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Plasma oxytocin concentrations following MDMA or intranasal oxytocin in humans

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Abstract

MDMA (±3,4-methylenedioxymethamphetamine, 'ecstasy') is reportedly used recreationally because it increases feelings of sociability and interpersonal closeness. Prior work suggests that the pro-social effects of MDMA may be mediated by release of oxytocin. A direct examination of plasma levels of oxytocin after acute doses of oxytocin and MDMA, in the same individuals, would provide further evidence for the idea that MDMA produces its prosocial effects by increasing oxytocin. Fourteen healthy MDMA users participated in a 4-session, double-blind study in which they received oral MDMA (0.75 and 1.5 mg/kg), intranasal oxytocin (20 IU or 40 IU), and placebo. Plasma oxytocin concentrations, as well as cardiovascular and subjective effects were assessed before and at several time points after drug administration. MDMA (1.5 mg/kg only) increased plasma oxytocin levels to a mean peak of 83.7 pg/ml at approximately 90–120 minutes, compared to 18.6 pg/ml after placebo. Intranasal oxytocin (40 IU, but not 20 IU) increased plasma oxytocin levels to 48.0 pg/ml, 30–60 min after nasal spray administration. MDMA dose-dependently increased heart rate, blood pressure, feelings of euphoria (e.g., 'High' and 'Like Drug'), and feelings of sociability, whereas oxytocin had no cardiovascular or subjective effects. The subjective and cardiovascular responses to MDMA were not related to plasma oxytocin levels, although the N was small for this analysis. Future studies examining the effects of oxytocin antagonists on responses to MDMA will help to determine the mechanism by which MDMA produces pro-social effects.

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Keywords

MDMA; oxytocin; mood; plasma; pharmacokinetics; humans

INTRODUCTION

The recreational drug ±3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”) is typically used in social settings and produces feelings of sociability and interpersonal closeness (Bravo, 2001; Kelly et al., 2006; Rodgers et al., 2006; Sumnall et al., 2006). In controlled studies, acute doses of MDMA increase self-reports of euphoria, friendliness and closeness to others (Harris et al., 2002; Tancer and Johanson, 2003; Bedi et al., 2010; Hysek and Liechti, 2012; Kirkpatrick et al., 2012). MDMA also improves recognition of positive mental states, such as friendliness in others (Hysek et al., 2012a), while impairing recognition of negative states such as expressions of anger or fear (Bedi et al., 2010; Hysek et al., 2012a). Thus, MDMA may facilitate social behavior both by producing positive and pro-social subjective states, and by modulating sensitivity to positive and negative emotions in others. While it is known that MDMA is a potent releaser of the monoamine neurotransmitters: dopamine (DA), serotonin (5HT), and norepinephrine (NE) (Rothman et al., 2001; Han and Gu, 2006; Verrico et al., 2007), there is also evidence that it produces its social effects by releasing oxytocin (OT).

OT is a peptide important in mammalian social bonding (Bos et al., 2012). In humans, MDMA increases OT levels in blood plasma (Dumont et al., 2009; Hysek et al., 2012a; Hysek et al., 2013), which are correlated with increased subjective feelings of sociability (Dumont et al., 2009). In rats, MDMA increases the release of OT via 5HT1A receptors in the brain (Thompson et al., 2007), and both exogenous OT and MDMA increase “adjacent lying”, thought to be indicative of prosocial behavior (Ramos et al., 2013). In humans, other serotonergic drugs, such as *d*-fenfluramine also increase OT (Lee et al., 2003), and intranasal OT (IN-OT; 18–40 IU) produces psychological effects that are consistent with pro-social, anxiolytic and affiliative effects (Kosfeld et al., 2005; Lim and Young, 2006; Domes et al., 2007a, b; Zak et al., 2007; Di Simplicio et al., 2009; Bos et al., 2012; Shahrestani et al., 2013). Some of these effects, such as enhanced recognition of positive emotions (Marsh et al., 2010) and impaired recognition of negative emotions (Di Simplicio et al., 2009), closely resemble the effects observed with MDMA.

We found some support for the idea that the prosocial effects of MDMA may be mediated by OT in a recent study. Healthy MDMA users (N=65) completed measures of subjective sociability and social and emotional processing after MDMA (0.75 and 1.5 mg/kg) and IN-OT (20 and 40 IU) (Kirkpatrick et al., 2014). Interestingly, although the drugs differed on many measures, both increased feelings of sociability. IN-OT subjective responses were small but positively correlated to MDMA responses on two subjective measures of sociability, suggesting that individuals who were sensitive to MDMA-related subjective effects were similarly sensitive to IN-OT subjective effects. However, it is still unknown if the similarities between the two drugs were partially due to similar effects on endogenous oxytocin release. Several studies report that IN-OT increases plasma OT levels although the

pharmacokinetics of intranasally administered OT are not fully understood (Domes et al., 2010; Gossen et al., 2012; Striepens et al., 2013). Additionally, it is difficult to compare the plasma levels of OT across studies with MDMA and exogenously administered IN-OT because of differences in procedures and assay methods. To our knowledge, there have been no studies in which MDMA and IN-OT were administered in the same subjects, to determine and physiological outcomes such as plasma OT levels and its time course of effects.

Thus, in this study we tested single doses of oral MDMA (0.75 and 1.5 mg/kg) and IN-OT (20 IU and 40 IU) in healthy young adults, using a mixed between- and within-subjects design. We assessed the drugs' effects on plasma OT levels, cardiovascular measures and several self-reported measures of subjective drug effects and feelings of sociability. We hypothesized that 1) both MDMA and IN-OT would dose-dependently increase plasma OT levels; 2) MDMA would dose-dependently enhance self-report measures of sociability and "positive" mood; and 3) MDMA-related increases in feelings of sociability would be positively correlated to increases in plasma OT.

METHODS

Participants

Healthy adults (N=14) who reported having used MDMA 4–40 times in their lifetime were recruited via newspaper, community bulletin board, and online advertisements. Potential participants completed an initial telephone and an in-person psychiatric evaluation and medical examination, including an electrocardiogram and physical examination. Inclusion criteria were: age between 18 and 35, at least a high school education, fluency in English, and BMI between 18 and 30. Candidates were excluded if they smoked more than 10 tobacco cigarettes per day, if they had any significant cardiovascular, neurological, or major psychiatric illness including all Axis I disorders or sinus infection or other condition blocking access to the olfactory epithelium.

Participants provided written informed consent prior to participation. They were told they might receive a stimulant (such as amphetamine or ecstasy), a sedative (such as Valium), a cannabinoid, a hormone (such as OT), or placebo. Participants were instructed to consume their normal amount of caffeine before sessions, but were asked to refrain from tobacco use for 9 hrs, and other drug use for 48 hrs, prior to each session. Women not using hormonal contraceptives were tested only during the follicular phase (days 2–14; White et al., 2002). Participants were debriefed following the study. This study was conducted according to the principles expressed in the Declaration of Helsinki. The study was approved by the Institutional Review Board at the University of Chicago in accordance with the Code of Federal Regulations (Title 45, Part 46) adopted by the National Institutes of Health and the Office for Protection from Research Risks of the US Federal Government.

Design

The study used a within-and-between-subjects, double-dummy design in which participants received two doses of MDMA (0.75 and 1.5 mg/kg), one dose of IN-OT (20 or 40 IU), and

placebo. After an initial orientation session, participants completed four outpatient sessions separated by at least five days as a washout period (Abraham et al, 2009). Dosing order was randomized. On each session participants ingested a capsule (placebo or MDMA) and received a nasal spray (placebo or IN-OT). Eight participants received 20 IU IN-OT and 8 participants received 40 IU. Blood samples were collected before and at several time points for 4 hours after drug administration. Participants' mood states and cardiovascular measures were monitored regularly. Plasma OT levels for a total of two participants in the 20 IU group were univariate outliers and likely occurred because of blood sampling issues resulting in hemolysis. These two participants were not included in the analyses.

Procedure

Sessions were conducted between 0900h and 1330h in order to minimize any diurnal variation in biological measures. Upon arrival participants provided urine and breath samples to confirm abstinence from alcohol (as measured by an Alco-Sensor III Breathalyzer, Intoximeters Inc., St Louis, MO), amphetamine, cocaine and opiates (as measured by urine toxicology: Ontrak TesTstik, Roche Diagnostic Systems Inc., Somerville, NJ), and marijuana (as measured by a saliva test: Oratect, Branan Medical Corp., Irvine, CA), and women were tested for pregnancy. Sessions were rescheduled if the participant tested positive for drugs. An intravenous catheter was inserted into the participant's non-dominant arm for blood sampling. At 0920h, pre-capsule measures of heart rate and blood pressure were obtained, a blood sample was obtained, and participants completed self-report mood and drug effects questionnaires (see below). At 0930h, participants ingested capsules containing either MDMA or placebo, and at 1000h they received an intranasal spray containing either IN-OT or placebo (see below). Physiological and subjective measures were obtained at 1030, 1100, 1130, and 1330h (i.e., 60, 90, 120, and 240 min post capsule administration). During times when no measures were scheduled the participants were allowed to relax and watch movies or read. At 1330 pm, the catheter was removed and the participants were discharged provided that their heart rate and blood pressure had returned to baseline levels.

Physiological measures

Cardiovascular measures—Heart rate and blood pressure were measured at regular intervals throughout the sessions using portable monitors (Life Source, A&D, Tokyo, Japan).

Plasma oxytocin levels—At each time point, the study nurse drew a 10 ml blood sample drawn into a pre-cooled purple top tube containing disodium EDTA. The samples were placed on ice and then were centrifuged in a refrigerated 4°C centrifuge (3000 rpm, for 15 min) at a consistent post-draw interval for all sessions. They were then stored immediately in a −80°C freezer. Prior to assaying, samples were first purified by solid phase extraction (Seltzer et al 2010). One ml of plasma was run through solid phase extraction (Sep-Pak Light C18 cartridges) and eluted with 1ml 80% acetonitrile. Three hundred µl of ethanol was added to ensure that the proteins were all denatured and then the sample was dried and resuspended in Assay Buffer. Samples were then analyzed by enzyme immunoassay (EIA) using the Assay Designs EIA kit (Assay Designs, Inc. Ann Arbor, MI, USA). This kit has

been validated in a range of species and across different biological media including urine (Wismer-Fries et al., 2005; Carter et al., 2007; Gray et al., 2007; Seltzer and Ziegler, 2007; Seltzer et al., 2010; Snowdon et al., 2010; Feldman et al., 2011). The specificity of the antibody used in this assay has been repeatedly validated via high-performance liquid chromatography (HPLC) and results across different species and biological media indicate that the assay antibody binds only to intact OT and does not show cross-reactivity with other peptide hormones (Wismer-Fries et al., 2005; Carter et al., 2007; Seltzer and Ziegler, 2007). This assay should be considered a reliable but conservative measure of OT, since the assay antibody responds primarily to the intact OT molecule and not to OT metabolites (Seltzer and Ziegler, 2007).

Subjective Effects

Participants completed subjective effect questionnaires before and at several time points after capsule and nasal spray administration. They completed a series of visual analog scales (VAS: 0 to 100 mm; ‘not at all’ to ‘extremely’) that consisted of adjectives describing several MDMA-related mood effects (i.e., ‘I feel…’ ‘Anxious,’ ‘Dizzy,’ ‘Elated,’ ‘Restless,’ ‘Sedated,’ ‘Stimulated’) and “prosocial” effects (i.e., ‘I feel…’ ‘Confident,’ ‘Friendly,’ ‘Insightful,’ ‘Loving’, ‘Lonely,’ ‘Playful,’ ‘Sociable’). They also completed the drug-effect questionnaire (DEQ), a visual analogue questionnaire designed to assess the extent to which participants experienced the effects of the drugs: ‘Feel Drug’, ‘Feel High’, ‘Like Drug’, ‘Dislike Drug’, and ‘Want More’ (Fischman and Foltin, 1991; Justice and De Wit, 2000). Each item was presented with a 100-mm line labeled ‘not at all’ at one end and ‘extremely’ at the other end.

Drugs

Drugs were administered in randomized order, under double-blind conditions. Capsules and nasal sprays were prepared by The University of Chicago Hospitals investigational pharmacy. MDMA powder (0.75 and 1.5 mg/kg) was encapsulated in 00 opaque capsules with lactose filler. Placebo capsules contained only lactose. These MDMA doses were selected based on our previous studies indicating that the drug reliably increases positive mood and alters emotional processing at these doses (Bedi et al., 2009, 2010). Intranasal OT (20 and 40 IU) doses were prepared within 24 hours of use. A single dose of Pitocin (OT Injection USB; Monarch Pharmaceuticals; concentration: 10 or 20 IU Pitocin/1 ml) was transferred into two, 1 ml intranasal atomizers (MAD300 by LMA Inc., San Diego, CA). Placebo nasal sprays consisted of Ocean Spray Nasal Solution (Valeant Pharmaceuticals, Bridgewater, NJ). The doses of 20 and 40 IU IN-OT were chosen based on previous studies utilizing intranasally administered OT and the structurally similar neuropeptide, vasopressin (Bos et al., 2012; MacDonald et al., 2011). Nasal sprays were administered by trained personnel in four doses to each nostril over the course of 15 minutes. During the administration, participants sat comfortably in reclined position, with their heads tilted back to maximize absorption.

Data Analysis

Acute drug-related effects—To characterize the acute effects of MDMA, subjective, cardiovascular, and plasma data were analyzed with repeated measures analyses of variance (ANOVAs) with two within-subject factors. The within-subjects factors were Drug Dose (placebo, 0.75 and 1.5 mg/kg MDMA) and Time of assessment. Planned t-tests were conducted to compare mean responses between the doses: 1) placebo versus all active MDMA doses and 2) 0.75 mg/kg versus 1.5 mg/kg MDMA.

Similarly, to characterize the acute effects if IN-OT, subjective, cardiovascular, and plasma data were analyzed with ANOVAs with two within-subject factors and one between-subjects factor. The within-subjects factors were Drug Dose (placebo and active OT) and Time of assessment. The between-subjects factor was OT dose level Group (20, 40 IU). Planned t-tests were conducted to compare mean responses between the doses: 1) placebo and active OT in each OT dose level group and 2) 20 IU group versus 40 IU group.

Correlations between MDMA-related "prosocial" subjective effects and plasma oxytocin—We conducted Pearson's correlational analyses to investigate the relationship between subjective responses to MDMA and MDMA-induced increases in plasma OT. To summarize subjective and physiological effects across the entire session, we calculated area-under-the-curve (AUC) for plasma OT levels and each prosocial subjective item, relative to the participant's pre-drug baseline, using the trapezoidal method (Tallarida and Murray, 1981). Subjective ratings from MDMA sessions were compared to plasma OT levels.

For all analyses and comparisons, *p* values were considered statistically significant at less than 0.05 with Bonferroni adjustments for multiple comparisons.

RESULTS

Sample Characteristics

In total, 14 volunteers (2 Female, 12 Male) completed the study. They were 25.4 ± 3.7 (mean ± SD) years old, had a BMI of 23.5 ± 2.9, and had completed 14.7 ± 1.5 years of formal education. They had used MDMA a mean of 13.5 ± 12.0 times (range 4–40 lifetime); on average their last use of MDMA was 22.1 ± 35.1 months prior to study participation (range 0.25–120 months). Ten participants currently drank caffeinated beverages (1–3 cups/day), seven smoked tobacco (1–20 cigarettes/month), thirteen drank alcohol (2–18 drinks/week), and ten currently smoked marijuana (1–30 days/month). Participants who received 20 or 40 IU IN-OT did not differ on any demographic measure.

Acute Drug-related Effects

Plasma Oxytocin Levels—MDMA (1.5 mg/kg) but not MDMA (0.75 mg/kg) significantly increased plasma OT levels over the course of the session (Figure 1, top left panel; Dose x Time interaction: $F[8, 104] = 13.9$, $p < 0.001$, $\chi^2 = 0.17$). Mean peak plasma concentrations were reached at 90–120 min after capsule ingestion, and all 14 participants showed some increase in OT levels following the larger MDMA dose (Figure 1; bottom left

panel). Plasma OT levels following MDMA (0.75 mg/kg) were slightly increased compared to placebo but this difference did not reach significance (t[13] = 2.96, p = 0.07, d = 0.79).

Relative to placebo, IN-OT (40 IU, but not 20 IU) increased mean plasma OT levels following the nasal spray (t[7] = 3.77, $p < 0.05$, d = 1.33). The increased plasma level was significant 30 min after nasal spray administration (Figure 1, top middle and right panels; t[7] = 5.66, $p < 0.01$, d = 2.00). Individual responses to each active nasal spray are shown in Figure 1 (bottom middle and right panels).

Post hoc t-tests revealed that peak plasma levels were greater following the larger MDMA dose compared to either IN-OT dose (20 IU: t[5] = 4.8; 40 IU: t[7] = 3.3, $p < 0.05$ for both comparisons, d = 3.22 and 1.16, respectively).

Cardiovascular and Subjective Effects—MDMA dose-dependently increased heart rate and blood pressure compared to placebo (Main effect of Dose: F[2, 26] = 17.5–35.2, $p < 0.001$, χ^2 = 0.26–0.36; Table 3), and the larger dose produced a greater cardiovascular response (i.e., heart rate and systolic pressure) compared to the lower dose (t[13] = 3.2–5.7, $p < 0.05$ for both comparisons, d=0.85–1.51). Peak cardiovascular effects occurred between 90 and 120 min.

MDMA produced robust increases on several self-reported ratings of euphoria and feelings of sociability. For example, both MDMA doses increased ratings of ‘Feel Drug,’ ‘Like Drug,’ and ‘Want More’ (Table 1; Figure 2 left panel, Main effect of Dose: F[2, 26] = 20.0–47.7, $p < 0.001$, χ^2 = 0.24–0.30), and this effect was greater with the larger dose compared to the lower dose (t[13] = 3.3–5.8, $p < 0.01$ for all comparisons, d=0.88–1.54). Additionally, both MDMA doses significantly increased ratings of ‘Insightful’ and the larger dose increased ratings of ‘Sociable’ compared to placebo (Figure 2 middle and right panels, Main effect of Dose: F[2, 26] = 7.9–18.6, $p < 0.01$, χ^2 = 0.18–0.26). MDMA also increased ratings of positive mood states such as ‘Elated’ and negative states such as ‘Restless’ (Table 1). The drug’s effects on all subjective ratings peaked 60–120 min after capsule ingestion.

Mean ratings over the course of the entire session for all cardiovascular and self-report measures following IN-OT administration are provided in Table 2. Overall neither dose of IN-OT (20 or 40 IU) produced systematic changes in heart rate, blood pressure, or subjective effects compared to placebo.

Correlations between MDMA-related prosocial subjective effects and plasma oxytocin levels

None of the subjective or cardiovascular responses to MDMA (0.75 or 1.5 mg/kg) were significantly correlated with plasma OT levels (N=14; r = −0.46–0.38; p = 0.100–0.984).

DISCUSSION

The current findings show that single doses of either oral MDMA or IN-OT dose-dependently increased plasma OT levels. Following the larger MDMA dose (i.e., 1.5 mg/kg), plasma OT levels were significantly increased 60 minutes after capsule administration

and remained elevated throughout the session. Interestingly, there was substantial individual variability in both the magnitude and time course of MDMA-induced plasma OT response. However, MDMA-induced plasma OT response was unrelated to drug-related mood response. Intranasal OT (40 IU) produced only a brief elevation in plasma OT, detectable only at 30 and 60 minutes after administration. Thus, both MDMA and IN-OT increased plasma OT levels, as reported previously (Dumont et al., 2009; Domes et al., 2010; Gossen et al., 2012; Hysek et al., 2012a), but the time course and magnitude of the effect were markedly different. Compared to MDMA (1.5 mg/kg), IN-OT (40 IU) produced earlier, smaller in magnitude, transient increases in plasma levels. Overall, these results replicate and extend previous studies by demonstrating the effects of a range of MDMA and IN-OT doses on plasma OT response.

The larger MDMA dose increased plasma OT concentrations, although there was variability in response patterns across participants. Plasma OT was significantly elevated within 60 minutes following capsule administration (i.e., at the first time point) and peaked at 120 minutes. The magnitude and time course are consistent with previous studies (Dumont et al., 2009; Hysek et al., 2012a), replicating that MDMA administration results in a marked OT release that can be measured in peripheral plasma. The lower dose of MDMA (0.75 mg/kg) did not significantly increase plasma OT levels, suggesting that there may be a qualitative difference in the subjective and behavioral effects of the drug depending upon the dose level. These data indicate that future studies investigating the pro-social effects of MDMA should use relatively larger doses. Interestingly, there was substantial individual variability in drug response: participants differed in both the peak (between 60 and 120 minutes) and magnitude (between a 20 and 150 pg/ml increase from baseline) of drug response. It is not known whether this variability in plasma response was related to individual differences in pharmacokinetics of the drug or to differences in sensitivity to MDMA-related prosocial behavioral effects. Unfortunately, one limitation of this study is that we did not include measures of social behavior or response to social stimuli. However, a post hoc analysis revealed that MDMA-induced increases in heart rate significantly covaried with some prosocial subjective effects (e.g., ratings of ‘Sociable’ and ‘Friendly’), but not with more general drug-related effects (e.g., ratings of ‘Feel Drug’ and ‘Feel High’). This suggests that variability in physiological response to MDMA may partially explain variability in its prosocial effects and will need to be further examined in future studies.

MDMA also dose-dependently increased ratings of euphoria (i.e., drug liking) as well as ratings of sociability such as feelings of friendliness, playfulness, and insightful, consistent with previous reports (Tancer and Johanson, 2003; Bedi et al., 2009, 2010; Hysek and Liechti, 2012; Hysek et al., 2012b; Kirkpatrick et al., 2012, 2014). In a recent study we found some support that the subjective prosocial effects of MDMA may be related to OT function (Kirkpatrick et al., 2014). Thus, we predicted that MDMA-related sociability ratings would be related to plasma OT concentrations. The current results do not support this hypothesis. Nevertheless, this is consistent with previous studies indicating that plasma OT levels were not correlated with several measures of pro-social feelings and behavior (Hysek et al., 2012a, 2013), but contrary to one previous study showing significant within-subject correlations between MDMA-induced plasma OT and two subjective measures of sociability (Dumont et al., 2009). However, the differences in statistical approaches between the current

study and Dumont et al. make it difficult to compare the two studies. The relationship between plasma OT and MDMA-related prosocial effects remains to be determined. Of course, it is unclear whether the presence – or *absence* – of a significant correlational relationship between hormone levels and subjective response would support a true physiological link between MDMA-related subjective response and oxytocin levels in the plasma. Regardless, these data suggest that MDMA produces many of its prosocial subjective effects through other neurochemical mechanisms. For example, a recent study indicates that both MDMA and exogenous oxytocin produces pro-social behavior via involvement of vasopressin receptors (Ramos et al., 2013). The ability of oxytocin to target homologous brain vasopressin receptors may also explain how exogenous oxytocin reverses social deficits found in oxytocin-receptor knock-out mice (Sala et al., 2011).

Intranasal OT also increased plasma OT levels, albeit to a lesser extent. Plasma OT concentrations following the 40 IU IN-OT dose were lower than MDMA-related levels (OT = 37 pg/ml vs MDMA = 84 pg/ml), peaked relatively early (i.e., 30–60 minutes vs 120 min after administration), and were short-lived (30 min vs 3 hours). However, responses were less variable than the OT levels after MDMA (7 of the 8 subjects exhibited peak response 30 min after administration, compared to a range of peak response times for MDMA). Overall, the pharmacokinetic time course of IN-OT is consistent with recent reports showing that 24–26 IU IN-OT increased plasma OT levels immediately following drug administration (Gossen et al., 2012; Striepens et al., 2013). We did not observe an increase in plasma OT following the 20 IU dose. However, the sample size in this study was small (N=6 for 20 IU and N=8 for 40 IU) and more subjects may have provided power to detect a subtle effect. Future investigations might investigate a wider range of intranasal doses using a within-subjects design and larger sample size.

The current results should be interpreted in the context of several potential limitations. One limitation of our study, and others investigating the central effects of OT, is that we measured OT levels in plasma, and we do not know how these levels correspond to OT levels in the brain. Some evidence suggests that OT has a more sustained action in the CNS compared to the periphery (Mens et al., 1983), suggesting that behavior may be influenced by central OT even after plasma levels have returned to baseline. It has been shown that OT and the closely related nanopeptide, arginine vasopressin, can be measured in cerebral spinal fluid (CSF) after intranasal administration (Born et al., 2002; Striepens et al., 2013), and that plasma oxytocin levels may not be related to CSF levels following acute administration. Future studies should further investigate the correspondence of central and peripheral OT levels and how these might relate to prosocial behaviors. Another limitation of the current study is that we utilized different routes of administration for OT (intranasal) and MDMA (oral). This difference makes it potentially difficult to directly compare the effects of the two drugs due to differences in rates of absorption and distribution. However, in order to minimize expectancies, participants received both a capsule and a nasal spray during each session. Finally, the formulation of IN-OT used in the current study (i.e., Pitocin) is less concentrated than the formulation used in typical oxytocin studies (i.e., Syntocin). This difference may influence absorption rates of the drug and thus, future studies directly comparing MDMA and IN-OT might utilize a range of oxytocin formulations.

In conclusion, MDMA dose-dependently increased plasma OT concentrations and feelings of euphoria and sociability. The larger dose of intranasal OT also increased plasma OT levels but these increases were relatively low and short-lived compared to those produced by MDMA. Additionally, MDMA-induced increases in mean plasma OT concentrations were unrelated with mean levels of subjective sociability in our study. MDMA-related subjective effects may be mediated by mechanisms that are not reflected in plasma OT levels, such as central OT, vasopressin, or monoamine neurotransmitter signaling. Thus, future studies will need to parse out contributions of monoamine and central neuropeptide brain pathways to the prosocial effects of MDMA. These data provide further information about the pharmacokinetics of plasma OT following administration of two drugs believed to produce prosocial behavioral effects in humans.

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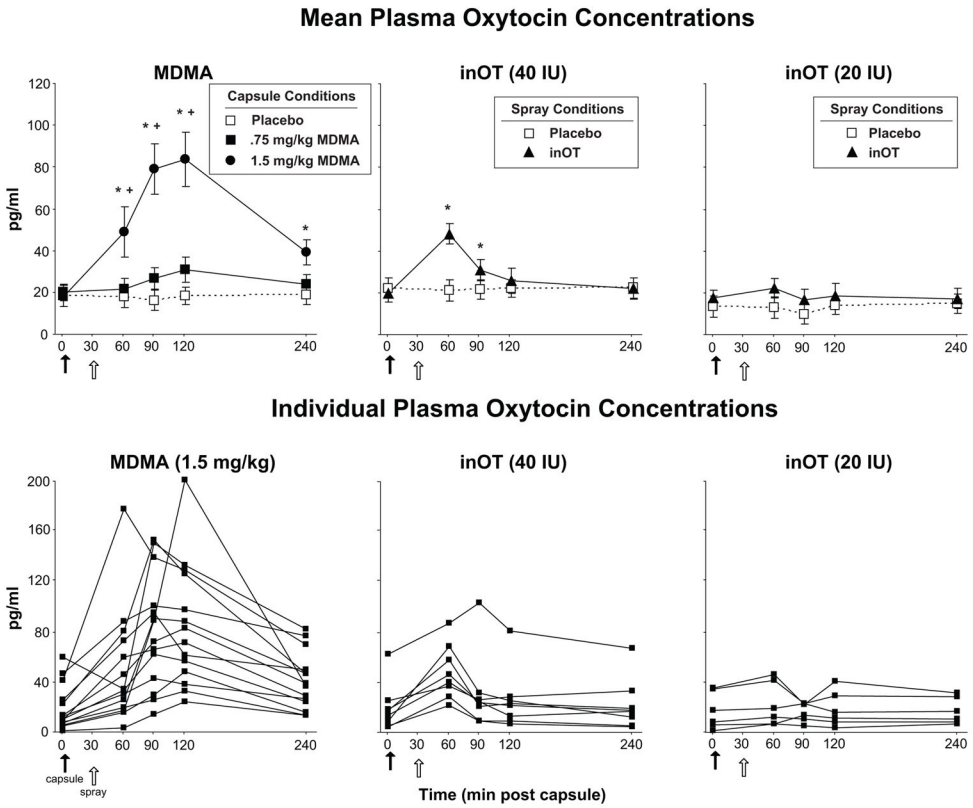

Figure 1.

Top panels: Mean plasma OT concentrations scores following administration of MDMA, IN-OT, or placebo as a function of dose and time. *Bottom panels*: Individual plasma OT concentrations scores following administration of placebo, MDMA (1.5 mg/kg: *left panel*), or IN-OT (20 IU and 40 IU: *center and right panels*) as a function of time. The closed arrow denotes time of capsule administration. The open arrow denotes time of nasal spray administration. An * indicates 1.5 mg/kg MDMA significantly different from placebo ($p<0.05$). A + indicates 1.5 mg/kg MDMA significantly different from 0.75 mg/kg MDMA ($p<0.05$). Error bars represent one SEM.

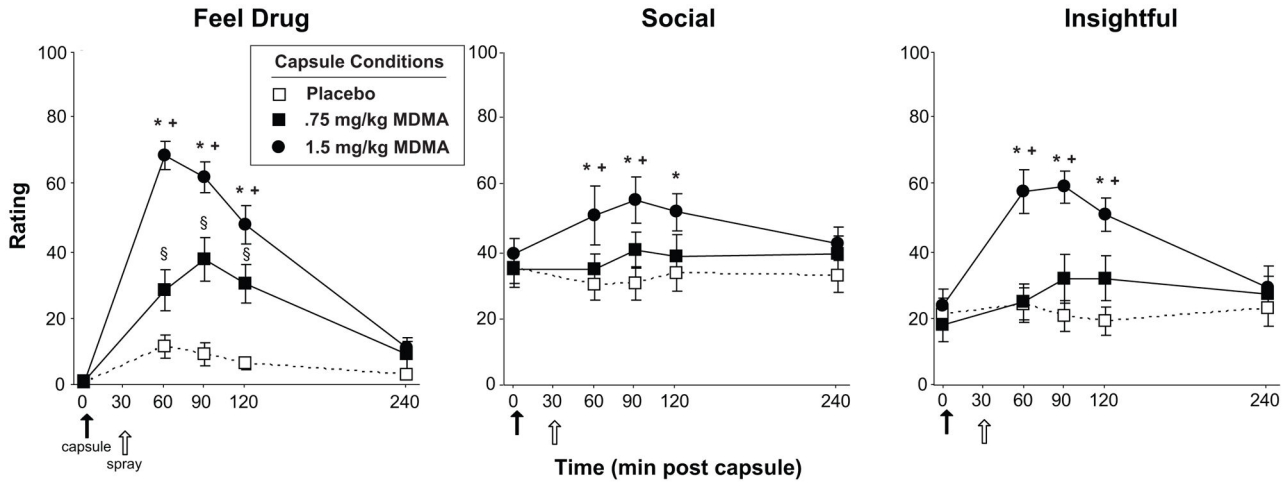

Figure 2.

Selected mean scores on subjective ratings following administration of MDMA or placebo as a function of dose and time. The closed arrow denotes time of capsule administration. The open arrow denotes time of nasal spray administration. An * indicates 1.5 mg/kg MDMA significantly different from placebo ($p<0.05$). A + indicates 1.5 mg/kg MDMA significantly different from 0.75 mg/kg MDMA ($p<0.05$). A § indicates 0.75 mg/kg MDMA significantly different from placebo ($p<0.05$). Error bars represent one SEM.

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Table 1

MDMA-related mean (SEM) heart rate, blood pressure, and self-report ratings over the entire session, calculated as change from pre-capsule.

	Drug Condition								
	Placebo		0.75 mg/kg MDMA		1.5 mg/kg MDMA		Main Effect of Dose		
	Mean	(SEM)	Mean	(SEM)	Mean	(SEM)	*F* (2,26)	*p*	χ^2
Cardiovascular measures									
Heart Rate	1.7	(0.7)	8.7	(1.7) *	16.0	(2.9) *§	17.5	<0.001	0.26
Systolic Pressure	1.2	(2.5)	14.5	(1.9) *	27.1	(2.2) *§	35.2	<0.001	0.36
Diastolic Pressure	0.4	(1.2)	6.7	(1.2) *	11.5	(1.2) *	23.8	<0.001	0.27
Drug Effects Questionnaire									
Feel Drug	6.4	(2.3)	24.4	(4.7) *	44.4	(3.9) *§	47.7	<0.001	0.27
Feel High	5.4	(2.3)	20.6	(4.8) *	43.7	(3.2) *§	59.7	<0.001	0.28
Like Drug	5.0	(3.0)	22.4	(4.7) *	47.8	(4.0) *§	39.6	<0.001	0.30
Dislike Drug	7.9	(2.9)	12.8	(2.9)	15.3	(5.5)	4.7	0.018	0.06
Want More	6.4	(3.1)	22.5	(6.1) *	41.5	(6.2) *§	20.0	<0.001	0.24
Visual Analog Scales									
Anxious	2.2	(4.0)	11.5	(4.3)	14.2	(4.0)	2.3	0.124	0.04
Confident	−3.9	(1.9)	1.3	(2.4)	10.1	(4.9)	5.2	0.013	0.17
Dizzy	5.3	(3.2)	6.4	(5.4)	15.4	(6.4)	5.9	0.008	0.06
Elated	2.6	(1.6)	16.0	(4.4) *	33.3	(5.4) *§	23.3	<0.001	0.25
Friendly	−3.2	(2.5)	5.0	(3.0)	17.8	(4.3) *	13.6	<0.001	0.24
Insightful	0.7	(1.7)	10.5	(4.8)	23.7	(5.4) *	18.6	<0.001	0.26
Lonely	−0.1	(1.8)	4.8	(3.7)	11.1	(5.5)	1.1	0.363	0.03
Loving	0.3	(1.6)	4.7	(2.8)	28.6	(5.8) *§	18.2	<0.001	0.26
Playful	−4.5	(2.5)	5.4	(2.9)	15.7	(5.6)	4.5	0.021	0.12
Restless	7.2	(3.0)	18.1	(4.2)	27.3	(5.5) *	10.2	0.001	0.13
Sedated	1.8	(3.7)	0.6	(2.6)	5.0	(2.8)	0.8	0.464	0.01

	Drug Condition								
	Placebo		0.75 mg/kg MDMA		1.5 mg/kg MDMA		Main Effect of Dose		
	Mean	(SEM)	Mean	(SEM)	Mean	(SEM)	*F* (2,26)	*p*	χ^2
Sociable	−3.6	(2.2)	4.5	(3.8)	11.8	(5.2) *	7.9	0.002	0.18
Stimulated	4.2	(2.0)	19.2	(4.5)	36.3	(5.3) *	40.4	<0.001	0.28

* significantly different from placebo

§ significantly different from 0.75 mg/kg

Table 2

Oxytocin-related mean (SEM) heart rate, blood pressure, and self-report ratings over the entire session, calculated as change from pre-capsule. There were no significant differences between oxytocin and placebo.

	Oxytocin Group										
	20 IU (N=6)				40 IU (N=8)						
	Placebo		Oxytocin		Placebo		Oxytocin		Dose x Group		
	Mean	(SEM)	Mean	(SEM)	Mean	(SEM)	Mean	(SEM)	*F* (1,12)	*p*	χ^2
Cardiovascular measures											
Heart Rate	0.8	(1.1)	0.2	(1.4)	2.6	(0.9)	1.1	(1.2)	0.1	0.717	0.00
Systolic Pressure	2.2	(3.9)	5.2	(3.2)	0.2	(3.3)	−1.7	(2.8)	1.1	0.309	0.01
Diastolic Pressure	−0.3	(1.8)	3.3	(1.5)	1.1	(1.6)	−0.7	(1.3)	5.3	0.041	0.05
Drug Effects Questionnaire											
Feel Drug	6.1	(3.5)	3.0	(1.6)	6.8	(3.0)	2.7	(1.4)	0.0	0.861	0.00
Feel High	4.6	(3.5)	0.3	(1.2)	6.2	(3.0)	3.5	(1.0)	0.0	0.841	0.00
Like Drug	5.9	(4.5)	3.2	(5.2)	4.1	(3.9)	9.6	(4.5)	0.1	0.797	0.00
Dislike Drug	8.3	(4.3)	4.2	(2.9)	7.5	(3.8)	2.5	(2.5)	0.2	0.649	0.00
Want More	7.9	(4.6)	2.8	(5.6)	4.9	(4.0)	10.1	(4.8)	1.3	0.284	0.02
Visual Analog Scales											
Anxious	2.1	(6.1)	0.3	(2.3)	2.4	(5.3)	−0.7	(2.0)	3.0	0.107	0.01
Confident	−5.8	(2.9)	−1.6	(3.2)	−2.1	(2.5)	−5.2	(2.8)	0.2	0.663	0.00
Dizzy	4.0	(4.9)	0.1	(3.9)	6.5	(4.2)	2.7	(3.4)	0.2	0.658	0.00
Elated	1.8	(2.4)	−1.5	(2.4)	3.4	(2.1)	1.5	(2.1)	1.2	0.293	0.01
Friendly	−4.0	(3.8)	−1.7	(3.7)	−2.4	(3.3)	−2.3	(3.2)	1.1	0.32	0.00
Insightful	2.0	(2.6)	2.1	(2.8)	−0.7	(2.3)	2.8	(2.4)	0.7	0.414	0.00
Lonely	−0.2	(2.7)	−1.8	(1.4)	0.0	(2.3)	1.3	(1.2)	0.5	0.503	0.00
Loving	−1.4	(2.5)	−2.8	(2.7)	2.0	(2.1)	1.2	(2.3)	0.0	0.895	0.00
Playful	−8.1	(3.7)	−3.5	(1.9)	−0.9	(3.2)	1.9	(1.6)	0.2	0.683	0.00
Restless	8.3	(4.6)	0.1	(2.7)	6.1	(4.0)	1.5	(2.3)	0.6	0.452	0.00
Sedated	6.1	(5.6)	−1.7	(5.2)	−2.6	(4.8)	5.1	(4.5)	0.7	0.421	0.01
Sociable	−6.0	(3.3)	0.7	(3.2)	−1.3	(2.8)	−2.6	(2.8)	0.8	0.396	0.00

	Oxytocin Group											
	20 IU (N=6)				40 IU (N=8)							
	Placebo		Oxytocin		Placebo		Oxytocin		Dose x Group			
	Mean	(SEM)	Mean	(SEM)	Mean	(SEM)	Mean	(SEM)	*F* (1,12)	*p*	χ^2	
Stimulated	2.9	(3.0)	3.7	(3.1)	5.6	(2.6)	3.2	(2.7)	3.6	0.081	0.01	