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Intranasal oxytocin administration is associated with enhanced endogenous pain inhibition and reduced negative mood states

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Abstract

Objectives—This study examined whether the administration of intranasal oxytocin was associated with pain sensitivity, endogenous pain inhibitory capacity, and negative mood states.

Methods—A total of 30 pain-free, young adults each completed three laboratory sessions on consecutive days. The first session (baseline) assessed ischemic pain sensitivity, endogenous pain inhibition via conditioned pain modulation (CPM), and negative mood using the Profile of Mood States (POMS). CPM was tested on the dominant forearm and ipsilateral masseter muscle using algometry (test stimulus) and the cold pressor task (conditioning stimulus; non-dominant hand). For the second and third sessions, participants initially completed the State-Trait Anxiety Inventory (STAI) and then self-administered a single (40IU/1mL) dose of intranasal oxytocin or placebo in a randomized counter-balanced order. Thirty minutes post-administration, participants again completed the STAI and repeated assessments of ischemic pain sensitivity and CPM followed by the POMS.

Results—Findings demonstrated that ischemic pain sensitivity did not significantly differ across the three study sessions. CPM at the masseter, but not the forearm, was significantly greater following administration of oxytocin compared to placebo. Negative mood was also significantly lower following administration of oxytocin compared to placebo. Similarly, anxiety significantly decreased following administration of oxytocin but not placebo.

Discussion—This study incorporated a placebo-controlled, double-blind, within-subjects crossover design with randomized administration of intranasal oxytocin and placebo. The data suggest that the administration of intranasal oxytocin may augment endogenous pain inhibitory capacity and reduce negative mood states including anxiety.

Keywords

Intranasal oxytocin; pain sensitivity; pain inhibition; negative mood state; anxiety

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INTRODUCTION

Initial evidence from pre-clinical research has demonstrated a role for oxytocin as a neurotransmitter with modulatory effects on somatosensory transmission including nociception and the experience of pain.¹ Oxytocin is a small nonapeptide produced in the supraoptic and paraventricular nuclei of the hypothalamus, and following secretion into the blood, is best known for its hormonal roles in parturition and lactation.² However, oxytocinergic neurons of the paraventricular nuclei also form synaptic connections throughout the central nervous system and with neurons in the dorsal horn of the spinal cord.^{3,4,5} These synaptic connections allow oxytocin to function as a neurotransmitter and directly influence the transmission of pain signals.^{4,6,7,8}

Clinical research in humans has generally suggested that low levels of endogenous oxytocin may be a component of various chronic pain conditions.¹ When compared to pain-free controls, blood plasma oxytocin concentrations were found to be significantly lower among patients with acute and chronic low back pain,⁹ as well as among children experiencing recurrent abdominal pain.^{10,11} Furthermore, low concentrations of blood plasma oxytocin were significantly associated with ratings of greater pain among women with fibromyalgia.¹² Similar lines of clinical investigation have revealed that the exogenous administration of oxytocin into the central nervous system can diminish pain severity in humans. For example, intrathecal oxytocin administration resulted in a reduction of pain severity in a placebo-controlled evaluation of men and women with acute or chronic low back pain.⁹ Likewise, a recent study found that the intranasal administration of oxytocin was significantly related to reports of decreased headache frequency and pain severity in a sample of individuals with chronic migraine.¹³

The mechanisms whereby oxytocin may influence the experience of clinical pain in humans have received minimal attention in previous studies. However, it is plausible that oxytocin could influence clinical pain severity by altering sensitivity to painful stimuli as well as by acting upon important pain-related psychological factors such as mood. At present, the few studies that have examined oxytocin in relation to experimental pain sensitivity have produced mixed results. For instance, low levels of plasma oxytocin were associated with reduced pain tolerance for noxious cold and ischemic stimuli in healthy women.¹⁴ Relative to placebo, the intranasal administration of oxytocin resulted in increased pain threshold for a noxious cold stimulus.¹⁵ Similarly, the continuous intravenous infusion of oxytocin increased thresholds for colonic distention pain compared to placebo among adults with irritable bowel syndrome.¹⁶ Conversely, it has also been shown that intranasal administration of oxytocin to healthy men was unrelated to ratings of pain unpleasantness in response to noxious electrical stimulation.¹⁷ Regarding psychological factors, evidence supports several candidate mechanisms that may help explain the pain relieving effects of oxytocin. For example, higher levels of plasma oxytocin have been associated with less severity of reported depressive symptoms.^{18,19} Compared to placebo, oxytocin infusion into healthy men resulted in increased calmness, reduced anxiety, and increased feelings of wellness that were corroborated by a concomitant suppression of salivary free cortisol.²⁰

Given the paucity of published research related to oxytocin and pain to date, the current study examined the effects of intranasally-administered oxytocin and placebo on pain sensitivity and pain-relevant mood states as part of a randomized, double-blind, crossover design in humans. Furthermore, this study also included tests of endogenous pain inhibition using a conditioned pain modulation (CPM) model. The inclusion of dynamic models of endogenous pain modulation, along with unidimensional measures of pain sensitivity such as pain threshold and pain tolerance, may be necessary to optimally characterize the effects of oxytocin on pain sensitivity.²¹ It was hypothesized that intranasal oxytocin would be associated with less sensitivity to induced ischemic pain, greater endogenous pain inhibition (CPM), and less negative mood (e.g., anxiety) compared to placebo.

MATERIALS AND METHODS

Overview of Study Design

The current study was a double-blind, placebo-controlled, within-subjects crossover design that incorporated three separate study sessions completed on three consecutive days. All study protocols were approved by the University of Alabama at Birmingham (UAB) Institutional Review Board and carried out in accordance with guidelines for the ethical conduct of research. Study sessions were completed at the Clinical Research Unit within the UAB Center for Clinical and Translational Science. Medical oversight was primarily provided for each session by the study physician (T.J.N.) and the research nurses in the Clinical Research Unit. Participants were compensated a total of \$150 cash (\$50 following each study session) for their involvement in the study. Matriculation through the study is shown as a flow diagram in Figure 1. Following a telephone-based screening session to determine eligibility for the study, eligible participants were scheduled to complete a baseline session that included provision of informed consent and assessment of ischemic pain sensitivity, endogenous pain inhibition, and negative mood states. Pain sensitivity and endogenous pain inhibition were examined using quantitative sensory testing. Participants then received intranasal oxytocin and intranasal placebo during two experimental sessions on consecutive days. Assessments of pain sensitivity, endogenous pain inhibition, and negative mood states were again completed following administration of oxytocin and placebo. As part of the two experimental sessions, state anxiety was also examined pre- and post-administration of intranasal oxytocin and placebo.

Given the within-subjects crossover study design, all participants received both intranasal oxytocin and intranasal placebo. The order of administration was randomized, in counterbalanced fashion, such that 15 participants non-consecutively received placebo followed by oxytocin and the other 15 participants received oxytocin followed by placebo. The randomization schedule was created using non-commercially available software and the allocation ratio of participants to order of administration was 1:1. Only the study co-investigator (M.T.R.) was aware of the randomization schedule prior to completion of the study. The study experimenters and participants were both blinded to the order of administration. To ensure blinding, oxytocin and placebo were contained in identical 5 mL bottles and on the bottom of each bottle was a sticker labeled with either an “A” or a “B”. The bottle labeled “A” was always administered prior to the bottle labeled “B”, and these

labels corresponded to the randomized order of administration for intranasal oxytocin and placebo, respectively. Each participant was assessed by the same study experimenter for all three sessions. Of the study experimenters, two were male, one was female, and all were non-Hispanic White. The sex of the experimenter was not matched to the sex of the participant for this study.

Participants

A total of 35 individuals were screened for study inclusion and were determined to be eligible. However, five of these individuals did not participate in the study for the following reasons: one woman discovered she was pregnant prior to initiating the first study session and was excluded, while four individuals simply did not present for their first scheduled study session. Therefore, the final sample consisted of 30 young, healthy adults recruited from the UAB campus community using posted fliers. Of these 30 participants, each completed the study in its entirety. Participant self-reported criteria for inclusion into the study were as follows: (a) between the ages of 18 and 45 years; (b) no ongoing chronic pain problems; (c) no episodes of acute pain within two weeks prior to study participation; (d) not diagnosed with hypertension or taking medications for blood pressure; (e) no circulatory disorders; (f) no history of cardiac events; (g) no history of metabolic disease or neuropathy; (h) not currently using prescription medications including analgesics, tranquilizers, antidepressants, or other centrally acting agents; (i) no diagnosed mental health disorders; (j) not pregnant; (k) no liver or kidney disease; and (l) no disorders involving the neuroendocrine system. None of the participants reported use of alcohol, opioid pain medications, or non-steroidal anti-inflammatory drugs within the previous 24 hours of all study sessions. In order to rule out possible interactions of intranasal oxytocin with fluctuations of gonadal steroids over the menstrual cycle, all sessions for women were conducted during the follicular phase as assessed by self-report of last menses.

Procedures

Baseline session—To begin the baseline session, participants had their height and weight measured for determination of BMI. Female participants completed a urine pregnancy test to confirm pregnancy status; all tests were negative. Resting blood pressure was assessed three consecutive times to ensure that none of the participants were hypertensive. Participants were then subjected to the ischemic pain task (IPT) to assess baseline pain sensitivity, which included ratings of pain intensity and unpleasantness as well as pain tolerance. Following a five minute rest period, participants completed three consecutive hand immersions into a refrigerated water bath using a cold pressor task with decreasing temperatures of 12°C, 8°C, and 5°C. This was done to individually tailor temperatures of the cold water for use as a moderately painful conditioning stimulus in the assessment of endogenous pain inhibition via conditioned pain modulation (CPM). The CPM procedure was then completed following an additional five minute rest period. Lastly, negative mood states were assessed at the end of the baseline session.

Experimental sessions—There were two experimental sessions that occurred on consecutive days following the baseline session. Prior to presenting for the first of these two sessions, participants were randomly assigned to receive intranasal oxytocin and intranasal

placebo in counterbalanced fashion. Each participant received both oxytocin and placebo across the two experimental sessions, thereby acting as his or her own control. Upon arrival for each experimental session, participants reported their level of state anxiety using the State-Trait Anxiety Inventory (STAI). They then self-administered the intranasal oxytocin and intranasal placebo under the supervision of a study experimenter. Following a 30 minute rest period, participants again reported their level of state anxiety. Additional assessments of ischemic pain sensitivity and CPM using the tailored cold water stimuli were then completed consistent with the baseline session. At the end of each experimental session, reports of negative mood states were again collected. Upon study completion, participants were asked whether they noticed any differences between the two experimental sessions due to administration of oxytocin and placebo, and if so, to report the differences. They were also asked to report during which experimental session they believed intranasal oxytocin was received.

Intranasal oxytocin and placebo administration—Participants received a single intranasal dose of 40 IU active oxytocin nonapeptide dissolved in a 1mL aqueous solution of glycerol and purified water. The 40 IU of oxytocin represents a safe dose that is commonly incorporated for short-term use in humans, and intranasal administration has been shown to be an effective method of delivering oxytocin into the central nervous system.²² The nasal spray pump was primed and then a total of 10 puffs of oxytocin was administered (5 puffs per nostril), such that each puff delivered 4 IU of oxytocin. One puff was delivered to each nostril in one minute increments; thus, the total time for administration was five minutes. This method of administration was chosen to maximize absorption and prevent the spray from dripping down the posterior pharynx to be swallowed.²³ In addition to oxytocin, the spray contained the following preservatives and buffering agents: propyl parahydroxybenzoate, methyl parahydroxybenzoate, chlorobutanol hemihydrate, citric acid, sodium chloride, and sorbitol. Similarly, participants also received a 1mL dose of intranasal placebo that contained all of the same ingredients except the oxytocin. The intranasal placebo was administered in the same fashion as the oxytocin. The 30 minute duration between administration of the spray and initiation of pain sensitivity testing was chosen because prior research has shown this timeframe to be sufficient for oxytocin to reach peak concentrations in humans.²⁴ Both the intranasal oxytocin and placebo sprays were manufactured by a fully licensed pharmaceutical wholesaler in Switzerland that was approved by Swiss Health Authorities (Victoria Apotheke, Zurich, Switzerland, www.pharmaworld.com). An investigational new drug exempt status was obtained by the U.S. Food and Drug Administration for this study.

Quantitative sensory testing

Cold pressor task—To tailor the cold water conditioning stimulus for use in the CPM protocol, participants immersed their non-dominant hand up to the wrist three consecutive times in the cold water maintained at 12°C, 8°C, and 5°C. The water temperatures were maintained ($\pm .05^\circ\text{C}$) by a refrigeration unit (Neslab, Portsmouth, NH), and water was constantly circulated to prevent local warming around the submerged hand.²⁵ Ratings of pain intensity and unpleasantness were obtained at 30 seconds and 60 seconds. For each participant, the cold water temperature that produced a moderately intense pain rating of ~50

(range: 40–60) on the 0–100 numeric rating scale²⁶ was selected. On this numeric rating scale, 0 = “no pain” and 100 = “the most intense pain imaginable” or the “most unpleasant pain imaginable”. The maximum duration of each hand immersion was 60 seconds and there was a five minute rest period between each immersion. Following the tailoring procedure, the cold pressor task was subsequently used to deliver the moderately painful conditioning stimulus for the purpose of CPM assessment.

Ischemic pain task—The IPT consisted of a modified submaximal effort tourniquet procedure that involved exercising the hand as blood flow to the arm was occluded, evoking ischemic pain.²⁷ According to standard IPT procedure, maximum grip strength of the dominant hand was determined using a Lafayette hand-held dynamometer (Lafayette Instrument Co., Lafayette, IN). Participants elevated the dominant arm above heart level for 30 s to drain blood from the arm. The arm was then occluded with a standard blood pressure cuff positioned proximal to the elbow and inflated to 240 mmHg using a Hokanson E20 rapid cuff inflator (D.E. Hokanson, Inc., Bellevue, WA). Participants performed 20 handgrip exercises of 2 second duration with 4 second rest intervals at 50% of their maximum grip strength. Pain ratings were collected at 30 second intervals by asking participants for verbal self-reports on the 0–100 numeric rating scales. Overall pain intensity and pain unpleasantness were calculated by averaging the respective ratings across the IPT. The duration of exposure was recorded and classified as pain tolerance, whether the participant completed the entire task or terminated the IPT prior to the allotted maximum time of exposure of 900 seconds. Participants were instructed to say “stop” at any time if they felt that the pain had become intolerable. The 900 second duration for IPT is common and consistent with previous research.²⁸

CPM trials—Dysfunction of endogenous inhibition of pain is often assessed in humans using a “pain-inhibition-by-pain” model where pain in a local area (test stimulus) is inhibited by a second pain (conditioning stimulus).²⁹ The term “conditioned pain modulation” (CPM) is used to refer to this inhibitory phenomenon rather than the more traditionally termed “diffuse noxious inhibitory controls” because the exact mechanism in humans is not established.³⁰ For this study, CPM was tested on the dominant dorsal forearm and ipsilateral masseter muscle using algometry (test stimulus) and the cold pressor task (conditioning stimulus). A handheld algometer (Somedic AB, Horby, Sweden) was alternately applied three times at each anatomical location, in counter-balanced fashion, to determine participants’ initial (or test) pressure pain thresholds (PPTs).³¹ Participants indicated when the increasing pressure stimulation first became painful. PPTs were measured in kilopascals (kPa). Following test PPT determination, participants underwent a series of four cold water immersions that consisted of placing the non-dominant hand, up to the wrist, into the circulating cold water for 1 minute. The cold water was maintained at the tailored temperature that produced a moderately painful sensation as determined during the baseline session. Participants were told they could remove their hand from the water at any time; however, none of the participants prematurely removed their hand prior to the allotted 1 minute for any of the four cold water immersions. Approximately 30 seconds after initiation of each cold water immersion, while the hand was still immersed, the algometer was used to deliver noxious mechanical stimulation to either the dorsal forearm (two CPM

trials) or the masseter muscle (two CPM trials); the site order was randomized. Participants again indicated when the increasing pressure stimulation first became painful, which represented their conditioned PPTs. There was a 2 minute rest period between each CPM trial. For the analysis of CPM, we followed recent recommendations for presenting results and calculation of CPM using the percent change.³⁰ Percent change for PPTs within each session was calculated according to the following formula:

$$[(\text{conditioned PPT} - \text{test PPT}) / \text{test PPT}] * 100.$$

Mood State Questionnaires

Profile of Mood States (POMS) – Brief Version for Adults—The POMS brief version for adults is a self-report questionnaire that allows for the quick assessment of transient, fluctuating mood states and also enduring mood.^{32,33} In the current study, emphasis was placed on transient, fluctuating mood; thus, participants were asked to complete the questionnaire according to their experienced mood states “right now.” The brief version of the POMS consists of 35 items grouped into seven subscales that include: anger-hostility, confusion-bewilderment, depression-dejection, fatigue-inertia, tension-anxiety, vigor-activity, and friendliness. Each item (e.g., “tense”, “lively”, “sad”) is evaluated on a 5-point scale (0-4), such that 0 = “Not at all” and 4 = “Extremely.” In this study a negative mood state composite score was created by summing participants’ responses to the anger-hostility, confusion-bewilderment, depression-dejection, fatigue-inertia, and tension-anxiety subscales. Scores on this negative mood state composite ranged from 0 to 20, with higher scores indicative of greater negative mood. The POMS is a commonly used measure in health outcomes research and has exceptional psychometric properties including reliability and validity.³²

State-Trait Anxiety Inventory (STAI)—The STAI is a self-report measure of anxiety comprised of 40 items that can be grouped into two subscales assessing temporary, state anxiety levels (20 items) versus long-standing, trait anxiety levels (20 items) in adults.³⁴ In this study, only the 20 item measure of the state anxiety subscale was administered to participants. The state anxiety subscale of the STAI asks respondents to indicate “how you feel right now, that is, at this moment” when answering each item (e.g., “I am worried”). Items are rated on a 4-point scale (1-4), whereby 1 = “Not at all” and 4 = “Very much so”. The total scores on the state anxiety subscale of the STAI range from 20 to 80, with higher scores indicating greater anxiety levels. The STAI has well well-documented validity and reliability and has been widely utilized in research and clinical care.³⁵

Data Analysis

A series of repeated measures analyses of variance (RM-ANOVA) with Greenhouse-Geisser corrections were carried out to examine differences in ischemic pain sensitivity and CPM across the three study sessions. In particular, ischemic pain sensitivity included duration of exposure (i.e., pain tolerance) and ratings of pain intensity as well as pain unpleasantness, while CPM included the masseter and forearm testing sites. Before assessing differences in CPM by body site across the three study sessions, paired t tests analyzing the changes

between test PPTs and conditioned PPTs were completed to verify the presence of significant CPM within each session. Additional RM-ANOVAs were completed to examine differences in negative mood across the three study sessions as well as differences in anxiety from pre- to post-administration of oxytocin and placebo. All study analyses were initially completed without consideration of participants' sex and order of administration, and then again to determine whether including these two factors significantly influenced the results.

Statistical adjustments for multiple comparisons and inflated family-wise error rates were employed. To accomplish this, we first categorized our dependent variables into separate "families" that included: (1) ischemic pain tolerance, pain intensity and pain unpleasantness ratings, (2) CPM at the masseter, (3) CPM at the forearm, (4) negative mood, and (5) anxiety. We then performed a Holm-Bonferroni procedure to obtain corrected P values.³⁶ Analyses include the squared partial eta (η_p^2) as a measure of effect size where appropriate. Following the conventions of Cohen,³⁷ $\eta_p^2 = 0.01$ is considered a small effect, partial $\eta_p^2 = 0.06$ a medium-sized effect, and $\eta_p^2 = 0.14$ a large effect. There was no missing data for any of the study variables. All analyses were carried out using SPSS, version 21.

RESULTS

Characteristics of the study sample

Characteristics of the 30 healthy, young adults who comprised this study sample are presented in Table 1. The mean age was 22.7 (SD = 3.98) years and the mean body mass index was 25.31 (SD = 5.42). The resting blood pressure for all participants fell within the normotensive to pre-hypertensive ranges. The sample consisted of an equal number of men and women. The majority of participants reported their ethnic background as Caucasian (60%). None of the participants reported a history of chronic pain, nor did they endorse any experiences of acute pain within the two weeks preceding participation. Likewise, none of the participants reported actively taking any prescribed or over-the-counter medications for pain. Of the female participants, only two of fifteen (13%) reported taking oral birth control medications. All participants had either obtained a college degree or were in the process of working toward a degree.

Intranasal oxytocin and ischemic pain sensitivity

As seen in Table 2, results demonstrated that ischemic pain tolerance did not significantly differ across the three study sessions ($F = 1.78$, $p = .18$; $\eta_p^2 = .06$). Given this non-significant finding, pain tolerance was not statistically controlled in the analyses examining ischemic pain ratings. Ratings of ischemic pain intensity also did not significantly differ across the three study sessions ($F = 2.36$, $p = .13$; $\eta_p^2 = .08$). However, ratings of pain unpleasantness did significantly differ across the three study sessions ($F = 4.12$, $p = .03$; $\eta_p^2 = .14$), such that when compared to baseline, ischemic pain unpleasantness ratings were reduced following administration of oxytocin ($F = 5.19$, $p = .03$; $\eta_p^2 = .17$) and placebo ($F = 4.56$, $p = .04$; $\eta_p^2 = .15$). These reductions did not remain significant after applying the Holm-Bonferroni correction for multiple comparisons. Furthermore, pain unpleasantness ratings did not significantly differ between the oxytocin and placebo sessions ($F = 0.40$, $p = .$

84; $\eta_p^2 = .002$). None of the findings related to ischemic pain sensitivity were altered by the inclusion of participants' sex and order of administration.

CPM

Pairwise *t* tests revealed significant CPM effects on PPT assessed at the masseter during the baseline ($t = 5.60$, $p < .001$), placebo ($t = 6.69$, $p < .001$), and oxytocin ($t = 8.18$, $p < .001$) sessions, such that conditioned PPTs obtained during concurrent application of cold water pain were significantly greater than the test PPTs. Additional pairwise *t* tests also revealed significant CPM effects on PPT assessed at the forearm during the baseline ($t = 4.73$, $p < .001$), placebo ($t = 4.75$, $p < .001$), and oxytocin ($t = 5.15$, $p < .001$) sessions. After Holm-Bonferroni adjustment and inclusion of participants' sex as well as order of administration, all CPM effects remained statistically significant. Means and standard deviations for CPM effects at the masseter and forearm are presented in Table 3.

Of the three potential tailored cold water intensities for the conditioning pain stimulus (i.e., 12°C, 8°C, and 5°C), the percentages of individuals who completed the CPM procedures using each of the respective temperatures was as follows: 70% at 12°C, 7% at 8°C, and 23% at 5°C. CPM at the masseter did not significantly differ as a function of the different temperatures used to individually tailor the cold water conditioning stimulus to a moderate level of pain ($F = 0.59$, $p = .75$), and neither did CPM at the forearm ($F = 0.15$, $p = .98$). This suggests that any differences in CPM effects across the baseline, placebo, and oxytocin sessions are likely to be independent of the intensity of the tailored cold water conditioning stimulus used to assess CPM.

Intranasal oxytocin and CPM

The magnitude of CPM effects at the masseter was found to be significantly different across the three study sessions ($F = 4.55$, $p = .023$; $\eta_p^2 = .15$). As shown in Figure 2A, this is because the CPM effect following administration of intranasal oxytocin was significantly greater than the CPM effects following administration of placebo ($F = 4.01$, $p = .049$; $\eta_p^2 = .13$) and at baseline ($F = 5.98$, $p = .022$; $\eta_p^2 = .19$). These results remained significant even after applying the Holm-Bonferroni correction. The CPM effect following administration of placebo was not significantly different than baseline ($F = 1.91$, $p = .18$; $\eta_p^2 = .06$). The findings did not change after including participants' sex and order of administration into the analysis. Regarding CPM effects at the forearm, significant differences were also found to be present across the three study sessions ($F = 3.84$, $p = .029$; $\eta_p^2 = .13$). Specifically, CPM effects following administration of oxytocin ($F = 4.96$, $p = .035$; $\eta_p^2 = .16$) and placebo ($F = 6.86$, $p = .014$; $\eta_p^2 = .21$) were each significantly greater than baseline (Figure 2B). Importantly, CPM effects were not significantly different when compared between oxytocin and placebo administrations ($F = 0.10$, $p = .96$; $\eta_p^2 = .01$). The findings did not change after including participants' sex and order of administration into the analysis, and they remained significant after applying the Holm-Bonferroni correction.

Intranasal oxytocin and negative mood states

Reports of negative mood were found to be significantly different across the three sessions ($F = 4.79$, $p = .01$; $\eta_p^2 = .16$; Table 4). As demonstrated in Figure 3, negative mood was

significantly lower following administration of oxytocin compared to placebo ($F = 8.70$, $p < .01$; $\eta_p^2 = .25$) but not baseline ($F = 3.29$, $p = .08$; $\eta_p^2 = .11$). Pre-administration reports of anxiety were not significantly different between the oxytocin and placebo sessions, ($F = 2.91$, $p = .10$; $\eta_p^2 = .09$). Results showed a significant decrease in anxiety from pre- to post-administration of oxytocin ($F = 9.16$, $p < .01$; $\eta_p^2 = .26$); however, anxiety did not significantly decrease from pre- to post-administration of placebo ($F = 3.79$, $p = .08$; $\eta_p^2 = .13$; Table 5). Post-administration reports of anxiety were significantly lower following the oxytocin session compared to the placebo session ($F = 4.29$, $p = .047$; $\eta_p^2 = .13$). The decrease in anxiety following oxytocin administration is presented in Figure 4. The difference in negative mood following administration of oxytocin compared to placebo, as well as the decrease in anxiety from pre- to post-administration of oxytocin, remained significant after applying the Holm-Bonferroni adjustment. These results did not significantly change after including participants' sex and order of administration.

Intranasal oxytocin side-effect profile

There were no adverse events in this study and no participant reported noteworthy negative side-effects from the intranasal administration of oxytocin or placebo. Commonly reported experiential differences between the oxytocin and placebo sessions included: smell/taste, feelings of warmth and calm, becoming flush, and ability to cope with the painful experiences. Although 73% of the sample reported noticing a difference between administration of oxytocin versus placebo, participants were not any better than chance at being able to accurately choose the study session in which oxytocin was administered ($\chi^2 = 2.16$, $p = .15$).

DISCUSSION

Several findings emerged from this double-blind, placebo-controlled, within-subjects crossover study that support our hypotheses and merit elaboration. First, the administration of a single dose of intranasal oxytocin was associated with a significant increase in CPM at the masseter and the forearm when compared to their respective baselines. When compared to placebo, intranasal oxytocin was only associated with a significant increase in CPM at the masseter, not the forearm. To date, this is the first study to suggest that intranasally-administered oxytocin may augment endogenous pain inhibitory capacity, albeit in a somewhat body site specific manner. There are two plausible pathways involving the delivery of intranasal oxytocin to the central nervous system that may help explain these findings. In addition to directly crossing the blood-brain barrier via olfactory bulb pathways,^{38,39} intranasal oxytocin can also be taken up by the trigeminal nerve to various brainstem structures.⁴⁰ Along this line, it has been suggested that, after crossing the blood-brain barrier, oxytocin binds to opioid receptors and may stimulate endogenous opioid release in the brain.⁴¹ Pain inhibitory processes, as modeled by CPM, are thought to be mediated by endogenous opioids.⁴²⁻⁴⁴ Therefore, it is possible that the intranasal administration of oxytocin enhances CPM via central effects on endogenous opioids. Further indirect support for this notion comes from previous research which has revealed that the pain alleviating effects of oxytocin can be blocked by the administration of μ - and κ -opioid antagonists.^{45,46} That CPM was significantly enhanced following intranasal oxytocin administration at the

masseter but not the forearm may be due to the fact that, unlike the muscles of the forearm, the masseter muscle is directly innervated by the mandibular branch of the trigeminal nerve.^{47,48} Oxytocin sprayed into the nose gets taken up by nerve terminals there, transported back to the trigeminal ganglia, and then becomes distributed throughout the entire trigeminal system where it accesses oxytocin receptors and decreases pain-evoked neural activity.⁴⁹ It has been suggested that this trigeminal pathway may be responsible, at least in part, for the headache alleviating effects of intranasal oxytocin among individuals with chronic migraine.^{50,51} Taken together, stimulation of endogenous opioids and trigeminal system activity may synergistically interact to enhance CPM effects, particularly when CPM is assessed at the masseter. Additional research is needed, however, to directly test the mechanistic pathways that may underlie the CPM enhancing effects of intranasal oxytocin.

A second finding revealed by this study was that intranasal oxytocin was significantly associated with reductions of self-reported negative mood and anxiety above and beyond placebo. These findings are particularly compelling when it is considered that the anxiolytic and negative mood reducing effects of oxytocin are not often observed in studies incorporating self-report measures of mood states.^{52,53} Rather it has been suggested that oxytocin mitigates negative mood states and stress by augmenting the effects of positive social interactions.⁵⁴ Therefore, it is often expected that the effects of oxytocin on negative mood will not be observed in the absence of positive social interaction. However, the results of this study offer tentative support that intranasal oxytocin may directly improve mood states irrespective of positive social interactions.

An increasing number of investigations into the effects of oxytocin on mood began following an animal study demonstrating that when rats were treated with oxytocin, they showed a decrease in plasma corticosterone levels as well as a decrease in anxiety behavior in response to stress when compared to treatment with placebo.⁵⁵ Along this line, in a placebo-controlled, double-blind study of healthy men, oxytocin infusion resulted in increased subjective reporting of calmness, reduced anxiety, and increased feelings of wellness there were corroborated by a concomitant suppression of salivary free cortisol.²⁰ Clinical studies addressing the association of oxytocin and mood factors have reported that patients with major depression possess significantly reduced levels of plasma oxytocin;¹⁸ and in turn, low levels of plasma oxytocin have been shown to predict greater severity of reported depressive symptoms.¹⁹ Additional evidence from human studies relating oxytocin to mood comes from research on relaxation techniques such as hypnosis and meditation, which have been shown to produce feelings of psychological well-being that are mediated by oxytocin.⁵⁶ Taken together, the findings relating oxytocin to mood states have important implications for pain in humans because mood states have been shown to predict pain sensitivity and chronic pain outcomes.⁵⁷ It may be that oxytocin exerts positive influences on mood and feelings of psychological well-being that, in turn, predict decreased pain sensitivity and increased ability for adjustment to chronic pain. Additional research is needed to address this topic.

The third and last finding revealed from this study was that intranasal oxytocin was not significantly associated with decreased ischemic pain sensitivity (i.e., pain tolerance, ratings of pain intensity and pain unpleasantness) when compared to placebo. This finding does not

support our hypothesis and is inconsistent with prior studies that have reported the exogenous administration of oxytocin is associated with decreased unidimensional measures of pain sensitivity such as threshold and tolerance.^{15,16} Unlike these prior studies that examined oxytocin and pain sensitivity using either balloon distention¹⁵ or cold water¹⁶, our study was the first to incorporate the ischemic pain task. One possible explanation for the lack of association between intranasal oxytocin and ischemic pain sensitivity may be that the ischemic pain task is not sensitive enough to detect changes in pain sensitivity associated with intranasal oxytocin. Indeed, the ischemic pain task has previously been found to have limited utility when assessing the effects of opioid analgesics on pain sensitivity.⁵⁸ When examining the mechanistic underpinnings of oxytocin effects on pain sensitivity in the future, it will likely be important for studies to include a combination of unidimensional measures and dynamic tests of endogenous pain modulation..

Two additional reasons for why intranasal oxytocin was found to be related to CPM at the masseter and mood states, but not ischemic pain sensitivity assessed at the forearm include: 1) lack of a fully developed empirical understanding regarding optimal dosing, and 2) individual differences in absorption of oxytocin through the nasal cavity. The 40 IU dose used in this study was chosen because it has been suggested that the short-term use of oxytocin delivered in doses between 18 and 40 IU is not associated with adverse side-effects.²² Although there were indeed no adverse side-effects reported, it may be that the 40 IU dose was not fully optimized for testing the associations between oxytocin and pain sensitivity. The upper limit for safe and effective dosing of intranasal oxytocin remains unclear. Future research addressing the effects of exogenously administered oxytocin on pain would benefit from a dose-response approach to assist with determination of the best dosing strategy. Furthermore, a substantial amount of research demonstrates that nasal anatomy influences absorption following nasal spray administration.⁵⁹ Size and volume of nasal cavities are highly variable across individuals and are likely related to differences in surface area that affect net oxytocin absorption.⁵⁹ It has been reported that small variations in nasal cavities and airways can significantly impact absorption of peptides inhaled through the nose.⁶⁰ In turn, differential oxytocin absorption rates could have implications for responses to pain sensitivity tests.

Some important limitations of this study merit caution when interpreting the findings and will need to be addressed in future research. First, participants were healthy young adults free of pain, and whether these findings extend to clinical pain populations and older adults needs further examination. Older adults have more pain-related chronic conditions than younger adults,⁶¹ and also demonstrate decreased capacity for endogenous pain inhibition (i.e., CPM).⁶² Replication of the current study's findings in older adults with and without chronic pain will be quite pertinent. Second, the clinical relevance of the results obtained from this study remains unclear. Intranasal oxytocin was found to be associated with enhanced endogenous pain inhibition and reduced negative mood states, factors that have all previously been reported as important for the experience of clinical pain. However, it remains to be tested whether oxytocin related changes in endogenous pain inhibition and mood states directly translates into improved clinical pain outcomes. Third, it was not feasible for the sex of the experimenters to be matched to the sex of the participants. A scant amount of previous literature has shown that pain responses to QST may differ according to

whether experimenter sex and participant sex is matched versus mismatched.⁶³ Fourth, although the conditioning stimulus for the assessment of CPM was tailored to each individual using either at 12°C, 8°C, and 5°C cold water, this study did not incorporate non-painful conditioning stimulus intensities. It has previously been reported that CPM effects can be elicited using non-painful conditioning stimuli.⁶⁴ The lack of a non-painful conditioning stimulus in the current study may have limited our ability to fully appreciate the influence of oxytocin on CPM. Lastly, a noteworthy limitation is that this study did not assess whether the administration of a 40 IU dose of intranasal oxytocin indeed resulted in increased oxytocin concentrations, either centrally or peripherally. The intranasal spray presumably increases oxytocin concentrations centrally. Detection of such an increase would require a technique such as lumbar puncture and assessment of cerebrospinal fluid for confirmation. Lumbar puncture can be risky and may not be practical to complete multiple times as part of a placebo-controlled, within-subjects crossover study design. Alternatively, a less risky and more common means of assessing oxytocin concentrations is peripherally via blood draw. The challenge is that, although peripheral and central release of endogenous oxytocin appears to be coordinated,⁶⁵ it remains to be determined whether peripheral concentrations in blood accurately reflect central concentrations following the exogenous administration of intranasal oxytocin.

In conclusion, with increased understanding of the neurobiology and pathophysiology of pain, new drug targets have been emerging, which may lead to novel therapeutic strategies. Currently, a number of potential targets including cannabinoids,⁶⁶ neurotrophic factors,⁶⁷ and calcium channel blockers⁶⁸ are being studied to determine whether they hold promise for future treatment of neuropathic and chronic pain conditions. One potentially important target to consider is the nonapeptide, oxytocin, which is uniquely multifunctional as it acts as both a neurotransmitter and a paracrine hormone to regulate multiple somatosensory functions. Oxytocin has recently been recognized for its role in the experience of pain. Along this line, our data tentatively suggest that the administration of intranasal oxytocin may augment endogenous pain inhibitory capacity (i.e., CPM) and reduce negative mood states including anxiety. This is potentially important because it has previously been suggested that treatments that improve clinical pain outcomes may do so by enhancing endogenous pain inhibitory capacity⁶⁹ as well as improving mood.⁷⁰ Taken together, this study provides initial support for the potential of oxytocin to act upon mechanisms believed to be implicated in the development and treatment of a variety of painful conditions.

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Figure 1.

This flow diagram depicts the overall protocol. CPT = cold pressor task, CPM = conditioned pain modulation

Figure 2.
Intranasal oxytocin and CPM at the masseter (A) and at the forearm (B); * = $p < .05$

Figure 3.
Intranasal oxytocin and negative mood states; ** = $p < .01$

Figure 4.
Intranasal oxytocin and anxiety states; ** = $p < .01$

Table 1

Characteristics of the participants in the study sample.

Characteristic	
Age (mean $\pm$ SD)	22.70 $\pm$ 3.98
BMI (mean $\pm$ SD)	25.31 $\pm$ 5.43
Resting BP (mean $\pm$ SD)	
Systolic	125.67 $\pm$ 13.66
Diastolic	76.97 $\pm$ 9.50
Sex (n, %)	
Men	15 (50)
Women	15 (50)
Ethnic background (n, %)	
Caucasian	18 (60)
African American	6 (20)
Asian/Pacific Islander	4 (13)
Hispanic	2 (7)
Education (n, %)	
College graduate	8 (27)
In college	22 (73)

Note: BMI = body mass index; BP = blood pressure

Table 2

Indicators of ischemic pain sensitivity (tolerance, pain intensity ratings, and pain unpleasantness ratings) during baseline, placebo, and oxytocin sessions.

	Baseline	Placebo	Oxytocin
Variables	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Pain Tolerance	461.77 $\pm$ 229.16	513.70 $\pm$ 239.84	505.30 $\pm$ 212.51
Pain Intensity	49.31 $\pm$ 21.58	44.94 $\pm$ 23.18	44.69 $\pm$ 22.78
Pain Unpleasantness *	53.60 $\pm$ 22.17	46.90 $\pm$ 23.37	47.48 $\pm$ 24.30

Note: Pain tolerance measured as seconds of exposure to ischemic pain task. Pain intensity and pain unpleasantness rated using 0-100 numeric rating scales.

* = Baseline > Placebo and Oxytocin

Table 3

Assessment of test and conditioned pressure pain thresholds (PPT) during concurrent cold water immersion to determine the magnitude of endogenous pain inhibition (CPM) at the masseter and forearm during baseline, placebo, and oxytocin sessions.

	Baseline	Placebo	Oxytocin
Variables	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Masseter			
Test PPT	209.97 $\pm$ 70.23	200.92 $\pm$ 65.38	212.09 $\pm$ 82.93
Conditioned PPT [*]	250.97 $\pm$ 95.73	255.00 $\pm$ 91.83	279.20 $\pm$ 112.48
CPM (% change) ^{**}	19.27 $\pm$ 18.03	25.91 $\pm$ 17.97	32.69 $\pm$ 20.15
Forearm			
Test PPT [#]	310.76 $\pm$ 109.68	277.92 $\pm$ 102.77	288.57 $\pm$ 108.19
Conditioned PPT	360.86 $\pm$ 152.23	352.22 $\pm$ 152.05	364.30 $\pm$ 158.51
CPM (% change) ^{##}	14.57 $\pm$ 17.28	26.46 $\pm$ 26.51	26.28 $\pm$ 24.39

Note: All pressure pain threshold (PPT) scores are presented as kilopascals (kPa). The magnitude of conditioned pain modulation (CPM) represents the percent change [(conditioned PPT – test PPT) / test PPT] *100] at each site.

^{*} = Oxytocin > Placebo and Baseline.

^{**} = Oxytocin > Placebo and Baseline.

[#] = Placebo < Baseline.

^{##} = Placebo < Baseline and Placebo.

Table 4

Mean differences in negative mood state (POMS) reported after experimental pain testing for baseline, placebo, and oxytocin sessions.

	Baseline	Placebo	Oxytocin
Variable	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Negative mood state (POMS) [*]	6.20 $\pm$ 5.30	7.47 $\pm$ 6.88	4.96 $\pm$ 4.54

^{*} = Oxytocin < Placebo

Table 5

Mean differences in state anxiety (STAI) reported pre- and post-administration of placebo and oxytocin

Variable	Placebo		Oxytocin	
	Pre-administration	Post-administration	Pre-administration	Post-administration
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
State anxiety (STAI)*	32.46 $\pm$ 9.47	30.99 $\pm$ 7.92	30.56 $\pm$ 7.56	28.53 $\pm$ 6.02

* = Significant decrease in state anxiety following oxytocin administration only.