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Original investigation

Effects of Intranasal Oxytocin on Stress-Induced Cigarette Craving in Daily Smokers

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Abstract

Background: Cigarette smoking is a well-known public health concern, and there is an urgent need to develop new treatments to reduce smoking or facilitate abstinence. One factor that is known to contribute to relapse is stress, making the stress response an important target for treatment. The neuropeptide oxytocin (OT) is believed to have stress-reducing effects, and in addition there is evidence that it reduces drug craving. The purpose of the present study was to examine the effects of intranasal OT on stress-induced cigarette craving in regular smokers after 12 h of abstinence.
Method: Daily smokers (n = 48) completed a stress induction task and a nonstressful control task at two different sessions, receiving intranasal OT (40 IU) or placebo (PBO) before or after the task. Subjects were randomly assigned to one of three groups: Group PP (n = 16) received PBO before and after the stress/control tasks, Group OP (n = 16) received OT before the tasks and PBO after, and Group PO (n = 16) received PBO before the tasks and OT shortly after completing the tasks. Cigarette craving as well as subjective and physiological responses to stress was assessed.
Results: OT did not alter responses to stress, whether it was administered before or after the stressful task, on measures of cigarette craving, anxiety, heart rate, blood pressure, and cortisol levels.
Conclusions: The current study findings do not support several previous reports that OT reduced either stress or drug craving.
Implications: This study finds a null result of the neuropeptide oxytocin on stress-induced cigarette craving. Reporting null findings is part of the process of identifying potential treatments for addictive disorders.

Introduction

Cigarette smoking continues to be a major public health concern. Despite declines in smoking over the past decade, an estimated 29.7 million people in the United States still smoke cigarettes daily,[1] and of those who try to quit, <1 in 10 succeed.[2–4] Among the many possible reasons for the high rates of relapse, one recognized risk factor is stress. Stress increases craving and rates of smoking and increases the likelihood of returning to smoking during a quit attempt.[5,6] Thus, a medication that reduces reactivity to acute or chronic stress would be of great value as an aid in quitting. Here, we explore the potential for the neuropeptide oxytocin (OT) as a stress-dampening aid to reduce cigarette craving.

OT has been proposed as a novel treatment for addiction.[7–9] In animal models, OT reduces conditioned place preference established by methamphetamine[10,11] and decreases self-administration of cocaine, opiate, and methamphetamine.[12–14] In humans, Miller et al.[15] reported that OT reduced craving for tobacco cigarettes induced by smoking-related cues in smokers who had abstained for 12 h. There is also evidence that the effects of OT on craving may be related to its stress-reducing properties: McRae-Clark et al.[16] reported that intranasal OT reduced craving for cannabis in regular users who were exposed to the Trier Social Stress Test (TSST). Indeed, in studies not related to drug taking, there are reports that OT reduces stress when administered before public speaking tasks.[17,18]

Several studies support the observation that acute stress increases cigarette craving and smoking.[19] In a naturalistic survey study of 1500 smokers, McKee et al.[20] found that relapse was related to stress resulting from a change of residence or adverse financial events. In laboratory studies, acute stress consistently increases craving for cigarettes among daily smokers.[21–23] Buchmann and colleagues (2010) found that stress increases cigarette craving and that stress-induced craving was positively correlated with cortisol response to stress. Given that aspects of the stress response (eg, cortisol, anxiety ratings) can covary with cigarette craving, pharmacological agents that can reduce stress responses might help dampen stress-induced cigarette craving.

The purpose of the present study was to examine the effects of intranasal OT (40 IU) on cigarette craving induced by the TSST, a stressful public speaking task, under controlled laboratory conditions. This dose was selected based on prior studies that have found it to be effective at reducing stress-induced craving[16] and smoking behavior.[24] We examined the effects of OT administered before or shortly after the TSST. By administering OT before the task, we could determine whether OT dampened the experience of the stressor itself. By administering OT soon after the task, we could determine whether OT dampened the responses induced by the TSST (ie, recovery). We hypothesized that (1) the speech task would increase smoking craving, (2) OT administered before the speech task would reduce responses to the TSST and stress-induced craving, and (3) OT administered just after the TSST would dampen the stress responses (ie, hasten the return to normal after stress).

Methods

Study Design

This study used a mixed between- and within-subjects design to examine the effects of intranasal OT on stress-induced cigarette craving. Daily smokers participated in two sessions during which they completed a stress task and a nonstressful control task, each after abstaining from smoking for 12 h. During the 3-h sessions, subjects received nasal sprays containing OT (40 IU) or placebo (PBO) before and after completing the stress task or nonstressful control task. Subjects were randomly assigned to one of three groups who received (1) PBO before and just after the tasks at both sessions (Group PP), (2) OT before and PBO after the tasks (Group OP), or (3) PBO before and OT after the tasks (Group PO; Table 1). Within each group, participants received the same drug (OT or PBO) in the same order at both sessions. The verbal stress task consisted of the TSST[25] and the nonstressful control task consisted of a simple conversation with a research assistant. The two tasks occurred in counterbalanced order across subjects. At regular intervals throughout the sessions, participants rated craving for cigarettes and mood, had cardiovascular measures recorded, and provided saliva samples. The primary outcome measure was craving for cigarettes. We were also interested in changes in mood, and cardiovascular and salivary cortisol response to the TSST.

Participants

Daily cigarette smokers were recruited from the University of Chicago and surrounding area. Participants were 18–35 years old and healthy apart from cigarette smoking. Screening included a physical exam and clinical interview, and a current and lifetime nonmedical drug use history. Participants were required to have a minimum of a high school education and fluency in English to participate. Potential participants with Major Axis I psychiatric disorders,[26] serious medical conditions, regular medications, current or past year substance dependence (excluding nicotine dependence), and contraindications for intranasal drug administration (eg, prior nasal surgery) were excluded. In addition, women taking hormonal birth control and women who were pregnant, planning to become pregnant, or lactating were excluded. Women completed their study sessions during the follicular phase of their menstrual cycle to minimize variability in stress responses and fluctuations in endogenous OT related to hormone levels.[27,28] Five additional participants did not complete both study sessions for reasons unrelated to the experimental procedure; only participants who completed both sessions (n = 48, 21 women) were included in the analyses. Participants provided written informed consent and received monetary compensation for completing the study. This study was approved by the University of Chicago Biological Sciences Division Institutional Review Board.

Procedure

Orientation

Participants attended a 30-min orientation session prior to the experimental sessions to discuss study logistics and obtain informed consent. They were told that the purpose of the study was to explore the effects intranasal OT, a naturally produced hormone, on responses to verbal tasks. Participants were made aware that the tasks would differ on the 2 days and that they might be video recorded. Participants were told to abstain from alcohol for 24 h before each session, recreational drugs for 48 h, marijuana for 7 days, and cigarettes or other nicotine containing products for 12 h. Normal caffeine intake was permitted. Participants were informed that they would be tested for recent drug use before each session. Participants also completed practice versions of cigarette craving and mood questionnaires and provided information on their smoking habits, including the Fagerström Test for Nicotine Dependence (FTND).[29]

Experimental Sessions

Participants completed two 3-h experimental sessions beginning at noon, 3–7 days apart. Subjects were randomly assigned to one of the three groups described earlier (Group OP: OT before task and PBO after, Group PO: PBO before task and OT after, and Group PP:

Table 1. Details of Study Design for the Three Subject Groups (order of TSST or control was counterbalanced across subjects)

	Session 1			Session 2		
	Spray 1	TSST or control	Spray 2	Spray 1	TSST or control	Spray 2
Group PP	Placebo		Placebo	Placebo		Placebo
Group OP	Oxytocin		Placebo	Oxytocin		Placebo
Group PO	Placebo		Oxytocin	Placebo		Oxytocin

TSST = Trier Social Stress Test.

placebo in both sprays). On the two sessions, they received either OT (40 IU) or PBO nasal sprays under double-blind conditions before and shortly after a verbal task (TSST or control). Task order was counterbalanced.

Upon arriving at each session, recent drug use was assessed using a breathalyzer (Alco-sensorIII, Intoximeters, St Louis, MO), urine drug test (ToxCup, Branan Medical Corporation, Irvine, CA), and expired-air CO level (Bedfont Scientific piCO+ Smokerlyzer, coVita, Santa Barbara, CA). Following previous studies, 12 ppm of CO in expired-air was used as a cutoff for a positive test.[30] Women were tested for pregnancy (AimStickPBD, hCG professional, Craig Medical Distribution, Vista, CA). Positive drug tests resulted in rescheduling that session. Next, participants completed baseline cigarette craving and mood questionnaires, and baseline cardiovascular measures; baseline saliva samples, to measure salivary cortisol, were obtained with unflavored cotton Salivettes® (Sarsdedt, Inc, Newton, NC). At 1 PM, participants received their first nasal spray containing OT (40 IU for Group OP) or PBO (for the other two groups), which took 10 min. Twenty minutes later, they completed cigarette craving and mood questionnaires, and cardiovascular measures, and provided a saliva sample. Then at 1:40 PM, they received instructions for the verbal task to be completed that day (either TSST or control; described in the following) and had 10 min to prepare for the task. Prior studies have demonstrated the effects of OT on public speaking tasks approximately 1 h after administration.[17,18] The task itself occurred from 1:50 PM to 2:00 PM. At 2:01 PM subjects completed cigarette craving and mood questionnaires, as well as cardiovascular measures, and at 2:10 PM, saliva samples were collected. At 2:11 PM a second set of nasal sprays (OT 40 IU for Group PO and PBO for the other two groups) was administered, at 2:20 PM a saliva sample was collected, and at 2:50 PM participants completed cigarette craving and mood questionnaires, and cardiovascular measures, and provided final saliva samples. After the second session, participants were compensated for their participation and debriefed.

Drug

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

Trier Social Stress Test

The TSST began 50 min after the first nasal spray and followed the procedure outlined by Kirschbaum et al. The interval of 50 min was used based on Gossen et al.,[31] showing peak plasma concentrations at 30–90 min following intranasal OT administration, and in accordance with the protocol used in Heinrichs et al.[17] First, participants were told about the task for the day and given 10 min to prepare. They were told that they would be giving a 5-min speech describing their qualifications for their ideal job, and performing a 5-min mental arithmetic test to assess working memory capacity (counting down from 6233 by 13) in front of two "judges." Participants were informed that their interview would be recorded. The two confederates were unknown to the subjects and were trained to maintain neutral facial expressions and minimize nonverbal behavior. The primary confederate was male and the same across all subjects. During the speech and mental arithmetic test, participants were prompted to continue or to start over when they paused or made an error. Participants were debriefed on the TSST after completing all study requirements.

Control Verbal Task

The control task began 50 min after the first nasal spray and involved speaking with a research assistant and playing a computer game. Before the task, participants were given 10 min to prepare for a discussion of a movie, program, play, or book that they recently viewed or read. They then spoke with a research assistant that they had not previously met about their chosen topic for 5 min. Following the conversation, they played Solitaire on the computer for 5 min. This task has been previously used by other studies in our lab.[32–34]

Dependent Measures

Cigarette Craving

Craving was measured with subscales of the Short Tobacco Craving Questionnaire (S-TCQ).[35] The S-TCQ is a validated 12-item scale assessing subjective tobacco craving that includes subscales about anticipation of positive outcomes from smoking (Expectancy; eg, "I would enjoy a cigarette right now") and relief from negative mood (Emotionality; eg, "I would be less irritable now if I could smoke").

Mood

To assess mood during the experimental sessions, participants completed the Profile of Mood States (POMS).[36] The POMS is a standardized 72-item questionnaire consisting of 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." We focused on the anxiety subscale because we would expect the TSST to increase feelings of anxiety, whereas the control task should not increase anxiety.

Salivary Cortisol

Saliva samples were collected during the session in which participants completed the TSST at baseline, 20 min after the first spray, and 10, 20, and 50 min after the TSST. Saliva samples were assayed for cortisol by the Core Laboratory at the University of Chicago Hospitals General Clinical Research Center (Salimetrics LLC, State College, PA; sensitivity = 0.003 μg/dL). Saliva samples from four participants could not be analyzed because of insufficient quantities of saliva.

Cardiovascular Measures

Heart rate (HR) and blood pressure were collected at six timepoints throughout the session using a standard blood pressure cuff (Omron Healthcare, Inc, Lake Forest, IL). From these values, mean arterial pressure (MAP) was calculated using the formula: [systolic BP + (2 × diastolic BP)]/3.

Statistical Analyses

Data were analyzed using SPSS statistical software program version 22 (SPSS, Inc, IBM, Chicago, IL). Power was calculated using G*Power 3.[37] With the current sample size and study design, we were adequately powered (>80%) to detect effects in the small to moderate range. This study addressed two main questions: (1) Does OT reduce stress-induced cigarette craving when it is administered before the TSST, and (2) does OT reduces stress-induced cigarette craving when it is administered after the TSST (ie, during recovery)? For both questions, we used repeated measures ANOVA (group,

task, time) to examine changes in cigarette craving after OT and stress. For the first question, we examined the change in cigarette craving from before to after the study tasks (TSST vs control task) comparing the OP versus PP groups only. For the second question, we examined the change in cigarette craving after the task (but before the second spray) to craving reported 20 min after the spray, comparing the PO and PP groups only.

These and other analyses provided information on secondary questions. First, did OT alone affect mood, physiology, or craving independently of the TSST? To answer this question, we examined mood, craving, cortisol, HR, and MAP before and after the first spray in the OP and PP groups using repeated measures ANOVA (group, time). Second, did OT alter psychological or physiological responses to the TSST on measures of mood, cortisol, HR, and MAP? To answer this question, we compared these measures before and after the TSST in the OP and PP groups, using repeated measures ANOVA (group, time).

Results

Demographic Information

Participant demographic information and smoking characteristics are presented in Table 2. Participants in the three drug groups did not differ significantly in age, education, body mass index, current drug use, or average daily cigarette use. The groups also did not differ in FTND scores, $F(2, 45) = 1.00$, $p = .375$.

Effects of OT Independent of Stress

Independently of the TSST, OT did not affect any subjective or physiological measure assessed 20 min after the first spray. That is, the OP group did not differ from the PP group before the TSST, and the PP and PO groups did not differ from each other comparing between or within groups before each task. Thus, compared with PBO, OT had no effect on self-reported ratings including anxiety or cigarette craving, or on measures of cardiovascular function.

Effectiveness of Stress Induction and Effect of Stress on Craving

The TSST produced its expected effects on mood, cardiovascular function, and cortisol. Compared with the control task, the TSST significantly increased POMS anxiety (task × time), $F(4, 172) = 20.30$, $p < .001$, and MAP (task × time), $F(4, 188) = 4.24$, $p < .01$, and within the TSST session, salivary cortisol increased from before to after the TSST, $F(4, 172) = 7.66$, $p < .001$. These effects subsided during the hour following the TSST. The TSST had its predicted effects on cigarette craving. Compared with the control task, the TSST increased scores on both the TCQ Emotionality scale (task × time), $F(2, 54) = 12.2$, $p < .001$ (Figure 1), and the TCQ Expectancy scale (task × time) $F(2, 54) = 7.9$, $p < .01$, in all three groups. Means and standard errors for cigarette craving by task and group are presented in Table 3.

Effects of OT Administered Before the TSST

OT administered before the TSST did not decrease any of the responses to the stressor, including ratings of anxiety or cigarette craving, blood pressure, or cortisol levels. This was assessed by comparing the responses of the OP group to the PP group.

Effect of OT Administered After the TSST

OT administered shortly after the TSST had no significant effect on recovery from stress. This was determined by comparing responses of the PO and PP groups.

Table 2. Demographic Information, Current Drug Use and Smoking Characteristics for the Three Groups: PP (n =16) Placebo Before and After Stress Task, OP (n = 16) Oxytocin Before and Placebo After Stress Task, and PO (n = 16) Placebo Before and Oxytocin After Stress Task

Drug group	PP	OP	PO
Sex			
Male/female	9/7	9/7	9/7
Age (years)	26.6 (0.9)	25.3 (1.1)	26.4 (1.0)
Education (years)	14.6 (0.4)	13.9 (0.3)	13.6 (0.3)
BMI	26.8 (1.6)	24.7 (1.1)	25.3 (1.6)
Race			
Caucasian	37.5 (6)	56.3 (9)	31.3 (5)
African American	43.8 (7)	18.8 (3)	31.5 (5)
Asian	6.3 (1)	–	6.3 (1)
Mixed race	12.5 (2)	25.0 (4)	18.8 (3)
Unknown	–	–	12.5 (2)
Current drug use[a]			
Drinking occasions per week	2.4 (0.6); n = 13	3.0 (0.3); n = 16	3.4 (0.5); n = 15
Average number of drinks per occasion	3.1 (0.4); n = 15	4.1 (0.5); n = 16	4.1 (0.5); n = 16
Cannabis use in past month (days)	15.9 (3.5); n = 13	15.4 (3.4); n = 11	12.5 (2.8); n = 14
Smoking characteristics (past month)			
Average daily cigarettes	8.3 (0.9)	8.0 (1.3)	8.7 (1.1)
Maximum daily cigarettes	13.8 (1.7)	13.5 (2.0)	13.7 (1.5)
Minimum daily cigarettes	5.1 (0.9)	5.2 (0.9)	3.6 (0.8)
Average weekly cigarettes	59.2 (5.1)	62.4 (9.0)	54.5 (7.6)
FTND score	3.5 (0.5)	2.6 (0.5)	3.0 (0.5)

Values represent percent (n) or mean (SEM).

BMI = body mass index; FTND = Fagerström Test for Nicotine Dependence.

[a]Sample sizes for current drug use indicate the number of participants who reported any alcohol and cannabis use in the past month. Mean values are based on only those who reported using.

Discussion

In this study, we tested the effects of intranasal OT on physiological and subjective responses to the TSST and stress-induced cigarette craving in smokers. The TSST effectively increased blood pressure, cortisol, and subjective ratings of anxiety, and, as predicted, it increased cigarette craving. However, OT administration did not dampen any of the dimensions of stress measured, nor did it reduce stress-induced craving, whether it was administered before or after the TSST. If anything, participants who received OT before the TSST showed a trend toward further increased craving following the TSST relative to the other two groups (Figure 1), but this difference was not statistically significant. This null result was somewhat surprising, given the previous evidence that OT reduces responses to psychosocial stress. Heinrichs et al.[17] reported that OT attenuated cortisol and anxiety responses to the TSST. Notably, that study showed that OT only significantly dampened cortisol responses to the TSST when combined with social support, which we did not include in our study. Another study found that OT reduced stress-induced dysphoria, but only in individuals with borderline personality disorder.[38] In line with these findings, yet another group reported that OT reduced cortisol responses to stress in individuals with disordered emotion regulation.[39] Thus, there is some evidence that the effects of OT are most pronounced in individuals with poor emotional regulation. In contrast, in the present study we excluded anyone with clinical symptoms of mood dysregulation, leaving open the possibility that the anxiolytic effects of OT are limited to individuals with negative affective symptoms.

The present findings can be considered in light of other studies on the effects of OT on either cue-induced or stress-induced craving for drugs. Although both drug cues and acute stress are known to heighten craving in humans and increase relapse-like behavior in animal models,[40] they are thought to do so by separate mechanisms (eg, granular insular cortex activity for reinstatement

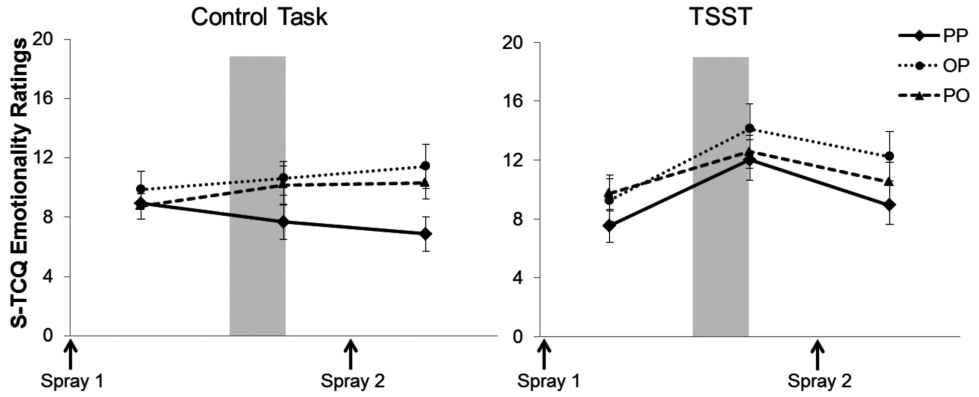

Figure 1. Mean ± (SEM) ratings of cigarette craving (Short Tobacco Craving Questionnaire [S-TCQ] Emotionality) before and after the control task and Trier Social Stress Test (TSST). The arrows indicate the timing of nasal sprays, and the gray bar indicates when the control task or TSST occurred. The pre-task measurement was taken 20 min after the first spray, the post-task measurement was taken immediately after the task, and the third measurement occurred 40 min after the second spray. The PP group received placebo at both sprays, the OP group received oxytocin at the first spray and placebo at the second spray, and the PO group received placebo at the first spray and oxytocin at the second spray. The TSST significantly increased cigarette craving compared with the control task, and there were no group differences in ratings of craving. Oxytocin had no significant effect in either the OP or PO group.

Table 3. Means (SEM) of Subjective and Cardiovascular Responses by Group and Task

Group	Control			TSST		
	Pre-control	Post-control	Post-spray #2	Pre-TSST	Post-TSST	Post-spray #2
TCQ expectancy						
Group PP	12.9 (1.2)	12.5 (1.3)	11.5 (1.4)	13.3 (1.1)	15.6 (1.0)**	14.5 (1.2)
Group OP	14.5 (1.4)	14.6 (1.5)	15.2 (1.4)	13.8 (1.8)	16.5 (1.7)*	15.7 (1.5)
Group PO	14.4 (1.5)	14.9 (1.6)	14.9 (1.6)	14.9 (1.5)	17.4 (1.2)*	16.8 (1.2)
POMS anxiety						
Group PP	6.4 (1.4)	4.5 (0.8)	5.8 (1.0)	5.7 (1.0)	11.4 (1.5)**	5.4 (1.0)
Group OP	7.4 (1.3)	6.6 (1.3)	5.8 (1.1)	4.9 (1.0)	14.8 (2.2)**	7.8 (1.1)
Group PO	5.9 (0.8)	6.0 (1.1)	5.5 (0.7)	5.6 (1.2)	9.6 (1.7)**	5.6 (0.8)
Heart rate						
Group PP	65.2 (2.5)	62.9 (2.2)	65.3 (2.0)	64.8 (2.4)	65.9 (2.4)	64.4 (2.0)
Group OP	70.0 (3.0)	68.7 (3.2)	66.1 (3.1)	71.9 (2.2)	68.1 (3.1)	70.4 (3.4)
Group PO	65.2 (1.9)	65.1 (2.1)	62.8 (2.0)	69.9 (1.8)	66.6 (3.4)	65.4 (2.6)
Blood pressure (MAP)						
Group PP	92.5 (3.3)	92.4 (2.7)	90.1 (2.0)	87.9 (2.0)	98.7 (2.1)**	89.1 (1.7)
Group OP	84.4 (1.7)	88.0 (2.0)*	88.0 (2.3)	83.6 (1.8)	91.1 (2.6)**	84.4 (2.0)
Group PO	94.4 (3.8)	94.6 (3.5)	92.7 (2.9)	92.8 (2.8)	97.8 (2.9)#	93.9 (3.0)

MAP = mean arterial pressure; POMS = Profile of Mood States; S-TCQ = Short Tobacco Craving Questionnaire; TSST = Trier Social Stress Test.
Significant increase as a result of the task. #$p < .10$, * $p < .05$, **$p < .01$.

by nicotine cues, and alpha-2-adreno-ceptors in central amygdala for reinstatement by acute stress). In the present study, we found that OT did not affect stress-induced cigarette craving, whereas in a previous study[15] we reported that OT reduced cigarette craving induced by smoking-related cues. In addition, McRae-Clark et al.[16] found that OT reduced stress-induced craving for cannabis among cannabis-dependent users. The explanation for these apparently discrepant findings is unclear. The three studies used comparable sample sizes. The precise conditions under which OT alters craving in response to drug-related cues, or stress, remain to be determined.

This study has several important limitations. First, our participants reported low to moderate levels of nicotine dependence despite being daily smokers. It is possible that OT would have more pronounced effects in more dependent smokers. Heavier smokers might report greater stress-induced craving, thus revealing an effect of OT. Second, we tested only one dose (40 IU) of OT. It is possible that higher, or lower, doses of OT may have differential effects. Third, our measure of OT effects before the stressor may have occurred too soon after the first spray to draw strong conclusions of the effects of OT independent of the TSST. These measurements were taken 20 min after the spray, and there is some evidence that plasma levels of OT peak 30–90 min after intranasal administration.[31] It is not yet known whether the central effects occur at the same time as the increase in plasma levels. Fourth, we did not assess other individual difference factors that might moderate the effects of OT (eg, attachment style, experiences of childhood trauma). Finally, our relatively small number of subjects did not permit an analysis of the influence of sex. Future investigations may include a more direct comparison of the effects of OT on cue- and stress-induced craving, a larger sample size capable of examining sex differences, and a measure of plasma OT levels during the procedure.

Taken together, we found no evidence that intranasal OT reduces stress-induced craving in abstinent cigarette smokers with low to moderate nicotine dependence. Although we found that the TSST did increase cigarette craving, OT did not affect this or any other indices of stress (subjective, hormonal, cardiovascular). It remains to be determined whether OT affects stress-induced craving under other conditions, including those where OT alone has altered stress responses.

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Declaration of Interests

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