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Urinary and plasma oxytocin changes in response to MDMA or intranasal oxytocin administration

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ABSTRACT

Background: The neuropeptide oxytocin (OT) has received increased experimental attention for its putative role in both normal social functioning and several psychiatric disorders that are partially characterized by social dysfunction (e.g., autism spectrum disorders: ASD). Many human experimental studies measure circulating plasma levels of OT in order to examine the relationship between the hormone and behavior. Urinary OT (uOT) assays offer a simple, easy, and non-invasive method to measure peripheral hormone levels, but the correspondence between uOT and plasma OT (pOT) levels is unclear. Here, we conducted two within-subjects, double-blind studies exploring changes in uOT and pOT levels following administration of two drugs: MDMA, an oxytocin-releasing drug (Study 1), and intranasal oxytocin (INOT: Study 1 and 2).

Methods: In Study 1, 14 adult participants (2 females) were each administered either oral 1.5 mg/kg MDMA or 40 IU INOT across two different study sessions. In Study 2, 10 male participants (adolescents and young adults) diagnosed with ASD received either 40 IU INOT or placebo across two different sessions. In both studies, blood and urine samples were collected before and after drug administration at each study session. For Study 1, 10 participants provided valid plasma and urine samples for the MDMA session, and 8 provided valid samples for the INOT session. For Study 2, all 10 participants provided valid samples for both INOT and placebo sessions. Pre- and post-administration levels of pOT and uOT were compared. Additionally, correlations between percent change from baseline uOT and pOT levels were examined.

Results: Study 1: Plasma OT and uOT levels significantly increased after administration of MDMA and INOT. Furthermore, uOT levels were positively correlated with pOT levels following administration of MDMA ($r = 0.57$, $p = 0.042$) but not INOT ($r = 0.51$, $p=0.097$). Study 2: There was a significant increase in uOT levels after administration of INOT, but not after administration of placebo. Under both conditions, INOT and placebo, significant increases in pOT levels were not observed. Additionally, change from baseline uOT and pOT levels were positively correlated ($r = 0.57$, $p=0.021$). There was no significant correlation between uOT and pOT levels following placebo administration.

Conclusion: Our results show a measurable and significant increase in pOT and uOT levels after the administration of MDMA (Study 1) and INOT (Study 1 and Study 2). Additionally, a positive correlation between uOT and pOT levels was observed in both samples (healthy adults and ASD patients) in at least one condition. However, uOT and pOT levels were not correlated under all conditions, suggesting that uOT levels do not fully correspond to pOT levels in the time windows we measured. Future studies should further examine the relationship between levels of pOT and uOT in healthy and clinical populations on measures of social behavior because uOT may serve as an additional non-invasive method to measure peripheral OT changes.

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1. Introduction

Over the past 25 years, oxytocin (OT) – a neuropeptide synthesized in the paraventricular nucleus and supraoptic nucleus of the hypothalamus and released to both central and peripheral circulation – has received increased attention for its role in social functioning. Evidence from preclinical, clinical, and human laboratory studies indicate that OT is involved in social behavioral and cognitive domains, including attachment and pair bonding in laboratory animals, as well as social affiliation, parental care behaviors, socioemotional processing, social reward, and generosity in humans (Carter et al., 2008; Donaldson and Young, 2008; Feldman et al., 2010; Insel and Young, 2001; Macdonald and Macdonald, 2010). It is important to note that evidence concerning the role of OT in some social domains in humans remains mixed. While some studies show a relationship between OT and trust (Heinrichs et al., 2009), others do not (Christensen et al., 2014). Nevertheless, there is mounting evidence that OT functioning is involved in several psychiatric disorders that have social dysfunction including autism spectrum disorders (ASD), depression, anxiety, drug abuse, and schizophrenia (Burkett and Young, 2012; Francis et al., 2014; McGregor and Bowen, 2012; McQuaid et al., 2014; Souza et al., 2010a; Souza et al., 2010b; Teltsh et al., 2012; Weisman et al., 2013). Continued examination of OT will be required to understand its neurobiological role in modulating both typical and atypical social behaviors.

Given the challenges, risk, and invasiveness of measuring OT in cerebrospinal fluid (csfOT), many experimental and observational studies measure peripheral levels of the hormone as a proxy for central hypothalamic release. The relationship between central and peripheral OT levels is complex. Studies comparing basal csfOT and plasma OT (pOT) levels have yielded mixed results: i.e., both positive correlations (Carson et al., 2015) and no correlation (Kagerbauer et al., 2013). Studies utilizing exogenous OT administration have shown increases in both central and peripheral OT levels, in animals and humans (i.e. intranasal OT or intravenous OT; Dal Monte et al., 2014; Freeman et al., 2016; Striepens et al., 2013), with some correspondence observed between central and peripheral OT levels in non-human primates and rats (Dal Monte et al., 2014; Freeman et al., 2016; Neumann et al., 2013), but no correlation between pOT and csfOT levels in humans (Striepens et al., 2013). Nevertheless, pOT levels have been found to be positively associated with several behavioral outcomes, including less anxiety in children (Carson et al., 2015), and parents' positive communication and social engagement with their children (Feldman et al., 2011), suggesting that this peripheral measure may be an indicator of OT functioning in the brain.

Another method to determine peripheral levels of OT is to measure urine OT (uOT). This is a simple method and can be calibrated for fluid intake/excretion variability. Urine OT may not replace measuring OT levels in CSF or plasma, but it is a non-invasive approach for studying OT and its relationship with behaviors. Researchers have reported associations between social outcomes and uOT (Feldman et al., 2011; Saito et al., 2014; Seltzer et al., 2010). However, while there are associations between social outcomes and pOT and uOT levels (Carter et al., 2007; Feldman et al., 2011; Parker et al., 2014; Seltzer et al., 2010), there is ongoing controversy about the relative value of each method. Although some researchers suggest that pOT sampling remains the method of choice for measuring peripheral OT levels (Hoffman et al., 2012), there remains limited data directly comparing pOT with uOT levels. Some correlational evidence suggests correspondence between pOT and uOT (Hoffman et al., 2012), while other studies have reported a lack of correspondence between the two measures (Feldman et al., 2011). Some of these discrepancies may be related to differences in time course and steady-state in different body fluids, which have varying volume distributions and clearance processes. Behavioral effects of OT and other neuropeptides often correlate with CSF changes measured 10–120 min after intranasal administration (Born et al., 2002; Striepens et al., 2013). OT changes in blood and plasma occur on the time course of minutes whereas changes in urine occur over hours (Fig. 1).

Non-invasive methods of measuring peripheral OT levels – such as urine assay – will move the field forward, as research into the role of OT in social behavior continues to increase. This is especially important in studies with children or in disorders where repeated blood draws for non-essential measures are challenging. Therefore, to further understand the relationship between pOT (invasive) and uOT (non-invasive) levels we analyzed data from two studies where we collected both urine and plasma before and after administration of MDMA (±3,4-methylenedioxymethamphetamine), INOT (intranasal oxytocin), and/or placebo. Our laboratory and others have demonstrated that MDMA dose-dependently increases acute pOT levels (Dumont et al., 2009; Hysek et al., 2012; Hysek et al., 2014; Kirkpatrick et al., 2014a; Schmid et al., 2014), and pOT levels increase following INOT to a lesser degree (Gossen et al., 2012; Striepens et al., 2013). Here, Study 1 extends upon our previously published study, which examined MDMA- and INOT-induced changes in both pOT levels and self-reported feelings of sociability (Kirkpatrick et al., 2014a). Study 2 introduces data collected from individuals with ASD during an INOT single-dose versus placebo challenge.

These studies not only provide an opportunity to further evaluate the association between pOT and uOT levels, but also provide a chance to examine the relationship between pOT and uOT levels in both healthy (Study 1) and clinical (Study 2) populations. Overall, this could provide information to a growing set of researchers interested in the influence of OT on normal social behavior and behavioral disruptions associated with a number of disorders. While there have been studies comparing *baseline* pOT and uOT levels (Feldman et al., 2011; Hoffman et al., 2012), to our knowledge there have been no published reports comparing the two assays following administration of either MDMA or INOT. We predicted that uOT and pOT levels would increase after the administration of MDMA (Study 1) and INOT (Studies 1 and 2). We further predicted that levels of uOT would be positively correlated with pOT levels under the drug conditions.

2. Materials and methods

2.1. Study 1: MDMA- and INOT-related effects in healthy adult participants

2.1.1. Participants

Healthy adults with past MDMA experience were recruited via community billboard advertisement and then completed an in-person psychiatric evaluation and medical examination, including an electrocardiogram and physical examination. Exclusion criteria included any significant cardiovascular, neurological, or major psychiatric illness including all Axis I disorders that might increase risk for an MDMA-related adverse event (Kirkpatrick et al., 2014b), or if they smoked more than 10 tobacco cigarettes per day, to reduce the likelihood of acute tobacco withdrawal-related mood alterations (Hughes and Hatsukami, 1986). Female participants (N = 2) did not use hormonal contraceptives and were tested only during the follicular phase (days 2–14: White et al., 2002). Participants provided written informed consent prior to participation. The study was approved by the Institutional Review Board (IRB) at the University of Chicago in accordance with the Code of Federal Regulations (adopted by the National Institutes of Health and the Office for Protection from Research Risks of the US Federal Government).

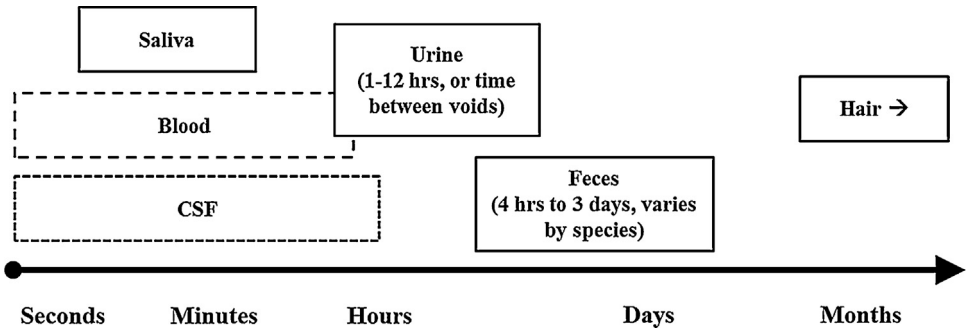

Fig. 1. Timescales captured by different types of biosamples. Figure depicting the different timescales captured by various types of biosamples including urine (adapted from Anestis, 2010). As displayed in the figure, blood and CSF reflect changes on the order of minutes to hours (Born et al., 2002; Striepens et al., 2013).

In total, 14 participants (2 female, 12 male) completed the study. A total of 10 participants (2 female, 8 male) provided valid urine and plasma samples during the MDMA session, and a total of 8 participants (2 female, 6 male) provided valid samples during the INOT session. These 10 participants were 25.8 ± 4.3 (mean ± SD) years old, had a BMI of 24.1 ± 2.7, and had completed 14.4 ± 1.6 years of formal education. They had used MDMA a mean of 13.1 ± 12.0 times (range 4–40 lifetime). Seven participants currently drank caffeinated beverages (1–3 cups/day), five smoked tobacco (1–12 cigarettes/month), nine drank alcohol (2–7 drinks/week), and six currently smoked marijuana (1–18 days/month). None of these measures differed between the entire sample and the analyzed subsample.

2.1.2. Design

The current analysis is part of a larger previously published 4-session, within-subjects, placebo-controlled, double-dummy study (Kirkpatrick et al., 2014a), during which participants ingested a capsule that contained either MDMA or placebo and then received a nasal spray that contained either INOT or placebo (i.e., saline). There were four randomized drug conditions (i.e., one for each session): two MDMA conditions (0.75 and 1.5 mg/kg), one INOT (40 IU), and one placebo. For the purposes of the current analysis, we are presenting a subset of data from the two sessions during which participants received either oral 1.5 mg/kg MDMA or 40 IU INOT. Urine samples for uOT analysis were collected once at the beginning of the session (i.e., before drug administration, baseline) and once at the end of the session (i.e., 4 h after drug administration). Blood samples for pOT analysis were collected, through an indwelling catheter, before and at several time points for 4 h after drug administration. Additionally, participants' mood states and cardiovascular measures were monitored regularly. Plasma OT levels, subjective effects, and cardiovascular measures have been presented previously (Kirkpatrick et al., 2014a). Participants were compensated monetarily and debriefed following the study.

2.1.3. Drugs

MDMA powder (1.5 mg/kg), manufactured and provided by Dr. David Nichols of Purdue University, was encapsulated in 00 opaque capsules with lactose filler by The University of Chicago Hospitals investigational pharmacy. This MDMA dose was selected based on our previous studies indicating that MDMA reliably increases positive mood and alters emotional processing at these doses (Bedi et al., 2009; Bedi et al., 2010). INOT (40 IU) was prepared within 24 h of use. Four doses of Pitocin (OT Injection USB; Monarch Pharmaceuticals; concentration: 10 IU Pitocin/1 mL) were transferred into two, 3 mL intranasal atomizers (MAD300 by LMA Inc., San Diego, CA). The INOT dose was chosen based on previous studies utilizing intranasally administered OT and the structurally similar neuropeptide, vasopressin (AVP; Bos et al., 2012; MacDonald et al., 2011). Placebo nasal sprays consisted of Ocean Spray Nasal Solution (Valeant Pharmaceuticals, Bridgewater, NJ). Again, note that in the current analysis, uOT and pOT data from the placebo condition are not presented. Nasal sprays were administered by trained personnel in four doses to each nostril over the course of 15 min. During the administration, participants sat comfortably in a reclined position, with their heads tilted back to maximize absorption. Having used a within-subject design, all OT level comparisons in this paper are done with each participant's baseline levels prior to MDMA or INOT administration.

2.1.4. Procedure

Sessions were conducted between 0900 h and 1330 h in order to minimize any diurnal variation in basal hormonal measures (Broadbear et al., 1999). Note that there is limited human data about diurnal changes in pOT or csfOT and level patterns vary in animal studies, but timing here was optimized given that cortisol and other hormones can influence OT (Broadbear et al., 1999; Jacob et al., 2011). Upon arrival to the laboratory participants provided breath samples to confirm abstinence from alcohol (as measured by an Alco-Sensor III Breathalyzer, Intoximeters Inc., St Louis, MO). Then participants provided a urine sample (completely voiding their bladder) to be used for baseline OT assay. Additionally, a separated aliquot from this initial urine sample was tested for pregnancy in female participants, and to confirm abstinence from other drugs (i.e., amphetamine, cocaine and opiates: Ontrak TesTstik, Roche Diagnostic Systems Inc., Somerville, NJ). Finally, marijuana abstinence was confirmed by a saliva test (Oratect, Branan Medical Corp., Irvine, CA). Note that participants were told to consume their normal amount of caffeine prior to the session in order to minimize the potential effects of caffeine withdrawal.

An intravenous catheter was inserted into the participant's non-dominant arm for blood sampling. At 0920 h, a baseline blood sample was obtained, and participants completed self-report mood and drug effects questionnaires. At 0930 h, participants ingested capsules containing either 1.5 mg/kg MDMA or placebo and at 1000 h they received an intranasal spray containing either 40 IU INOT or saline. Blood samples were obtained at 1030, 1100, 1130, and 1330 h. These times correspond to 60, 90, 120, and 240 min after the 0930 h capsule administration; and 30, 60, 90, and 210 min following the start of the 1000 h nasal spray administration. Timing of blood samples were selected to correspond to a previous study conducted in our lab showing that acute MDMA subjective and physiological effects peak approximately 60–90 min post drug administration and return to approximate baseline levels 240 min post drug administration (Kirkpatrick et al., 2014b). In between assessments, participants were permitted to read or watch movies provided by the research staff. Participants were restricted to 20 oz. water per hour. At 1330 h, the catheter was removed and the participant provided the second urine sample for OT assay. The afternoon

urine collection (PM times) contained the pooled OT post drug administration.

2.1.5. Data analysis

In order to examine the effects of MDMA and INOT on uOT and pOT levels, data were analyzed using a repeated-measures analysis of variance (ANOVA) with one within-subject factor: Time of assessment (pre- and post-drug administration). Preliminary analyses revealed that there were no significant effects of session order (i.e., the order that participants received the different drug conditions) on either plasma or urine OT outcomes. Given that our hypothesis was directional (i.e., that we would observe a positive association between uOT and pOT levels after administration of MDMA and INOT), we conducted one-tailed Pearson's correlational analyses to investigate this relationship. We conducted separate analyses for each drug. We calculated three summary percent change from baseline variables for pOT: 1) peak response; 2) area-under-the-curve (AUC); and 3) the end-of-session time point (i.e., 4 h after drug administration). We selected these three summary measures to examine whether uOT levels were potentially related to either peak plasma levels, plasma response over the course of the entire session (AUC), and/or plasma levels measured at the same time point as urine levels (end-of-session). We also tested the potential correlation between uOT and pOT levels at baseline for each session. For all analyses and comparisons, p-values were considered statistically significant at less than 0.05.

2.2. Study 2: INOT-related effects in adolescents and young adults with ASD

2.2.1. Participants

Participants in this study were returning participants originally recruited through the Developmental Disorders Clinic of the University of Illinois at Chicago (UIC) Institute for Juvenile Research for genetic studies. Participants were required to meet ASD or autism criteria on the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1999; Gotham et al., 2007) and on the Autism Diagnostic Interview, Revised (ADI-R; Rutter et al., 2003; Risi et al., 2006). ASD diagnosis was confirmed by a clinician experienced in ASD diagnosis in accordance with the DSM-IV-TR (American Psychiatric Association., 2000) ASD classification. Participants taking medications were required to have a stable medication routine for at least 3 months prior to the first session visit, and remain stable throughout the study. Exclusion criteria included any significant medical history that might interfere with completing study tasks. This included, but was not limited to drug and alcohol abuse, impairment of renal function, evidence or history of malignancy or any significant hematological, endocrine, respiratory, hepatic, cardiovascular or gastrointestinal disease. Additionally, participants with significant nasal pathology (atrophic rhinitis, recurrent nose bleeds, or history of hypophysectomy) were excluded (Anagnostou et al., 2014). Our previous research in ASD has shown that average pOT levels are higher before puberty (Hammock et al., 2012), so this study focused on adolescents and young adults, 17.60 ± 3.34 years old (N = 10). Participation in the study was voluntary. Participants over 18 years of age provided written informed consent. For participants under 18 years old, parents provided written informed consent and participants provided verbal and written assent prior to participation. The participants received monetary compensation by mail within 2 weeks of each session visit. The study was approved by the IRB at the UIC 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.

2.2.2. Design

The study was a double-blind placebo-controlled cross-over challenge study of a single dose of INOT versus placebo. The two sessions were separated by approximately two weeks. At each session, the participant received either 40 IU INOT or placebo. Urine was collected twice during the session, once before drug administration and once after administration. Blood samples were also collected twice, pre- and post-drug administration. To control for the daily cycle of endogenous OT and the effects of diet, participants were instructed to return for the second session at the same time of day and to the best of their ability, to eat the same foods and consume the same beverages. Participants were allowed to consume water if they were thirsty during the session or needed water to help facilitate urination.

2.2.3. Drug

The INOT (weight-adjusted dose based on 40 IU/67 kg dose, or 0.6 IU/kg/dose) formulation utilized in this study was Syntocinon, manufactured by Novartis (Basel, Switzerland). This dosage was chosen based upon previous studies of INOT single tolerability (Anagnostou et al., 2014; MacDonald et al., 2011) and chronic dosing safety in ASD youth (Anagnostou et al., 2014). The placebo formulation, provided by Novartis, was manufactured by Advantage Pharmaceuticals Inc. (Rocklin, CA). The UIC investigational drug pharmacy stored and prepared nasal sprays for administration during the double-blinded study sessions. At each session, the bottle was first primed by pressing the nozzle until a full spray was released. Then the participants were asked to sit up straight and tilt their head back. They pointed the nozzle towards the rear and center of their nose. The participants then exhaled, and while pressing down on the dispenser inhaled deeply. They waited approximately 10–15 s and performed the same procedure in the other nostril. Nostrils were alternated until full dosage was administered.

2.2.4. Procedure

After completing the consent process at the first session, pre-administration (i.e., baseline) collection of urine and plasma began. INOT was immediately administered after these baseline sample collections. Blood samples were collected approximately 85 min, and urine at approximately 120 min, after drug administration. The collection time points were chosen to prioritize the behavioral effects of INOT as observed in a study conducted by Andari et al. (2010), and to allow participants to perform behavioral tasks during peak csfOT periods based on significant findings published with AVP (Born et al., 2002). Participants were asked not to urinate until the appointed time in order to pool uOT for full session. If participants indicated they could not wait until the appointed time, they were allowed to urinate and collection time was recorded. All urine samples were collected utilizing the same protocol as Study 1 (see below). In between sample collections, participants performed tasks measuring social information processing (including face and expression recognition).

2.2.5. Data analysis

In order to examine the effects of INOT and placebo on uOT levels, data were analyzed using a repeated-measures ANOVA with one within-subject factor: Time of assessment (pre- and post-drug administration). Following this analysis, we conducted one-tailed Pearson's correlational analyses to investigate the relationship between INOT-induced increases in uOT and pOT levels (both calculated as % change from baseline). We also tested the potential relationship between uOT and pOT levels at baseline for each session. Separate analyses were conducted for each drug condition. For all analyses and comparisons, p-values were considered statistically significant at less than 0.05.

2.3. General protocols: urine and plasma oxytocin levels

2.3.1. Urine

We chose to collect urine only twice (i.e., once at baseline and once at the end of the session) based on the rationale that all the OT is excreted in a pooled manner in urine (without the pulsatile variability), so the design was optimized to collect all the urine from the beginning to the collection point in the session. Participants were asked to urinate into a urine hat or cup; the sample was then stirred with a disposable pipette. The same plastic pipette was used to measure two 2 mL and two 4 mL aliquots. The aliquots were snap frozen by placing the vials immediately in dry ice. The samples were moved to long-term storage (−80 °C) shortly after snap freezing. To measure OT levels in the urine sample, the samples were thawed and the OT extracted with solid phase extraction (SPE) columns, which purified the urine and removed possible contaminates (Seltzer et al., 2010). The samples were assayed with ASSAY Design ELISA kits (Enzo Life Sciences, Ann Arbor, MI) per kit instructions as described in Bick and Dozier (2010), Gray et al. (2007), Seltzer et al. (2010), and Wismer Fries et al. (2005). To compensate for participants' potential daily variable fluid intake, creatinine levels were measured in each urine sample and divided into the hormonal concentration ([OT]/[creatinine]), therefore uOT levels are expressed as the OT to creatinine ratio (pg/mg creatinine). The assay procedures are described in detail in Ziegler et al. (1995).

2.3.2. Plasma

After collection, 10 mL blood samples were centrifuged in a refrigerated 4 °C centrifuge (3000 rpm, for 15 min), plasma and remaining blood products were aliquoted separately, and then stored in a −80 °C freezer. Prior to assaying, samples were first purified by SPE (Yuen et al., 2014). One mL of plasma was run through SPE (Sep-Pak Light C18 cartridges) and eluted with 1 mL 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. Extracted 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 (Carter et al., 2007; Feldman et al., 2011; Gray et al., 2007; Seltzer and Ziegler, 2007; Seltzer et al., 2010; Snowdon et al., 2010; Wismer Fries et al., 2005).

3. Results

3.1. Study 1: MDMA- and INOT-related effects in healthy adult participants

3.1.1. MDMA-related effects on urinary oxytocin levels and correlations with plasma oxytocin levels

Overall, MDMA (1.5 mg/kg) produced a significant increase in uOT (Main effect of Time; $F(1,9) = 80.5$; $p < 0.001$; $\eta_p^2 = 0.90$) and pOT levels (Main effect of Time: $F(1,9) = 67.6$; $p < 0.001$; $\eta_p^2 = 0.88$); the mean difference between pre- and post-drug administration uOT levels was 86.0 ± 9.6 pg/mg creatinine and the difference for pOT levels was 11.2 ± 1.4 pg/mL. Supplementary Fig. 1a and Fig. 2a show that MDMA increases both pOT and uOT levels for each individual. Fig. 3a shows that the percent change from baseline of uOT levels (% change uOT) were significantly and positively associated with percent change of AUC for pOT levels (% change AUC_{pOT}; $r = 0.57$; $p = 0.042$). However, percent change uOT levels were not significantly associated with either end-of-session or peak pOT.

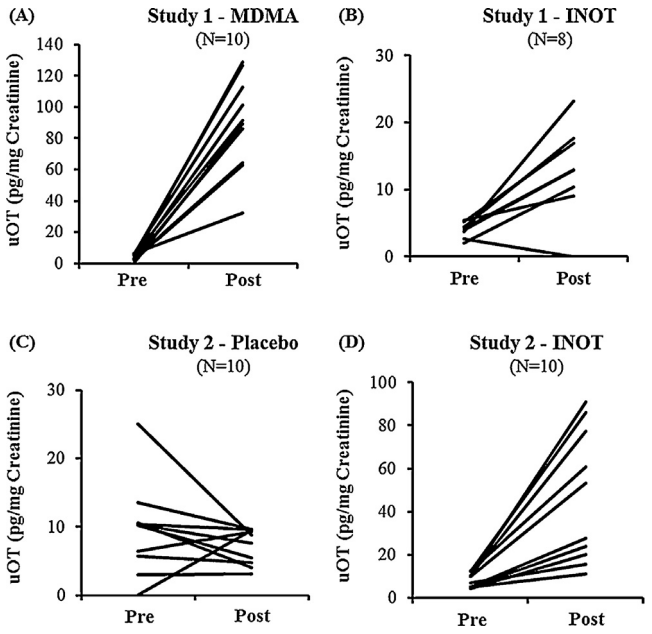

Fig. 2. Change in urinary OT levels for each individual. Study 1 individual participant traces showing the change in urinary oxytocin (uOT) levels before and after MDMA (2A; N = 10) and 40 IU INOT (2B; N = 8) administration. Individual participant traces for Study 2 under placebo (2C; N = 10) and 40 IU INOT (2D; N = 10) conditions.

3.1.2. INOT-related effects on urinary oxytocin levels and correlations with plasma oxytocin levels

INOT (40 IU) produced a significant increase in uOT (Main effect of Time; $F(1,7) = 15.0$; $p = 0.006$; $\eta_p^2 = 0.68$) and pOT levels (Main effect of Time: $F(1,7) = 6.0$; $p = 0.045$; $\eta_p^2 = 0.46$); the mean difference between pre- and post-drug administration uOT levels was 8.9 ± 2.3 pg/mg creatinine and the difference for pOT levels was 1.3 ± 0.5 pg/mL. Supplementary Fig. 1b and Fig. 2b show the individual pOT and uOT responses to 40 IU INOT. Fig. 3b depicts the relationship between percent change from baseline uOT and percent change AUC_{pOT}. Unlike the MDMA session, these results were not significantly correlated ($r = 0.51$; $p = 0.097$).

3.1.3. Correlations between baseline urinary and plasma oxytocin levels

The correlation between pre-administration levels (i.e., baseline) of uOT and pOT was significant during the MDMA session ($r = 0.56$; $p = 0.045$). By contrast, during the INOT session there was no significant correlation observed between pre-administration levels of uOT and pOT ($r = 0.04$; $p = 0.463$).

3.2. Study 2: INOT-related effects in ASD patients

3.2.1. INOT-related effects on urinary oxytocin levels and correlations with plasma oxytocin levels

In the ASD sample, INOT (40 IU) produced a significant increase in uOT levels (Main effect of Time; $F(1,9) = 12.0$; $p = 0.007$; $\eta_p^2 = 0.68$), but not a significant increase in pOT levels (Main effect of Time; $F(1,9) = 3.1$; $p = 0.112$). The mean difference between pre- and post-drug administration uOT levels was 38.6 ± 8.9 pg/mg creatinine and the mean difference for pOT levels was 3.5 ± 2.0 pg/mL. Supplementary Fig. 1d and Fig. 2d show individual pOT and uOT responses to 40 IU INOT. We also noted two apparently distinct uOT groups (Fig. 2d): low INOT responders (pre-administration: 5.34 ± 1.05 pg/mg creatinine; change from baseline: 14.30 ± 6.92 pg/mg creatinine) and high INOT responders (pre-administration: 10.92 ± 1.34 pg/mg creatinine; change from baseline: 62.80 ± 16.28 pg/mg creatinine). Fig. 3d shows

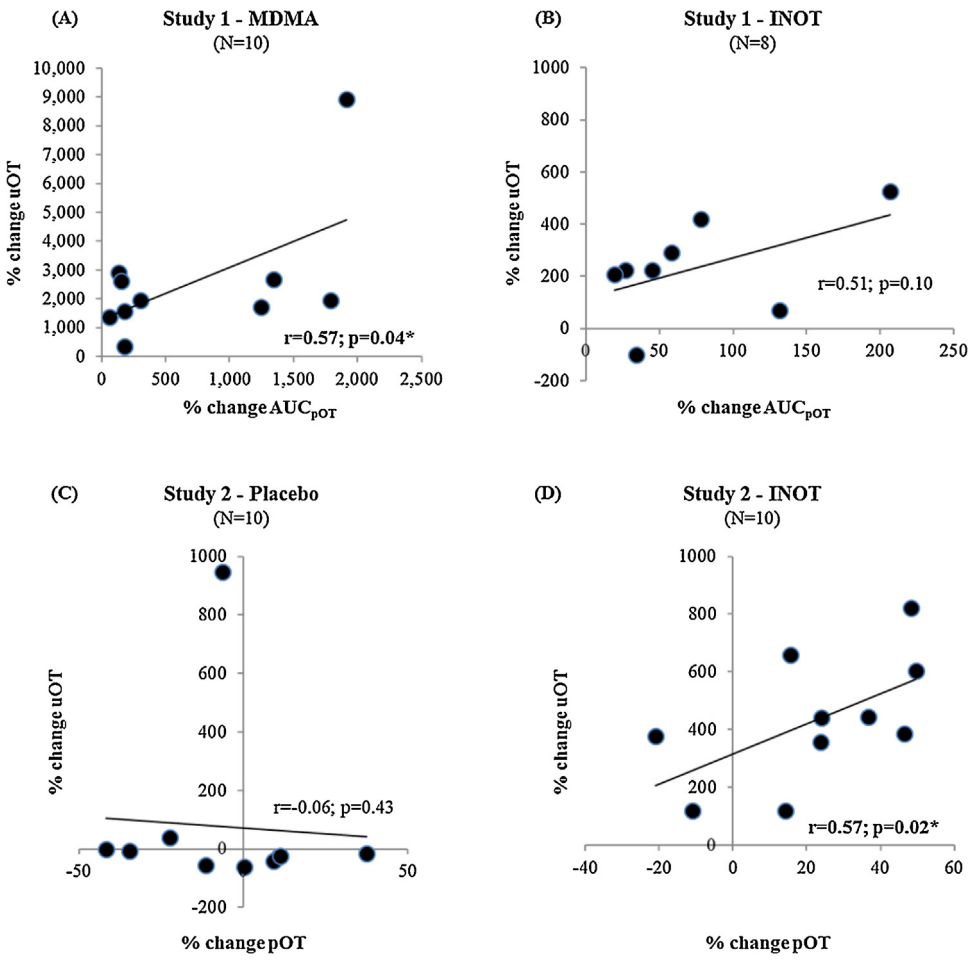

Fig. 3. Correlations between urinary and plasma OT levels. Scatterplots depicting the correlation between percent change from baseline urinary oxytocin levels (% change uOT) and percent change in AUC for plasma oxytocin levels (% change AUC_{pOT}) for MDMA (3A) and INOT (3B) in typical adults. 3C and 3D depict the correlations between percent change uOT and percent change from baseline plasma oxytocin levels (% change pOT) in the placebo (3C) and INOT (3D) conditions. Correlations are significant for the Study 1 MDMA ($p < 0.05$) and Study 2 INOT ($p < 0.05$) conditions. * denotes significance.

that percent change uOT was significantly and positively associated with percent change from baseline pOT levels (% change pOT; $r = 0.57$; $p = 0.021$). By contrast, uOT levels were neither significantly increased nor correlated with pOT following placebo administration (Fig. 2c and 3c).

3.2.2. Correlations between baseline urinary and plasma oxytocin levels

There were no significant correlations between pre-administration levels of uOT and pOT under placebo or INOT conditions (placebo: $r = 0.07$, $p = 0.420$; INOT: $r = 0.21$, $p = 0.282$).

3.3. Concordance correlations between urine and plasma oxytocin levels (study 1 and 2)

To determine precision, accuracy, and reproducibility between uOT and pOT measures we calculated the Lin concordance correlation coefficient (ρ_c; Lin, 1989). The Lin concordance correlation coefficient analysis yielded a "weak" score (Study 1-XTC: $\rho_c = 0.20$; Study 2-OT: $\rho_c = 0.03$), suggesting the two assay methods are not interchangeable.

4. Discussion

Several of our results were consistent with our hypotheses – we observed significant increases in uOT levels after administration of MDMA (Study 1) and INOT (Study 1 and 2); and we noted significant increases in pOT levels post administration of MDMA (Study 1) and INOT (Study 1). In agreement with the second part of our hypothesis, percent change from baseline levels of uOT and pOT were positively significantly correlated in two different study populations: healthy adults (post-MDMA administration) and ASD patients who ranged in age from 13 to 24 years (post-INOT administration). While our findings demonstrate correspondence between increased uOT and pOT levels following administration of oral MDMA in a healthy population and INOT in an ASD sample, we did not find evidence for correspondence between the levels of uOT and pOT in all study conditions. Correlations between uOT and pOT did not reach significance following administration of INOT (Study 1) and in the placebo session (Study 2). This evidence suggests that correspondence between uOT and pOT levels may be more readily observed following administration of MDMA because it reliably produces relatively large increases in endogenous OT release. INOT studies may have more variable results given the lower level of peripheral OT detected.

Our overall findings are consistent with previous studies showing that drug-related increases in OT can be reliably ascertained using peripheral assay measures (e.g., plasma: Dumont et al., 2009; Hysek et al., 2012; Hysek et al., 2014; Kirkpatrick et al., 2014a; Schmid et al., 2014). These data are also consistent with at least one previous study showing that peripheral OT levels measured by plasma and urine may have overlap in the information they cap-

ture. That is, Hoffman et al. (2012) reported a significant positive correlation between pOT and uOT levels in a population of female anorexia patients, however this association was only observed after removing data from two participants who may or may not have been outliers. Further, our findings that *baseline* uOT and pOT levels were for the most part not associated is consistent with Feldman et al. (2011) who reported a lack of correspondence between levels of pOT and uOT in a study of parent-infant behavioral and affective synchrony. This lack of correspondence between uOT and pOT is underscored by calculating the Lin concordance correlation coefficients (ρ_c; Lin, 1989). Our analysis yielded a "weak" score, suggesting the two methods are not interchangeable. Given our results and this analysis we propose that measuring peripheral OT levels utilizing urine is an *additional* research tool, not a direct replacement method for measuring peripheral OT utilizing plasma.

Some of the inconsistency in the literature and in our current results may stem from the different time scales captured by pOT versus uOT assays. Changes in plasma may reflect immediate and real-time fluctuations in release versus blood circulation clearance, while urine may measure OT that has been pooled in the bladder over a longer period of time after kidney clearance (see Fig. 1; Anestis 2010; Reyes et al., 2014). The differences in the timescale may lead to differences in sensitivity to pulsatile variability in blood. Compared to OT levels in urine, resting state/baseline OT levels measured in blood plasma can be subject to relatively large pulsatile variability (Cyranowski et al., 2008), leading to inconsistent results when comparing single measurements. Note, we observed a significant correlation between pre-administration values of uOT and pOT levels in only one condition (Study 1: MDMA; $r = 0.56$, $p = 0.045$). It is possible that collecting both assay samples at identical time points may not result in correlated uOT and pOT levels, because the uOT is a cumulative and "non-transient" measure. However, sampling both assays within the same study, may better capture change over the time period of behaviors being measured, and give a more complete timing of the interactions between induced OT increases and OT catabolism.

Interestingly, in Study 1 we found stronger correlations between end-of-session uOT and AUC pOT levels, which reflects the plasma response over the entire session and may be more analogous to the end-of-session uOT measure. The correlations between uOT (end-of-session) and pOT (AUC) levels were similar between both conditions (MDMA: $r = 0.56$; INOT: $r = 0.51$), but only significant for the MDMA condition ($p = 0.042$). This suggests that a relationship between the two biological measures might have been observed given a larger sample size during the INOT session. On the other hand, we did find a significant relationship during the INOT session in Study 2, despite a similarly small sample size. It is unclear why we found this discrepancy in INOT results between Study 1 and Study 2. One difference between the two studies is the number of blood draws. In Study 2, we were not able to do more than two independent blood samples. It is very difficult to perform repeated measure blood draws in youths, especially if they have no clinical indication for frequent sampling. Additionally, in Study 2 post-drug administration plasma samples were collected approximately 85 min after drug administration. This may have been after pOT peaked in these participants. However, urine samples were collected at 120 min post administration and may capture the full time window of peripheral OT levels including an earlier peak. In contrast, Study 1 collected urine was collected at 210 min after drug administration. It is possible that the decreased time between pOT and urine OT sample collection in Study 2 may have been more appropriate for detecting associations between uOT and pOT following the relatively small and acute INOT-related change in levels. Overall these findings suggest that future studies examining the relationship between uOT and pOT levels should take into account potential time differences in expression of OT between urine and plasma assays, along with other factors that can affect release and clearance of the hormone.

The primary focus of this paper was to compare measurement alternatives of OT in the periphery when studying OT-related drugs, although Study 2 highlights OT research in ASD rather than a typical or healthy population. Research involving OT has been steadily increasing especially the number of studies investigating the role and treatment potential of OT in disorders such as ASD, schizophrenia, substance dependence and anxiety. Individuals with ASD have been reported to have lower than average blood OT levels in comparison to typically developing controls matched for age (Modahl et al., 1998; Andari et al., 2010), however, these results are not universal and can depend on sex differences and assay methodology (Miller et al., 2013). Higher levels of oxytocin precursor- peptides have also been reported to be expressed in early ASD development with subsequent decrease with age (Green et al., 2001). This complex relationship is of note, as we observed two distinct uOT groups: low INOT responders and high INOT responders (Fig. 3d) in Study 2. This is consistent with previous studies indicating differences in INOT response based on individual characteristics, such as mother-infant attachment representations and social functioning (Bartz et al., 2010, 2011). However, this pattern was not evident in the pOT data for the same participants, thus it is not clear if this group distinction in urine is a true indicator of INOT treatment response. Responder subgroups are of interest because there are a growing number of clinical trials with INOT in ASD and other disorders. Currently, over 100 studies (from clinicaltrials.gov as of April 25, 2016) are exploring the therapeutic value of INOT and it will be helpful to have biological as well as behavioral response measures characterized. Future studies with larger samples will have to confirm if either uOT or pOT levels will serve as biomarkers of any therapeutic response that is targeted.

As research in OT expands, hopefully several potential limitations of our study will be addressed. The two main limitations are sample size and differences in study design. The sample sizes were small, although the within-subjects design decreases between-subject variability. Although the effect sizes for the main analyses from these two studies are large, any results here should be considered preliminary. Large samples will be required to examine factors that can affect OT such as, the natural variability in uOT and pOT levels, sex differences, and age. Due to the total exclusion of female participants (Study 2) or low number (Study 1; 2 female participants), sex differences could not be examined in these studies. In addition, there is evidence that age affects OT levels in ASD samples and this may be related to pubertal status (Hammock et al., 2012). Although the age criteria for Study 2 focused on adolescents and young adults, variability in development may have resulted in mixed pubertal status in the lower age range of our sample. A larger sample with broad ranges of age, development, and pubertal status as well as both sexes will be required to quantify the ranges of individual and group OT differences in healthy as well as clinical populations.

The other main limitation in our study is the difference in study design. These two studies were designed independently, however, both examined the relationship between uOT and pOT levels using identical collection and assay methodology. The design differences cannot be overlooked when discussing variability between the results of INOT administration in the two studies. The primary differences are clinical versus non-clinical participants, age, and formulation of INOT (i.e., Pitocin in Study 1, Syntocinon in Study 2). Even though investigational drug pharmacies in Study 1 and 2 worked to optimize OT delivery at doses that were targeted, nasal spray carrier fluid content and formulations varied.

Finally, these results point to two main future directions. Although there is some preclinical evidence suggesting that INOT produces parallel increases in both the brain and peripheral plasma

of rats (Neumann et al., 2013), it is unclear if these findings translate to humans (e.g., Striepens et al., 2013 found no correspondence between csfOT and pOT following INOT administration in humans, although their dose and sample size was smaller than in our studies). Additionally, given that uOT may be yet another step removed from central OT it is not clear whether uOT concentrations accurately reflect OT levels in the brain within a given time period. Future studies should further examine the relationship between plasma and urine, as well as saliva – another noninvasive assay method that can be performed within or outside of a strict research setting – on a larger varied sample of males and females. It is important to note that saliva is challenging with INOT studies because salivary fluids will pick up exogenously administered OT remaining in the oropharynx and the time course for salivary clearance is yet to be determined. Another future direction is to assess the relationship between peripheral measures of OT and observable social behavior. Although we designed the plasma collection time points to correspond with the behavioral effects of the administered drugs, future studies should explicitly examine the correspondence of social behavior to several biological markers of OT.

5. Conclusion

In conclusion, our present data demonstrate that administration of two drugs (MDMA and INOT) acutely increases peripheral OT. Furthermore, these increases in uOT levels measured as changes from baseline were positively correlated with changes in pOT levels after MDMA administration in healthy adults and INOT administration in adolescent and young adults with ASD, although uOT and pOT measure did not fully overlap. INOT results in a lower magnitude of measurable, peripheral OT and may be influenced by formulation of INOT, dosing, age, or diagnoses of participants. These data suggest that assessing uOT levels may be an additional and useful non-invasive tool to provide insight into the relationship between endogenous OT levels and behavior. When formulating hypotheses and designing experiments, variation of timing of csfOT, pOT, and uOT changes need to be considered especially when studies are evaluating behavioral effects of OT and seeking biomarker correlations. Future research should examine the correspondence between levels of uOT and pOT in other clinical populations, and how each assay relates to observable social behavior.

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Authors' contributions

HdW (Study 1) and SJ (Study 2) were the principal investigators for the studies and coordinated the projects and SJ contributed to OT sample collection and methods for both studies. MGK and HdW contributed to Study 1 design, and SJ designed Study 2 with contributions from SMF. Data collection was performed by MGK (Study 1) and SMF (Study 2). Analyses were performed by SMF, MGK, and SJ. All authors contributed to manuscript preparation, read and approved of the final manuscript.

Conflicts of interest

There are no conflicts of interest for all authors.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2016.08.011.

References

American Psychiatric Association, 2000. Diagnostic and statistical manual of mental disorders, fourth ed text rev. Washington, D.C.

Anagnostou, E., Soorya, L., Brian, J., Dupuis, A., Mankad, D., Smile, S., Jacob, S., 2014. Intranasal oxytocin in the treatment of autism spectrum disorders: a review of literature and early safety and efficacy data in youth. Brain Res. 1580, 188–198.

Andari, E., Duhamel, J.R., Zalla, T., Herbrecht, E., Leboyer, M., Sirigu, A., 2010. Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. Proc. Natl. Acad. Sci. U. S. A. 107, 4389–4394.

Anestis, S.F., 2010. Hormones and social behavior in primates. Evol. Anthropol. Issues News Rev. 19, 66–78.

Bartz, J.A., Zaki, J., Ochsner, K.N., Bolger, N., Kolevzon, A., Ludwig, N., Lydon, J.E., 2010. Effects of oxytocin on recollections of maternal care and closeness. Proc. Natl. Acad. Sci. U. S. A. 107, 21371–21375.

Bartz, J.A., Zaki, J., Bolger, N., Ochsner, K.N., 2011. Social effects of oxytocin in humans: context and person matter. Trends Cogn. Sci. 15, 301–309.

Bedi, G., Phan, K.L., Angstadt, M., de Wit, H., 2009. Effects of MDMA on sociability and neural response to social threat and social reward. Psychopharmacology (Berl.) 207, 73–83.

Bedi, G., Van Dam, N.T., Redman, J., 2010. Ecstasy (MDMA) and high prevalence psychiatric symptomatology: somatic anxiety symptoms are associated with polydrug, not ecstasy, use. J. Psychopharmacol. 24, 233–240.

Bick, J., Dozier, M., 2010. Mothers' and children's concentrations of oxytocin following close, physical interactions with biological and non-biological children. Dev. Psychobiol. 52, 100–107.

Born, J., Lange, T., Kern, W., McGregor, G.P., Bickel, U., Fehm, H.L., 2002. Sniffing neuropeptides: a transnasal approach to the human brain. Nat. Neurosci. 5, 514–516.

Bos, P.A., Panksepp, J., Bluthe, R.M., van Honk, J., 2012. Acute effects of steroid hormones and neuropeptides on human social-emotional behavior: a review of single administration studies. Front. Neuroendocrinol. 33, 17–35.

Broadbear, J.H., Winger, G., Cicero, T.J., Woods, J.H., 1999. Effects of self-administered cocaine on plasma adrenocorticotropic hormone and cortisol in male rhesus monkeys. J. Pharmacol. Exp. Ther. 289, 1641–1647.

Burkett, J.P., Young, L.J., 2012. The behavioral, anatomical and pharmacological parallels between social attachment: love and addiction. Psychopharmacology (Berl.) 224, 1–26.

Carson, D.S., Berquist, S.W., Trujillo, T.H., Garner, J.P., Hannah, S.L., Hyde, S.A., Sumiyoshi, R.D., Jackson, L.P., Moss, J.K., Strehlow, M.C., Cheshier, S.H., Partap, S., Hardan, A.Y., Parker, K.J., 2015. Cerebrospinal fluid and plasma oxytocin concentrations are positively correlated and negatively predict anxiety in children. Mol. Psychiatry 20, 1085–1090.

Carter, C.S., Pournajafi-Nazarloo, H., Kramer, K.M., Ziegler, T.E., White-Traut, R., Bello, D., Schwertz, D., 2007. Oxytocin: behavioral associations and potential as a salivary biomarker. Ann. N. Y. Acad. Sci. 1098, 312–322.

Carter, C.S., Grippo, A.J., Pournajafi-Nazarloo, H., Ruscio, M.G., Porges, S.W., 2008. Oxytocin, vasopressin and sociality. Prog. Brain Res. 170, 331–336.
Christensen, J.C., Shiyanov, P.A., Estepp, J.R., Schlager, J.J., 2014. Lack of association between human plasma oxytocin and interpersonal trust in a Prisoner's dilemma paradigm. PLoS One 9, e116172.
Cyranowski, J.M., Hofkens, T.L., Frank, E., Seltman, H., Cai, H.M., Amico, J.A., 2008. Evidence of dysregulated peripheral oxytocin release among depressed women. Psychosom. Med. 70, 967–975.
Dal Monte, O., Noble, P.L., Turchi, J., Cummins, A., Averbeck, B.B., 2014. CSF and blood oxytocin concentration changes following intranasal delivery in macaque. PLoS One 9, e103677.
Donaldson, Z.R., Young, L.J., 2008. Oxytocin, vasopressin, and the neurogenetics of sociality. Science 322, 900–904.
Dumont, G.J., Sweep, F.C., van der Steen, R., Hermsen, R., Donders, A.R., Touw, D.J., van Gerven, J.M., Buitelaar, J.K., Verkes, R.J., 2009. Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. Soc. Neurosci. 4, 359–366.
Feldman, R., Gordon, I., Schneiderman, I., Weisman, O., Zagoory-Sharon, O., 2010. Natural variations in maternal and paternal care are associated with systematic changes in oxytocin following parent-infant contact. Psychoneuroendocrinology 35, 1133–1141.
Feldman, R., Gordon, I., Zagoory-Sharon, O., 2011. Maternal and paternal plasma, salivary, and urinary oxytocin and parent-infant synchrony: considering stress and affiliation components of human bonding. Dev. Sci. 14, 752–761.
Francis, S.M., Sagar, A., Levin-Decanini, T., Liu, W., Carter, C.S., Jacob, S., 2014. Oxytocin and vasopressin systems in genetic syndromes and neurodevelopmental disorders. Brain Res. 1580, 199–218.
Freeman, S.M., Samineni, S., Allen, P.C., Stockinger, D., Bales, K.L., Hwa, G.G., Roberts, J.A., 2016. Plasma and CSF oxytocin levels after intranasal and intravenous oxytocin in awake macaques. Psychoneuroendocrinology 66, 185–194.
Gossen, A., Hahn, A., Westphal, L., Prinz, S., Schultz, R.T., Grunder, G., Spreckelmeyer, K.N., 2012. Oxytocin plasma concentrations after single intranasal oxytocin administration – a study in healthy men. Neuropeptides 46, 211–215.
Gotham, K., Risi, S., Pickles, A., Lord, C., 2007. The Autism Diagnostic Observation Schedule: revised algorithms for improved diagnostic validity. J. Autism Dev. Disord. 37, 613–627.
Gray, P.B., Parkin, J.C., Samms-Vaughan, M.E., 2007. Hormonal correlates of human paternal interactions: a hospital-based investigation in urban Jamaica. Horm. Behav. 52, 499–507.
Green, L., Fein, D., Modahl, C., Feinstein, C., Waterhouse, L., Morris, M., 2001. Oxytocin and autistic disorder: alterations in peptide forms. Biol. Psychiatry 50, 609–613.
Hammock, E., Veenstra-VanderWeele, J., Yan, Z., Kerr, T.M., Morris, M., Anderson, G.M., Carter, C.S., Cook, E.H., Jacob, S., 2012. Examining autism spectrum disorders by biomarkers: example from the oxytocin and serotonin systems. J. Am. Acad. Child Adolesc. Psychiatry 51, 712–721 (e711).
Heinrichs, M., von Dawans, B., Domes, G., 2009. Oxytocin, vasopressin, and human social behavior. Front. Neuroendocrinol. 30, 548–557.
Hoffman, E.R., Brownley, K.A., Hamer, R.M., Bulik, C.M., 2012. Plasma, salivary, and urinary oxytocin in anorexia nervosa: a pilot study. Eat. Behav. 13, 256–259.
Hughes, J.R., Hatsukami, D., 1986. Signs and symptoms of tobacco withdrawal. Arch. Gen. Psychiatry 43, 289–294.
Hysek, C.M., Domes, G., Liechti, M.E., 2012. MDMA enhances mind reading of positive emotions and impairs mind reading of negative emotions. Psychopharmacology (Berl.) 222, 293–302.
Hysek, C.M., Schmid, Y., Simmler, L.D., Domes, G., Heinrichs, M., Eisenegger, C., Preller, K.H., Quednow, B.B., Liechti, M.E., 2014. MDMA enhances emotional empathy and prosocial behavior. Soc. Cogn. Affect Neurosci. 9, 1645–1652.
Insel, T.R., Young, L.J., 2001. The neurobiology of attachment. Nat. Rev. Neurosci. 2, 129–136.
Jacob, S., Demosthenous, M., Carter, C.S., 2011. Neuropeptide and steroid hormones. In: Fein, A. (Ed.), The Neuropsychology of Autism. Oxford University Press, New York, pp. 451–468.
Kagerbauer, S.M., Martin, J., Schuster, T., Blobner, M., Kochs, E.F., Landgraf, R., 2013. Plasma oxytocin and vasopressin do not predict neuropeptide concentrations in human cerebrospinal fluid. J. Neuroendocrinol. 25, 668–673.
Kirkpatrick, M.G., Francis, S.M., Lee, R., de Wit, H., Jacob, S., 2014a. Plasma oxytocin concentrations following MDMA or intranasal oxytocin in humans. Psychoneuroendocrinology 46, 23–31.
Kirkpatrick, M.G., Lee, R., Wardle, M.C., Jacob, S., de Wit, H., 2014b. Effects of MDMA and Intranasal oxytocin on social and emotional processing. Neuropsychopharmacology 39, 1654–1663.
Lin, L.I., 1989. A concordance correlation coefficient to evaluate reproducibility. Biometrics 45, 255–268.
Lord, C., Rutter, M., DiLavore, P.C., Risi, S., 1999. Autism diagnostic observation schedule (ADOS) Los Angeles, California.
MacDonald, E., Dadds, M.R., Brennan, J.L., Williams, K., Levy, F., Cauchi, A.J., 2011. A review of safety, side-effects and subjective reactions to intranasal oxytocin in human research. Psychoneuroendocrinology 36, 1114–1126.
Macdonald, K., Macdonald, T.M., 2010. The peptide that binds: a systematic review of oxytocin and its prosocial effects in humans. Harv. Rev. Psychiatry 18, 1–21.
McGregor, I.S., Bowen, M.T., 2012. Breaking the loop: oxytocin as a potential treatment for drug addiction. Horm. Behav. 61, 331–339.
McQuaid, R.J., McInnis, O.A., Abizaid, A., Anisman, H., 2014. Making room for oxytocin in understanding depression. Neurosci. Biobehav. Rev. 45, 305–322.
Miller, M., Bales, K.L., Taylor, S.L., Yoon, J., Hostetler, C.M., Carter, C.S., Solomon, M., 2013. Oxytocin and vasopressin in children and adolescents with autism spectrum disorders: sex differences and associations with symptoms. Autism Res. 6, 91–102.
Modahl, C., Green, L., Fein, D., Morris, M., Waterhouse, L., Feinstein, C., Levin, H., 1998. Plasma oxytocin levels in autistic children. Biol. Psychiatry 43, 270–277.
Neumann, I.D., Maloumby, R., Beiderbeck, D.I., Lukas, M., Landgraf, R., 2013. Increased brain and plasma oxytocin after nasal and peripheral administration in rats and mice. Psychoneuroendocrinology 38, 1985–1993.
Parker, K.J., Garner, J.P., Libove, R.A., Hyde, S.A., Hornbeak, K.B., Carson, D.S., Liao, C.P., Phillips, J.M., Hallmayer, J.F., Hardan, A.Y., 2014. Plasma oxytocin concentrations and OXTR polymorphisms predict social impairments in children with and without autism spectrum disorder. Proc. Natl. Acad. Sci. U. S. A. 111, 12258–12263.
Reyes, T.L., Galinsky, A.M., Hoffmann, J.N., You, H.M., Ziegler, T.E., McClintock, M.K., 2014. Social peptides: measuring urinary oxytocin and vasopressin in a home field study of older adults at risk for dehydration. J. Gerontol. B Psychol. Sci. Soc. Sci. 69 (Suppl. 2), S229–237.
Risi, S., Lord, C., Gotham, K., Corsello, C., Chrysler, C., Szatmari, P., Cook Jr., E.H., Leventhal, B.L., Pickles, A., 2006. Combining information from multiple sources in the diagnosis of autism spectrum disorders. J. Am. Acad. Child Adolesc. Psychiatry 45, 1094–1103.
Rutter, M., Le Couteur, A., Lord, C., 2003. Autism diagnostic interview-revised (ADI-R), Los Angeles, California.
Saito, A., Hamada, H., Kikusui, T., Mogi, K., Nagasawa, M., Mitsui, S., Higuchi, T., Hasegawa, T., Hiraki, K., 2014. Urinary oxytocin positively correlates with performance in facial visual search in unmarried males, without specific reaction to infant face. Front. Neurosci. 8, 217.
Schmid, Y., Hysek, C.M., Simmler, L.D., Crockett, M.J., Quednow, B.B., Liechti, M.E., 2014. Differential effects of MDMA and methylphenidate on social cognition. J. Psychopharmacol. 28, 847–856.
Seltzer, L.J., Ziegler, T.E., 2007. Non-invasive measurement of small peptides in the common marmoset (Callithrix jacchus): a radiolabeled clearance study and endogenous excretion under varying social conditions. Horm. Behav. 51, 436–442.
Seltzer, L.J., Ziegler, T.E., Pollak, S.D., 2010. Social vocalizations can release oxytocin in humans. Proc. Biol. Sci. 277, 2661–2666.
Snowdon, C.T., Pieper, B.A., Boe, C.Y., Cronin, K.A., Kurian, A.V., Ziegler, T.E., 2010. Variation in oxytocin is related to variation in affiliative behavior in monogamous, pairbonded tamarins. Horm. Behav. 58, 614–618.
Souza, R.P., de Luca, V., Meltzer, H.Y., Lieberman, J.A., Kennedy, J.L., 2010a. Schizophrenia severity and clozapine treatment outcome association with oxytocinergic genes. Int. J. Neuropsychopharmacol. 13, 793–798.
Souza, R.P., Ismail, P., Meltzer, H.Y., Kennedy, J.L., 2010b. Variants in the oxytocin gene and risk for schizophrenia. Schizophr. Res. 121, 279–280.
Striepens, N., Kendrick, K.M., Hanking, V., Landgraf, R., Wullner, U., Maier, W., Hurlemann, R., 2013. Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans. Sci. Rep. 3, 3440.
Teltsh, O., Kanyas-Sarner, K., Rigbi, A., Greenbaum, L., Lerer, B., Kohn, Y., 2012. Oxytocin and vasopressin genes are significantly associated with schizophrenia in a large Arab-Israeli pedigree. Int. J. Neuropsychopharmacol. 15, 309–319.
Weisman, O., Zagoory-Sharon, O., Schneiderman, I., Gordon, I., Feldman, R., 2013. Plasma oxytocin distributions in a large cohort of women and men and their gender-specific associations with anxiety. Psychoneuroendocrinology 38, 694–701.
White, T.L., Justice, A.J., de Wit, H., 2002. Differential subjective effects of D-amphetamine by gender, hormone levels and menstrual cycle phase. Pharmacol. Biochem. Behav. 73, 729–741.
Wismer Fries, A.B., Ziegler, T.E., Kurian, J.R., Jacoris, S., Pollak, S.D., 2005. Early experience in humans is associated with changes in neuropeptides critical for regulating social behavior. Proc. Natl. Acad. Sci. U. S. A. 102, 17237–17240.
Yuen, K.W., Garner, J.P., Carson, D.S., Keller, J., Lembke, A., Hyde, S.A., Kenna, H.A., Tennakoon, L., Schatzberg, A.F., Parker, K.J., 2014. Plasma oxytocin concentrations are lower in depressed vs healthy control women and are independent of cortisol. J. Psychiatr. Res. 51, 30–36.
Ziegler, T.E., Scheffler, G., Snowdon, C.T., 1995. The relationship of cortisol levels to social environment and reproductive functioning in female cotton-top tamarins, Saguinus oedipus. Horm. Behav. 29, 407–424.