 5:00 pm, participants completed an end of study questionnaire and left the laboratory. After the second session, participants were compensated for their participation and the purpose of the study was explained.

Drug

The University of Chicago Hospitals Investigational Drug Pharmacy prepared intranasal OT and PBO doses immediately before each session. OT sprays consisted of one dose of 40 IU Pitocin (OT Injection USB; Monarch Pharmaceuticals; concentration 10 IU Pitocin/1 mL) transferred into four 1-mL syringes and administered with intranasal atomizers (MAD300 by LMA Inc., San Diego, CA). PBO sprays were Ocean Spray Nasal Spray (Valeant Pharmaceuticals, Bridgewater, NJ). Participants received 2 mL to each nostril administered over 10 min.

Smoking Period

The hour-long smoking choice period was scheduled 60 min after the nasal spray. Participants received seven cigarettes of their preferred brand, as well as six quarters (\$1.50) to purchase cigarettes. Each cigarette was marked with a red line at $\frac{1}{4}$ of the length between the end of the cigarette and the beginning of the filter (1.5 cm from the end of standard length cigarettes [$n = 33$] and 2 cm from the end of 100 s [$n = 2$]). This mark indicated how far they could smoke the cigarette at each choice. At the beginning of the 60-min smoking period, participants were required to take a single puff of their own brand of cigarette (which was then discarded). This was designed

as a priming dose. Then, every 10 min over the next hour they were permitted to smoke a new cigarette up to the red line, and, if they chose to smoke, they had to pay \$0.25 of their tab. Thus, they had a total of six opportunities to smoke or not smoke. Following each smoking opportunity participants rated their mood, desire to smoke at the moment, and how pleasurable the partial cigarette was if they recently smoked. Any money remaining at the end of the session was theirs to keep. Participants were tested alone in a comfortable room and were videotaped to ensure compliance.

Dependent Measures

Cigarette Craving

Craving was assessed using the Short Tobacco Craving Questionnaire (S-TCQ)¹⁹ and the Brief Questionnaire of Smoking Urges (B-QSU).²⁰ Participants completed these questionnaires at the beginning of the session, and 15, 45, 125, 145, and 165 min after the nasal spray. The S-TCQ is a 12-item validated measure of subjective tobacco craving that consists of four subscales that assess different aspects of craving. The subscales are Expectancy (eg, “I would enjoy a cigarette right now”), Purposefulness (“It would be hard to pass up the chance to smoke”), Emotionality (“I would be less irritable now if I could smoke”), and Compulsivity (“If I smoked right now, I would not be able to stop”). The B-QSU is a 10-item measure of smoking urges. The B-QSU consists of two subscales: Factor 1 measures desire to smoke for the positive effects of a cigarette and Factor 2 measures anticipation of relief from withdrawal symptoms. Scores on both subscales are also combined into a composite score. Participants were also asked to rate their desire to smoke after every smoking opportunity during the smoking period using a 100-mm Visual Analog Scale (VAS) anchored at “Not at All” and “Extremely.”

Cigarette Purchase Task

The cigarette purchase task (CPT)¹³ provides a measure of the monetary value of smoking. Participants indicate how many cigarettes of their preferred brand they would smoke during a typical day for various cigarette prices, assuming they (1) have no additional income/savings, (2) have no access to any other cigarettes or tobacco products, and (3) are not allowed to stockpile cigarettes for future days. Participants report how many cigarettes they would smoke at each of the following prices: \$0 (free), 2¢ to 50¢ in 2¢ intervals, 60¢, 70¢, 80¢, 90¢, \$1, \$2, \$3, \$4, \$5, \$10, \$15, \$20, \$25, \$30, \$35. Following Murphy and MacKillop,²¹ we calculated four values for each participant: (1) breakpoint (ie, the first price at which consumption is zero), (2) intensity of demand (ie, consumption at the lowest price), (3) O_{max} (maximum expenditure for cigarettes), and (4) P_{max} (ie, price at which expenditure is maximized).

Smoking Period Measures

The primary measure of interest during the 1-hour smoking period was the number of cigarettes participants chose to smoke, out of six opportunities. During this time, participants also rated the pleasure they felt from the cigarettes they smoked on a 100-mm Visual Analog Scale (VAS) anchored at “Not at All” and “Extremely.”

Subjective Effects

Mood and subjective effect ratings were obtained during the experimental sessions to assess subjective responses to OT. Participants completed the Profile of Mood States (POMS)²² and VAS measures of adjectives describing OT-related effects. The POMS is a standardized

questionnaire consisting of 72 adjectives that describe current positive and negative mood states. Participants rate how much they feel each adjective at the moment on a scale ranging from “Not at All” to “Extremely.” Following prior research,¹¹ we chose to focus on the subscales assessing anxiety, anger, and depression as these are common symptoms of nicotine withdrawal. On the VAS, participants rated the following adjectives on a 100-mm line with anchors at “Not at All” and “Extremely”: dizzy, light-headed, focused, and nauseous.

Statistical Analyses

Data were analyzed using SPSS statistical software program version 22 (SPSS Inc., IBM, Chicago, IL). With our current design and sample size we have 80% power to detect small to moderate effects, which are typical of intranasal oxytocin studies.^{5,23} Cigarette craving was compared at baseline, and 15 and 45 min after the sprays across both sessions using a 2 (drug) × 3 (time) repeated measures ANOVA. Desire for a cigarette was compared for OT and PBO during the first smoking opportunity at each session. The four outcome values on the CPT (breakpoint, intensity, O_{max} , and P_{max}) were compared across the two sessions and with the values provided on the CPT at orientation. The number of cigarettes smoked during OT versus PBO sessions was compared with a Wilcoxon signed ranks test, and pleasure from cigarette was compared for the first cigarette smoked after OT and PBO. Subjective effects were compared at baseline, and 15 and 45 min after the sprays across both sessions using a 2 (drug) × 3 (time) repeated measures ANOVA.

Results

Demographic Characteristics

Participant demographics and information on smoking behavior are displayed in Table 1. Our sample was racially diverse, smoked 8.2

Table 1. Demographic information and baseline characteristics of participants (*N* = 35)

	Percent (<i>N</i>) or Mean (SEM)
Sex	
Male/female	18/17
Age (years)	26.9 (0.6)
Education (years)	14.3 (0.3)
BMI	26.4 (1.1)
Race	
Caucasian	28.6% (10)
African-American	37.1% (13)
Asian	8.6% (3)
Mixed Race	22.9% (8)
Unknown	2.9% (1)
Current drug use	
Drinking occasions per week	3.9 (0.3); <i>n</i> = 29
Average number of drinks per occasion	4.0 (0.3); <i>n</i> = 29
Cannabis use days in past month	14.5 (2.3); <i>n</i> = 31
Smoking characteristic (past month)	
Average daily cigarettes	8.2 (0.8)
Maximum daily cigarettes	12.6 (1.0)
Minimum daily cigarettes	5.0 (0.7)
Average weekly cigarettes	57.7 (5.4)
FTND score	3.1 (0.3)

FTND = Fagerström Test for Nicotine Dependence. Sample sizes for current drug use indicate the number of participants who reported alcohol and cannabis use in the past month.

cigarettes per day on average, and most reported regular cannabis use. Similar to our previous study,¹¹ participants reported low to minimal nicotine dependence on the FTND.

Dependent Measures

Cigarette Craving

Craving, as measured by the TCQ or B-QSU, declined from baseline to the beginning of the smoking period in both drug conditions with no difference between OT and PBO (F -values < 1.82, p -values > .18). Yet, on the simple rating of “desire to smoke” after the first smoking opportunity, OT decreased desire to smoke compared to PBO ($t(34) = -2.1$, $p < .05$; Figure 1).

Cigarette Purchase Task

Compared with PBO, OT did not alter the economic value of a cigarette (F -values < 1.39, p -values > .26). That is, breakpoint, intensity of demand, O_{max} , or P_{max} were similar at baseline (orientation) and during both sessions.

Smoking Period Measures

During the sessions, participants smoked between one and six cigarettes, with a mean of 4.11 cigarettes during the PBO session (SEM = 0.26) and a mean of 3.66 cigarettes during the OT sessions (SEM = 0.27). Thus, OT decreased the number of cigarettes smoked, compared to PBO, $Z = -2.48$, $p = .01$ (Figures 2 and 3). Ninety-one and 94 percent of participants smoked during the first opportunity during the PBO and OT sessions, respectively (Table 2). The distribution of choices across the session indicated that the effects of OT were more pronounced after the first 20 min of the access period. But, OT did not change ratings of pleasure from the first cigarette smoked ($t(32) = 1.0$, $p > .05$).

Subjective Effects

OT did not affect anxiety, anger, or depression on the POMS (F -values < 2.13, p -values > .15) or VAS ratings of dizzy, light-headed, focused, or nauseous (F -values < 1.25, p -values > .30).

Figure 1. Mean ± (SEM) ratings of desire to smoke after the first smoking opportunity during each smoking period. Desire to smoke was significantly lower after OT (* $p < .05$, paired t -test).

Figure 2. Mean ± (SEM) number of cigarettes smoked during the 60 min ad lib smoking period after OT and PBO. Cigarettes were the subject's usual brand and participants were allowed to smoke ¼ of each cigarette. Participants ($N = 35$) smoked fewer cigarettes after receiving an OT nasal spray, compared PBO (** $p = .01$, Wilcoxon signed rank test).

Figure 3. Number of participants who smoked fewer, the same, or more cigarettes during OT compared to PBO sessions. Participants were allowed to smoke ¼ of each cigarette, and cigarettes were their usual brand. More participants reduced their cigarette intake after OT than increased their intake.

Discussion

This study was designed to test the effect of intranasal oxytocin (OT) on cigarette craving, behavior economic indices of cigarette demand, and cigarette consumption in daily smokers, after 18 hours of abstinence. On measures of craving, OT decreased ratings of “desire to smoke,” but it did not affect scores on the standardized craving scales (S-TCQ and B-QSU). OT did not alter economic valuations of cigarettes on the CPT, and it did not decrease ratings of negative mood states. Notably, however, OT did reduce the number of cigarettes smoked during the 60-min smoking period. Thus, we found suggestive evidence that OT may decrease some indices of smoking desire and consumption, although the effects were modest. These findings support recent suggestions that OT has potential as a treatment for substance abuse.³

Table 2. Percent of subjects ($N = 35$) who chose to smoke at each of the six opportunities

Smoking opportunity	PBO	OT
1	91	94
2	71	71
3	51	42
4	68	54
5	57	54
6	71	51

OT reduced ratings of “desire for a cigarette” after subjects smoked their first cigarette, without reducing craving on the standardized measures, the S-TCQ and B-QSU. The lack of effect of OT on the standardized questionnaires stands in contrast with our previous findings¹¹ that OT reduced reports of craving on both of these measures. Power calculations indicated that we had adequate power to detect effects on the standardized questionnaires. Notably, however, the decreases in craving in the Miller et al.¹¹ study were detected only in response to smoking-related cues, which were not used in the present study. That is, in the Miller et al.¹¹ study, OT also did not decrease craving reported after 12 hours of abstinence, before cue presentation. McRae-Clark et al.,⁸ reported that OT reduced craving for marijuana, but only after administration of an acute social stress procedure. In the present study, we did not include procedures to stimulate craving prior to the smoking period (ie, smoking cues, stress induction); however, OT did decrease ratings of “desire to smoke” immediately after the first opportunity to smoke. These findings suggest that OT differentially affects different components of smokers’ subjective motivation for cigarettes. The finding that OT does not dampen spontaneous craving during abstinence, but does dampen responses to cues or stress or a priming dose of tobacco smoke suggests that these indices reflect different types of craving. Further research is needed to determine the biological and psychological underpinnings of spontaneous versus elicited craving.

OT did not affect the behavioral economic value of cigarettes assessed using the CPT. Even though this measure has been shown to be sensitive to smoking abstinence and the presence of smoking-related cues,¹⁴ OT did not change cigarette demand in our sample of daily smokers. Indeed, the reward value of cigarettes was similar during the orientation session when subjects had not abstained and after 18 hours of abstinence. Thus, the CPT was not a sensitive indicator of demand for our participants. It is possible that the smoking period, essentially a real-life cigarette purchase task, indirectly influenced their more hypothetical responses on the CPT.

Although prior research has provided evidence of anxiolytic effects of OT,⁵ we did not find such effects in our sample. Although nicotine abstinence often produces negative affect including anxiety,²⁴ our participants did not report strong feelings of anxiety at the beginning of their study sessions. This may be due to the relatively short period of abstinence (18 hours) or to the participants’ relatively low dependence on nicotine (Table 1). Thus, the reduction in smoking after OT did not appear to be related to a decrease in abstinence-induced negative mood states.

The most notable finding in the study was that OT reduced the number of cigarettes subjects smoked. Although about half the subjects smoked the same number of cigarettes on both sessions, 15 smoked fewer on the OT session. This finding supports results from preclinical studies on the effects of OT on drug self-administration in rats⁶ and it supports the idea that OT has potential in the treatment

of addiction.^{3,4} The behavioral and/or biological processes by which OT reduced smoking in the current study are not known. OT did not affect ratings of craving, mood, or pleasure from a cigarette. The effect of OT was more pronounced after the first cigarettes consumed, which may be related to effects of OT on clearance of nicotine, or delay in time to effect of the OT, or dampened enjoyment from the cigarettes that was not detected by our measures. The psychological or biological processes by which OT reduces smoking remain to be determined.

The study has several limitations. First, about 20% of participants ($n = 7$) smoked at every opportunity during the smoking periods at both sessions, making it difficult to know the sensitivity of the manipulation. It is possible that increasing the cost of each cigarette might have increased the sensitivity. Another potential limitation was that the expectancy of being able to smoke, either through instructions or the experience of the first session, might have influenced participants’ reports of cigarette craving. A third limitation is that the participants were light smokers, and five participants reported abstaining from cigarettes even longer than 24 hours before their session. In an informal post hoc examination of subjects’ craving in relation to the duration of their self-reported abstinence, we found no systematic relationship between abstinence duration and craving. These points indicate that future tests of the effectiveness of OT should be conducted with more dependent smokers. Our study sample also reported relatively frequent marijuana use, though prevalence of use was consistent with what has been previously reported among young adult smokers.²⁵ Finally, we did not obtain a systematic assessment of nicotine abstinence on mood or other measures, which may help to understand the mechanisms of effect of OT.

In conclusion, this study provides modest support for the idea that OT might be effective in the treatment of cigarette smoking, and perhaps substance abuse more generally.³ It is consistent with preclinical studies,^{6,7} where OT decreases drug self-administration in rats, and provides suggestive evidence that it decreases drug craving in humans. Future studies will need to determine the mechanisms by which OT affects cigarette consumption and whether the effects of OT are more pronounced in heavier smokers.

Funding

This work was supported by a Global Research Award for Nicotine Dependence (GRAND) from Pfizer, and by grants from NIDA (DA02812). KVH is currently supported by NIMH training grant (T32MH020065).

Declaration of Interests

de Wit has received support unrelated to this study from the following sources: consulting fees from Marinus and Jazz Pharmaceuticals; gift of a study drug from Indivior; and support for a research study from Insys Therapeutics.

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