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Publisher Psychology Press

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Social Neuroscience

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title-content=t741771143>

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Online Publication Date: 01 August 2009

To cite this Article Dumont, G. J. H., Sweep, F. C. G. J., van der Steen, R., Hermsen, R., Donders, A. R. T., Touw, D. J., van Gerven, J. M. A., Buitelaar, J. K. and Verkes, R. J. (2009) 'Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration', *Social Neuroscience*, 4:4, 359 — 366

To link to this Article: DOI: 10.1080/17470910802649470

URL: <http://dx.doi.org/10.1080/17470910802649470>

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Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration

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MDMA (3,4-methylenedioxymethamphetamine or “ecstasy”) is a recreationally used drug with remarkable and characteristic prosocial effects. In spite of abundant attention in the scientific literature, the mechanism of its prosocial effects has not been elucidated in humans. Recently, research in animals has suggested that the neuropeptide oxytocin may induce these effects. In a double blind, randomized, crossover, and placebo-controlled study in 15 healthy volunteers we assessed blood oxytocin and MDMA concentrations and subjective prosocial effects after oral administration of 100 mg MDMA or placebo. MDMA induced a robust increase of blood oxytocin concentrations and an increase of subjective prosocial feelings. Within subjects, the variations in these feelings were significantly and positively correlated with variation in oxytocin levels, and the correlations between these feelings and oxytocin were significantly stronger than those between these feelings and blood MDMA levels. MDMA induces oxytocin release in humans, which may be involved in the characteristic prosocial effects of ecstasy.

Keywords: MDMA; Ecstasy; Human; Oxytocin; Social cognition.

INTRODUCTION

Ecstasy (3,4-methylenedioxymethamphetamine (MDMA)) is a street drug, which gained widespread use in the “club” scene (Winstock, Griffiths, & Stewart, 2001). MDMA causes charac-

teristic behavioral effects of increased empathy and friendliness (Vollenweider, Liechti, Gamma, Greer, & Geyer, 2002). These unique prosocial effects led to MDMA being categorized as a separate drug class called “entactogens” (Nichols & Oberlander, 1990), as well as to (calls for)

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This research was supported by a grant of ZonMW (31000062), The Netherlands. We thank Jan Leytens for assistance during the experiments, Richard van Rossen for the MDMA analysis, and Justin Hay for proofreading the manuscript.

The authors have no conflict of interest.

clinical trials investigating the potential for therapeutic use of MDMA in psychiatric disorders (Parrott, 2007; Sessa, 2007; Sessa & Nutt, 2007). Although appropriate social behavior is vital for human health and well-being, as exemplified by many disorders that feature impaired social functioning (such as social phobia, psychopathy, and autism), the neurobiological mechanisms that mediate social behavior remain poorly understood.

A plausible mediator of MDMA's subjective effects is oxytocin, a neurohypophysial nonapeptide, which is synthesized in the supraoptic and the parvoventricular nuclei of the hypothalamus (Gimpl & Fahrenholz, 2001). Oxytocin has received abundant attention for both its peripheral effects (i.e. induction of parturition and lactation) and its role in social behavior. Previous research showed that oxytocin induces prosocial and affiliative behavior in animals as well as in humans (Campbell, 2008; Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Domes, Heinrichs, Michel, Berger, & Herpertz, 2007; Young, 2002; Zak, Stanton, & Ahmadi, 2007). A recent study showed that MDMA induced oxytocin release in rats, an effect that was blocked by 5-HT1a antagonism. MDMA's prosocial effects were attenuated by coadministration of the oxytocin receptor antagonist tocinoic acid, which had no effect on social behavior when given alone (Thompson, Callaghan, Hunt, Cornish, & McGregor, 2007). Other studies reported that high ambient temperature increased both the prosocial effects of MDMA and Fos expression (a marker of gene activation) of oxytocinergic cells in rats, further suggesting a role for oxytocin in the prosocial effects of MDMA (Cornish et al., 2003; Hargreaves, Hunt, Cornish, & McGregor, 2007).

One study assessed whether MDMA induced oxytocin release in humans (Wolff et al., 2006). The authors reported a trend for a small increase of plasma oxytocin concentration in volunteers with positive urine drug screens for MDMA. The results are arguable, however, because of the naturalistic design of this observational study, where subjects were assessed "pre- and post-clubbing", without actual control over drug intake or timing of blood sampling.

The aim of the present, randomized, placebo controlled, cross-over study was to investigate whether MDMA induces oxytocin release in humans.

METHODS AND MATERIALS

Study design

This study utilized a double blind, randomized, crossover, and placebo-controlled design and was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committee. Each volunteer received a capsule containing either MDMA 100 mg or a matched placebo with a washout period of 7 days.

Study outline

Subjects were admitted to each study day after a urinary drug check (opiates, cocaine, benzodiazepines, amphetamines, methamphetamines and delta-9-tetrahydrocannabinol; AccuSign[®], Princeton BioMeditech, Princeton, USA; drug use was not allowed 14 days prior to the first study day until study completion) and the recording of possible signs and symptoms of health problems. A light breakfast was offered. MDMA administration was scheduled at 10:30h. Subjects received a standardized lunch at 14:00h and were sent home at 17:00h. Outcome measures were assessed repeatedly and consisted of blood sampling for MDMA and oxytocin concentration and assessments of subjective effects as specified below. Subjects also performed an extensive cognitive test battery that will be reported elsewhere. To familiarize the subjects with the tests and procedures, subjects performed a practice session within one week before the first study day.

Subjects

Fifteen healthy volunteers (12 male, 3 female), regular users of ecstasy (lifetime drug exposure of 110.5 doses \pm 175.3 mean \pm SD, range 10–702), 18–24 years of age (21.1 \pm 1.7 mean \pm SD) and a body weight of 71.1 kg \pm 8.5 mean \pm SD (range 60–86), were recruited through advertisement on the internet and at local drug testing services. Physical and mental health was determined by assessment of medical history, a physical and ECG examination as well as standard haematological and chemical blood examination. Exclusion criteria included a diagnosis of psychiatric illness (assessed using the Structured Clinical Interview for DSM-IV Axis I disorders, non-patient version

(First, Frances, Pincus, Vettorello, & Davis, 1994), Axis II disorders were excluded using the Temperament and Character Inventory (Svrakic, Whitehead, Przybeck, & Cloninger, 1993) or substance dependence and pregnancy. The study was approved by the local Medical Ethics Committee. All subjects gave their written informed consent before participating in the study, and were paid for their participation. One subject did not refrain from drug use after the first study day; further study participation was denied. The data obtained during this day (MDMA condition) was included in the data analysis. Two subjects experienced mild psychological discomfort (mild anxiety resolving within 60 min) after MDMA administration that resulted in partially missing data.

Study drug

MDMA (or matched placebo) was given as a capsule in a single oral dose of 100 mg. MDMA was obtained from Lipomed AG, Arlesheim, Switzerland and encapsulated according to Good Manufacturing Practice by the Department of Clinical Pharmacy of Radboud University Nijmegen Medical Centre.

Blood sampling

Blood samples were obtained using an indwelling catheter. Blood samples for analysis of oxytocin content were taken at baseline, i.e. before MDMA administration, and 5, 20, 95, 110, 185, 200, 240 and 300 min post drug administration. Blood samples were immediately put on ice and were processed (spun at 1500g for 10 min at 4°C) within 30 min after collection. Blood samples for analysis of MDMA content were taken at baseline and at 15, 60, 105, 150, 240 and 300 min post drug administration. All plasma samples were stored frozen at -80°C until the time of analysis.

Analytical methods

MDMA plasma concentration was assessed by HPLC–diode array detection (HPLC-DAD) (Dumont et al., 2008). Blood oxytocin analysis was performed in serum after prepurification of oxytocin by means of Sep-Pak C18 columns by an in-house radioimmunoassay (RIA) employing ^{125}I -labelled oxytocin and an antibody raised in

rabbits, with sheep anti-rabbit antibodies to separate bound and free radioactivity. The average recovery was $78 \pm 6\%$. Within- and between-assay CVs were 2.2 and 6.6% at 7.2 pmol/l. The analytical range was 1–90 pmol/l with a sensitivity of 1 pmol/l. All reagents were of analytical grade.

Subjective effects

Subjective prosocial effects were assessed at baseline, and 15, 60, 105, 150, 240 and 300 minutes post drug administration using two items of the Bond and Lader (Visual Analogue) Mood Rating Scale (BLMRS) that specifically assess prosocial effects (antagonistic/amicable and withdrawn/gregarious) (Bond, James, & Lader, 1974).

Statistical analyses

Statistical evaluation (two-sided alpha of 0.05) of drug effects on subjective measures (using SPSS 14 for Windows) was performed with a mixed model analysis of variance with drug and time as fixed factors and subject as random factor (with variance components structure). Given the limited number of subjects and the large differences in variation found at different timepoints, it was not possible to formulate adequate mixed effect models for analysis of drug effects on oxytocin levels. Therefore the area under the curve (AUC, determined using the trapezoid rule, $\Sigma_n = (Y_n + Y_{n+1})/2t$, Y being oxytocin concentration per time point, and t the time in minutes per interval) was used to estimate the total amount of oxytocin and this was compared for the different conditions using a paired t -test.

The relationship between subjective feelings and oxytocin or MDMA concentrations was analyzed using a summary-statistics approach. Correlations between each of the subjective parameters and oxytocin or MDMA levels (using individual time points) were determined for each subject. In order to perform the correlation analysis in an equal number of samples, subjective measures were correlated with all MDMA time points, while the correlation with oxytocin was assessed using the time points closest to the MDMA sampling times. Next, using the Wilcoxon signed rank tests with exact p -values, we analyzed whether these correlations were symmetrical around 0 (indicating no relationship between a

subjective feeling and oxytocin or MDMA), and whether the correlations between each subjective parameter and oxytocin or MDMA were equally strong.

RESULTS

MDMA kinetics

The mean maximum plasma MDMA concentrations (C_{max}) were 222.7 $\mu\text{g/l}$ ($SEM = 9.8 \mu\text{g/l}$) 105 min after drug administration. Plasma MDMA concentrations showed a minimal decline and were 174.6 $\mu\text{g/l}$ ($SEM = 10.3 \mu\text{g/l}$) on average at 300 min after drug administration (Figure 1).

Oxytocin kinetics

Plasma oxytocin concentrations (transformed to AUC data) were significantly increased in the MDMA condition compared to placebo, $t(12) = 4.27$, $MSE = 1125.78$, $p = .001$. Mean plasma oxytocin concentrations increased from 0.8 pmol/l ($SEM = 0.3 \text{ pmol/l}$) at baseline to an average maximum concentration of 34.3 pmol/l ($SEM = 7.2 \text{ pmol/l}$) at 110 min after drug administration, and declined thereafter to an average of 4.0 pmol/l ($SEM = 0.8 \text{ pmol/l}$) at 300 min after drug administration (Figure 2). No treatment order effect was found.

Subjective prosocial effects

Subjective amicability showed a significant treatment effect, $F(1, 165) = 9.7$, $p = .002$. Subjective gregariousness showed a significant time effect, $F(6, 162) = 2.6$, $p = .018$. Both subjective amicability and subjective gregariousness showed a significant treatment by time interaction,

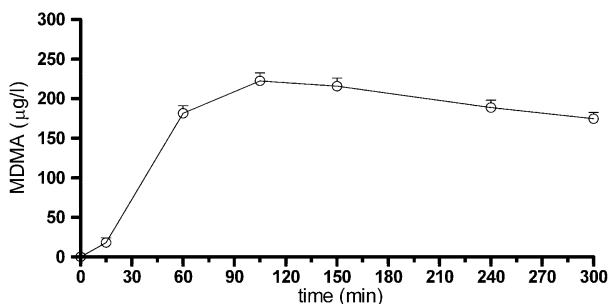


Figure 1. MDMA concentrations in time (mean, SEM).

$F(6, 164) = 3.5$, $p = .003$ and $F(6, 162) = 4.0$, $p = .001$, respectively (see Figure 3). Both subjective amicability and subjective gregariousness showed a significant positive correlation with oxytocin concentrations (median correlation obtained over subjects = 0.37, $p = .001$ and 0.29, $p = .049$ respectively). Subjective amicability was also significantly correlated with MDMA concentrations (median correlation obtained over subjects = 0.23, $p = .049$), but subjective gregariousness was not correlated with MDMA concentrations (median correlation obtained over subjects = 0.23, $p = .46$). Further analysis using the Wilcoxon signed rank tests with exact p -values showed that both subjective amicability and subjective gregariousness were correlated significantly more strongly with oxytocin than with MDMA ($p = .013$ and $p = .030$ respectively).

DISCUSSION

We here show that MDMA robustly increased oxytocin concentrations as well as subjective prosocial effects, and that the increase in prosocial effects correlated stronger with increased blood oxytocin concentrations than with blood MDMA concentrations. These findings tentatively suggest that oxytocin may be involved in the characteristic prosocial effects of MDMA.

A previous study reported a non-significant increase of plasma oxytocin (0.41 pmol/l) in a clubbing population that had positive urine MDMA tests post clubbing (Wolff et al., 2006). Our results show a much stronger effect of MDMA on plasma oxytocin concentration, with an average increase of 34.3 pmol/l and peak levels of 90 pmol/l. The naturalistic basis of the previous study is a likely cause of this discrepancy: Timelines between drug intake and blood sampling were not reported and it is likely that the robust increase of oxytocin concentrations was "missed" due to this study design.

Animal research has previously shown a role for oxytocin in social cognition and affiliative behavior (Campbell, 2007; Lim & Young, 2006). Thompson et al. (2007) confirmed a role for oxytocin in MDMA's prosocial effects in an elegant study where they showed that MDMA administration increased social interaction as well as oxytocin plasma concentrations in male rats. MDMA's prosocial effects were attenuated by coadministration of the oxytocin receptor antagonist tocinoic acid, which had no effect on social

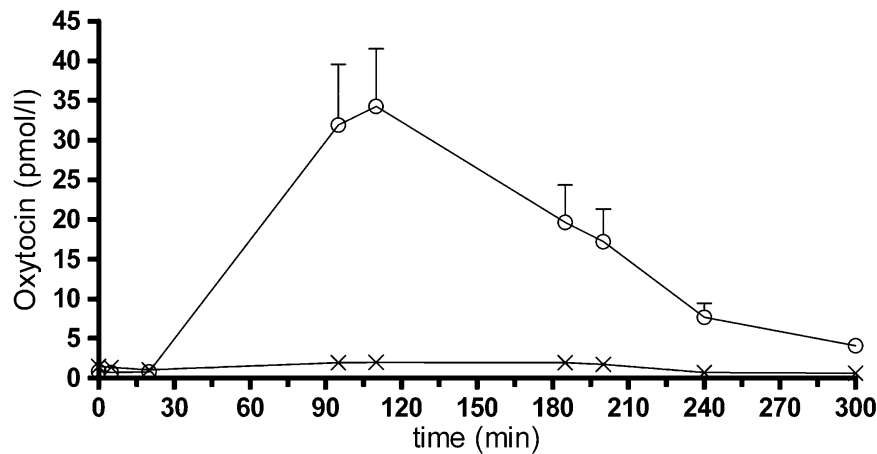


Figure 2. Oxytocin concentrations per condition in time (mean, *SEM*). Oxytocin concentrations were significantly increased in the MDMA condition compared to placebo, $F(1, 12), p = .001$.

behavior when given alone, thus confirming that oxytocin-mediated MDMA induced prosocial behavior. MDMA-induced oxytocin release was

shown to be mediated by the 5-HT_{1A} receptor, since oxytocin concentrations did not increase if administration of MDMA was preceded by

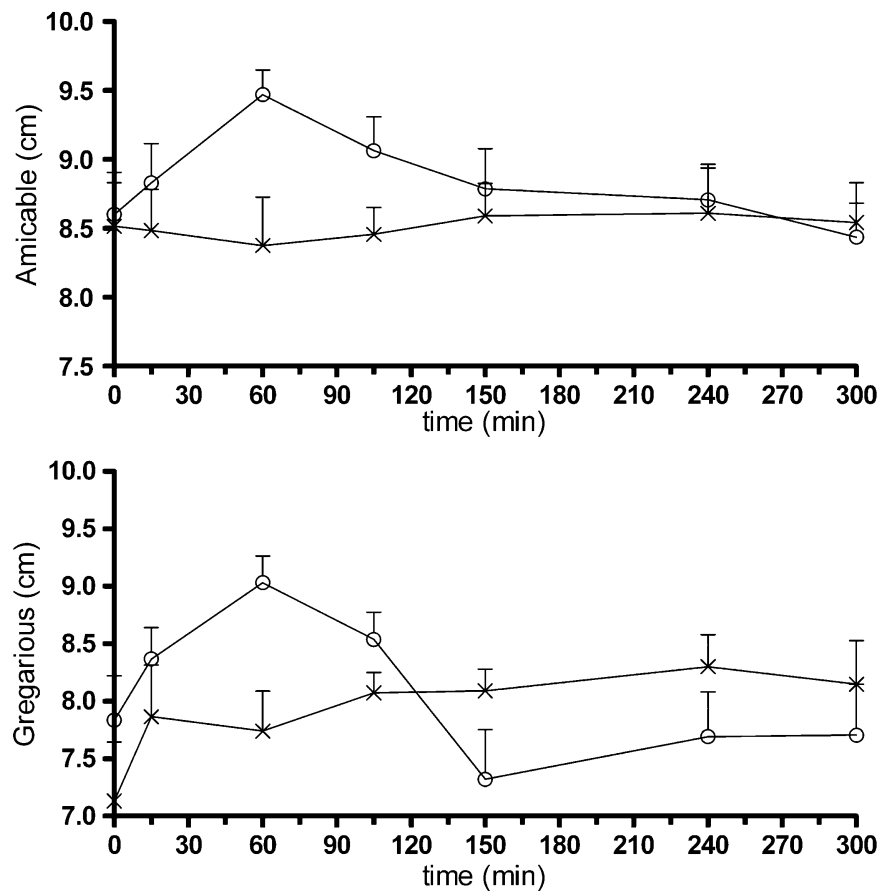


Figure 3. Subjective responses. Top: Subjective amicability per condition (mean, *SEM*). Subjective amicability showed a significant increase in the MDMA condition compared to placebo, Treatment = $F(1, 165) = 9.7, p = .002$; and Treatment \times Time, $F(6, 164) = 3.5, p = .003$. Subjective gregariousness showed a significant time effect. Bottom: Subjective gregariousness per condition (mean, *SEM*). Subjective gregariousness showed a significant increase in the MDMA condition compared to placebo, Time = $F(6, 162) = 2.6, p = .018$, Treatment \times Time, $F(6, 162) = 4.0, p = .001$. Legend: x = placebo, o = MDMA.

administration of a 5-HT1A antagonist (Thompson et al., 2007).

A plausible mechanism of action for oxytocin-mediated prosocial effects was reported in a study that showed that oxytocin attenuates the amygdala response to novel social encounters (Baumgartner et al., 2008). In addition, a recent report demonstrated that attenuation of the amygdala inhibits excitatory flow from the amygdala to brain stem sites mediating peripheral fear response (Huber, Veinante, & Stoop, 2005). For the case of MDMA, oxytocin may thus reduce anxiety related to social interaction, effectively promoting social behavior (Amaral et al., 2003; Rosen & Donley, 2006). When this is combined with its stimulating effects and mild enhancement of sensory input, it is not surprising that MDMA has become such a popular "club drug" (Dumont & Verkes, 2006; Vollenweider et al., 2002).

Although the results of animal research strongly support our conclusions, the findings of the present study should be considered exploratory and some limitations should be addressed.

Firstly, we measured oxytocin concentrations in blood, whereas cerebral spinal fluid oxytocin concentrations are expected to provide a more direct relation to the central effects. Indeed, a delay between maximal subjective effects ($t = 60$ min) and measured peak plasma oxytocin concentration ($t = 110$ min) was observed. Congruent with this finding, several reports have suggested that the release of oxytocin from the posterior pituitary gland into the peripheral circulation is preceded and driven by central, autostimulatory oxytocin release in the paraventricular nucleus and supraoptic nucleus (Ludwig & Leng, 2006; Armstrong, 2007; Amico, Tenicela, Johnston, & Robinson, 1983). However, this remains speculative as the relationship between peripheral and central oxytocin release has not yet been defined (Landgraf & Neumann, 2004).

Secondly, we assessed subjective prosocial effects. Future studies should employ objective measures of social interaction such as the Trust Game or Dictator Game (Sanfey, 2007) to verify that subjects not only perceive themselves as being friendlier but in fact show increased social behavior.

Thirdly, to reduce the variance in observed oxytocin concentrations, future studies should also consider dosing MDMA according to body weight, rather than administering a fixed dose.

Moreover, oxytocin concentrations should be assessed concurrently with MDMA and subjective assessments and between 20 and 95 min, where the current study did not assess oxytocin concentrations but did find the most pronounced subjective prosocial effects, to assess the onset of peripheral oxytocin level elevation and its relation to prosocial effects.

Lastly, although our results suggest that oxytocin is involved in MDMA's prosocial effects in humans, these results remain tentative as the current design cannot determine whether oxytocin really mediated MDMA's prosocial effects. This should be verified in an MDMA interaction study using an oxytocin receptor antagonist such as Atosiban (Uvnas-Moberg, Bruzelius, Alster, & Lundeberg, 1993), although several issues regarding oxytocin receptor antagonism remain (Chini & Manning, 2007).

In summary, we showed that MDMA, a drug with characteristic prosocial effects, robustly induces oxytocin release. The current results tentatively suggest that oxytocin may be involved in the characteristic prosocial effects of MDMA, congruent with previous reports of prosocial effects of oxytocin (Baumgartner et al., 2008; Domes et al., 2007; Guastella, Mitchell, & Dadds, 2008; Kirsch et al., 2005; Zak et al., 2007), and may have implications for diseases that are characterized by impaired social functioning, such as social phobia, psychopathy and autism. Indeed, several reports showed that there may be a link between these diseases and altered oxytocin function (Adolphs, 2003; Guastella et al., 2008; Hammock & Young, 2006; Lerer et al., 2008; McNamara, Borella, Bialowas, & Whitaker-Azmitia, 2008; Talarovicova, Krskova, & Kiss, 2007). Although many issues and questions regarding oxytocin and its effects need to be addressed, this neuropeptide may provide a promising insight into the neurobiology of human social behavior.

Manuscript received 18 September 2008

Manuscript accepted 19 November 2008

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