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RAPID REPORT

A ROLE FOR OXYTOCIN AND 5-HT$_{1A}$ RECEPTORS IN THE PROSOCIAL EFFECTS OF 3,4 METHYLENEDIOXYMETHAMPHETAMINE ("ECSTASY")

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Abstract—The drug 3,4 methylenedioxymethamphetamine (MDMA; ecstasy) has a widely documented ability to increase feelings of love and closeness toward others. The present study investigated whether oxytocin, a neuropeptide involved in affiliative behavior, may play a role in this effect. A moderate (5 mg/kg, i.p.) dose of MDMA increased social interaction in male Wistar rats, primarily by increasing the amount of time rats spent lying adjacent to each other. MDMA (5 mg/kg) activated oxytocin-containing neurons in the supraoptic and paraventricular nuclei of the hypothalamus, as shown by Fos immunohistochemistry. MDMA (5 mg/kg i.p.) also increased plasma oxytocin levels and this effect was prevented by pre-treatment with the 5-HT$_{1A}$ antagonist N-[2-[4-(2-methyoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinylcyclohexanecarboxamide maleate salt (WAY 100,635; 1 mg/kg i.p.). The oxytocin receptor antagonist tocinoic acid (20 μg, i.c.v.) had no effect on social behavior when given alone but significantly attenuated the facilitation of social interaction produced by MDMA (5 mg/kg). The 5-HT$_{1A}$ agonist 8-hydroxy-2-(di-n-propylamino)-tetraline) (8-OH-DPAT, 0.25 mg/kg, i.p.) increased social behavior in a similar way to MDMA and this effect was also significantly attenuated by tocinoic acid. Taken together, these results suggest that oxytocin release, stimulated by MDMA through 5-HT$_{1A}$ receptors, may play a key role in the prosocial effects of MDMA and underlie some of the reinforcing effects of the drug. © 2007 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: MDMA, 5-HT, oxytocin, social behavior, 5-HT$_{1A}$, 8-OH-DPAT.

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Abbreviations: MDMA, 3,4-methylenedioxymethamphetamine; PVN, paraventricular nucleus of the hypothalamus; SON, supraoptic nucleus; TOC/DPAT, tocinoic acid/8-hydroxy-2-(di-n-propylamino)-tetraline; TOC/MDMA, tocinoic acid/3,4-methylenedioxymethamphetamine; TOC/VEH, tocinoic acid/vehicle; VEH/DPAT, vehicle/8-hydroxy-2-(di-n-propylamino)-tetraline; VEH/MDMA, vehicle/3,4-methylenedioxymethamphetamine; VEH/VEH, vehicle/vehicle; WAY/MDMA, WAY 100,635/3,4-methylenedioxymethamphetamine; WAY/VEH, WAY 100,635/vehicle; WAY 100,635, N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinylcyclohexanecarboxamide maleate salt; 8-OH-DPAT, 8-hydroxy-2-(di-n-propylamino)-tetraline.

Widespread use of the illicit drug 3,4-methylenedioxymethamphetamine (MDMA; "ecstasy") is largely attributable to the unique acute psychological effects of the drug. MDMA increases the desire to converse and interact with other people, resulting in increased emotional experiences during social situations (Greer and Tolbert, 1986; Solowij et al., 1992; Vollenweider et al., 1998). Despite MDMA's unique effects and widespread popularity there is surprisingly little information regarding how MDMA acts to increase sociability. In an animal model of this effect, Morley and McGregor (2000) demonstrated that MDMA increased social interaction in Wistar rats meeting for the first time. This was predominantly due to an increase in adjacent lying behavior, where rats lie together for prolonged periods of time. This effect of MDMA was reversed by co-administration of the 5-HT$_{1A}$ receptor antagonist N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinylcyclohexanecarboxamide maleate salt (WAY 100,635) (Morley et al., 2005).

The neuropeptide oxytocin plays a key role in the regulation of social and maternal behavior in many species (Lim and Young, 2006). Interestingly, MDMA stimulates the release of oxytocin from isolated rat hypothalamus (Forsling et al., 2002) and a recent study found that MDMA users tested at a dance party had elevated blood oxytocin concentrations (Wolff et al., 2006). In rats, MDMA activates the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus, where the cell bodies of brain oxytocinergic neurons are located (Stephenson et al., 1999). The magnitude of this SON activation is greater when MDMA is administered at high ambient temperatures (Hargreaves et al., 2007). Interestingly, such temperatures also serve to increase the reinforcing and prosocial effects of MDMA in rats (Cornish et al., 2003).

The PVN and SON contain 5-HT$_{1A}$ receptors and these exert control over oxytocin release. Systemic or intra-hypothalamic administration of the 5-HT$_{1A}$ agonist 8-hydroxy-2-(di-n-propylamino)-tetraline (8-OH-DPAT) facilitates social behavior in rats (Picazo et al., 1995) and increases blood oxytocin levels, without affecting the closely related neuropeptide vasopressin (Jorgensen et al., 2003). Given 5-HT$_{1A}$ receptor involvement in the prosocial effects of MDMA in rats (Morley et al., 2005) and the ability of MDMA to increase oxytocin release, we tested the hypothesis here that oxytocin may be involved in MDMA induced prosocial behaviors

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in rats via indirect stimulation of 5-HT_{1A} receptors. A role for oxytocin in the psychological effects of MDMA has been recently hypothesized by others (Emanuele et al., 2006).

EXPERIMENTAL PROCEDURES

First, we used c-Fos immunohistochemistry to investigate the extent to which a moderate, prosocial dose of MDMA activates oxytocinergic neurons in the SON and PVN. We then determined whether this same dose of MDMA modulated plasma oxytocin levels in rats and whether this effect is mediated by 5-HT_{1A} receptors. Finally, the effect of the oxytocin receptor antagonist tocinoic acid was assessed on the prosocial effects of MDMA and the 5-HT_{1A} agonist 8-OH-DPAT. All experiments were approved by the University of Sydney Animal Ethics Committee and adhered to Australian and international guidelines for the use of experimental animals. The experiments were designed to minimize the number of animals used and their suffering.

The series of experiments reported below involved male Australian Albino Wistar rats housed in a colony at 22 °C with a 12-h light/dark reverse cycle (lights off at 08:00 h). Rats were housed in large tubs in groups of six to eight in experiments 1 and 2 and pair housed in experiments 3 and 4. All behavioral testing was undertaken between 11:00 and 15:00 h. In experiment 1, to determine activation of oxytocin containing cells following MDMA administration, rats (weighing 344±10 g) were injected i.p. with either physiological saline (n=7) or 5 mg/kg of ±MDMA (Australian Government Analytical Laboratories, Pymble, NSW, Australia, n=7). The MDMA was dissolved in 0.9% saline and injected at a volume of 1 ml/kg. Following injection, rats were moved to a "hot room" (ambient temperature of 28 °C) and placed in observation chambers for a period of 80 min. The 28 °C temperature has been previously shown to amplify the prosocial and neural effects of MDMA (Cornish et al., 2003). The rats were well handled and had received extensive habituation sessions in the test chambers. At the end of this period, rats were injected with 120 mg/kg sodium pentobarbital, perfused, and the tissue processed to visualize the Fos protein as previously described (Stephenson et al., 1999; Hargreaves et al., 2007). All tissue was double labeled to visualize oxytocin containing cells (Chemicon, Boronia, VIC, Australia: anti-oxytocin polyclonal antibody diluted 1:5000, catalogue No. AB911). Cell counts for Fos positive and Fos and oxytocin positive neurons were made by an observer blind to group assignment using a graticule and according to the methods previously described (Stephenson et al., 1999). For each rat, bilateral PVN counts were made at two levels of Bregma (−1.40 and −1.80 mm) using a 20× objective, while bilateral counts for SON quantification were made at −1.30 and −1.40 mm using a 40× objective. Counts were then summed over the four regions and averaged to give a single final count for the PVN and SON. The higher magnification was used for counting the SON as this region was too small to fill the graticule at lower magnifications.

In experiment 2, we examined the role of 5-HT_{1A} receptors in MDMA-induced modulation of plasma oxytocin levels in rats. Rats (n=31, weighing 272±5 g) received either a s.c. injection of 1 mg/kg WAY 100,635 (Sigma-Aldrich, Castle Hill, NSW, Australia) (dissolved in 0.9% saline and injected at a concentration of 1 mg/ml) or equivalent saline. This dose of WAY 100,635 was chosen as it attenuated MDMA-induced facilitation of social interaction in male Wistar rats in a previous experiment (Morley et al., 2005). Rats were then moved to a "hot room" (28 °C) and placed in observation chambers to which they had been previously habituated. Ten minutes following WAY 100,635 or vehicle treatment, rats were injected with either MDMA (5 mg/kg, i.p.) or saline. This resulted in four treatment groups: vehicle/vehicle (VEH/VEH n=9), vehicle/3,4-methylenedioxymethamphetamine (VEH/MDMA n=8), WAY 100,635/vehicle (WAY/VEH n=6) and WAY 100,635/3,4-methylenedioxymethamphetamine (WAY/MDMA n=8). Fifteen minutes following the i.p. administration of saline or MDMA, rats were decapitated and trunk blood was collected in heparinized tubes. Samples were placed on ice, centrifuged at 13,200 r.p.m. at 4 °C for 10 min and the plasma was aliquoted into Eppendorf tubes. Plasma oxytocin levels were then immediately measured using an Assay Designs EIA kit (Ann Arbor, MI, Catalogue No. 901-153).

Experiment 3 determined the effect of the oxytocin receptor antagonist tocinoic acid on MDMA-induced facilitation of social interaction. Rats (n=32, weighing 403±8 g), housed in pairs under a reverse 12-h light/dark cycle, were anesthetized and implanted with a cannula in the lateral ventricle (stereotaxic co-ordinates (Paxinos and Watson, 1998)=−0.5 mm posterior to Bregma, 1.5 mm lateral to the midline and 3.5 mm ventral to the surface of the skull). Testing was undertaken a minimum of 1 week following surgery.

On test days, rats received a 1 μl i.c.v. injection of either the oxytocin antagonist tocinoic acid (Sigma-Aldrich) or vehicle (80% saline/20% glycerol). A dose of 20 μg tocinoic acid was used (dose taken from study of Verty et al., 2004). Injections were given 30 min prior to the social interaction test. The rats then received MDMA (5 mg/kg, i.p.) or vehicle 20 min prior to testing. The 5 mg/kg dose has been shown to increase social interaction in previous studies (Morley and McGregor, 2000; Cornish et al., 2003; Morley et al., 2005). This resulted in four treatment groups: VEH/VEH (n=8) VEH/MDMA (n=8) tocinoic acid/vehicle (TOC/VEH: n=8) and tocinoic acid/3,4-methylenedioxymethamphetamine (TOC/MDMA: n=8).

Social interaction tests were conducted as described previously (Cornish et al., 2003; Morley et al., 2005) in a "hot room" (28 °C). Rats of approximately equal weight were placed in the social interaction arena with a novel conspecific from the same treatment group for a 10 min period while social interaction was scored (in an adjacent room via remote video link) by an observer blind to group assignment. The observer scored 3 subtypes of social behavior: adjacent lying, anogenital investigation and general investigation. These were summed to produce a total social interaction score. The non-social behavior of rearing was also scored.

Each rat was tested for social interaction twice, with the same drug treatment given each time, but with a different partner (given the same drug treatment) for each test. A period of 24 h separated the two tests. This provided a final dataset with eight unique pairs of rats per drug condition.

Experiment 4 determined whether the 5-HT_{1A} agonist 8-OH-DPAT had similar prosocial effects to MDMA and whether these effects could also be reversed by co-administration of tocinoic acid. Male Wistar rats (n=24, weighing 468±9 g) underwent the same stereotaxic surgery as described for experiment 3. Again, the rats received either tocinoic acid (20 μg in 1 μl vehicle, i.c.v.) or vehicle (20% glycerol) 30 min prior to the social interaction test. They then received either the 5-HT_{1A} agonist 8-OH-DPAT (Sigma-Aldrich) 0.25 mg/kg i.p. or saline 20 min prior to testing. This again resulted in four different treatment groups: VEH/VEH (n=6) vehicle/8-hydroxy-2-(di-n-propylamino)-tetraline (VEH/DPAT: n=6) TOC/VEH (n=6) and tocinoic acid/8-hydroxy-2-(di-n-propylamino)-tetraline (TOC/DPAT: n=6). The social interaction tests were run exactly as for the previous experiment under hot conditions (28 °C). Again, all rats were tested for social interaction on two separate occasions with different partners but the same drug treatment given on each test. Six days separated the two tests. This provided a final dataset with six unique pairs of rats per drug condition.

For all experiments, one-way ANOVA was used to identify overall group differences. In experiments 3 and 4, results from the first and second social interaction tests were pooled across days before analysis using a one-way ANOVA. When significant overall group effects were observed, Newman-Keuls post hoc tests were used for pairwise comparisons between groups.

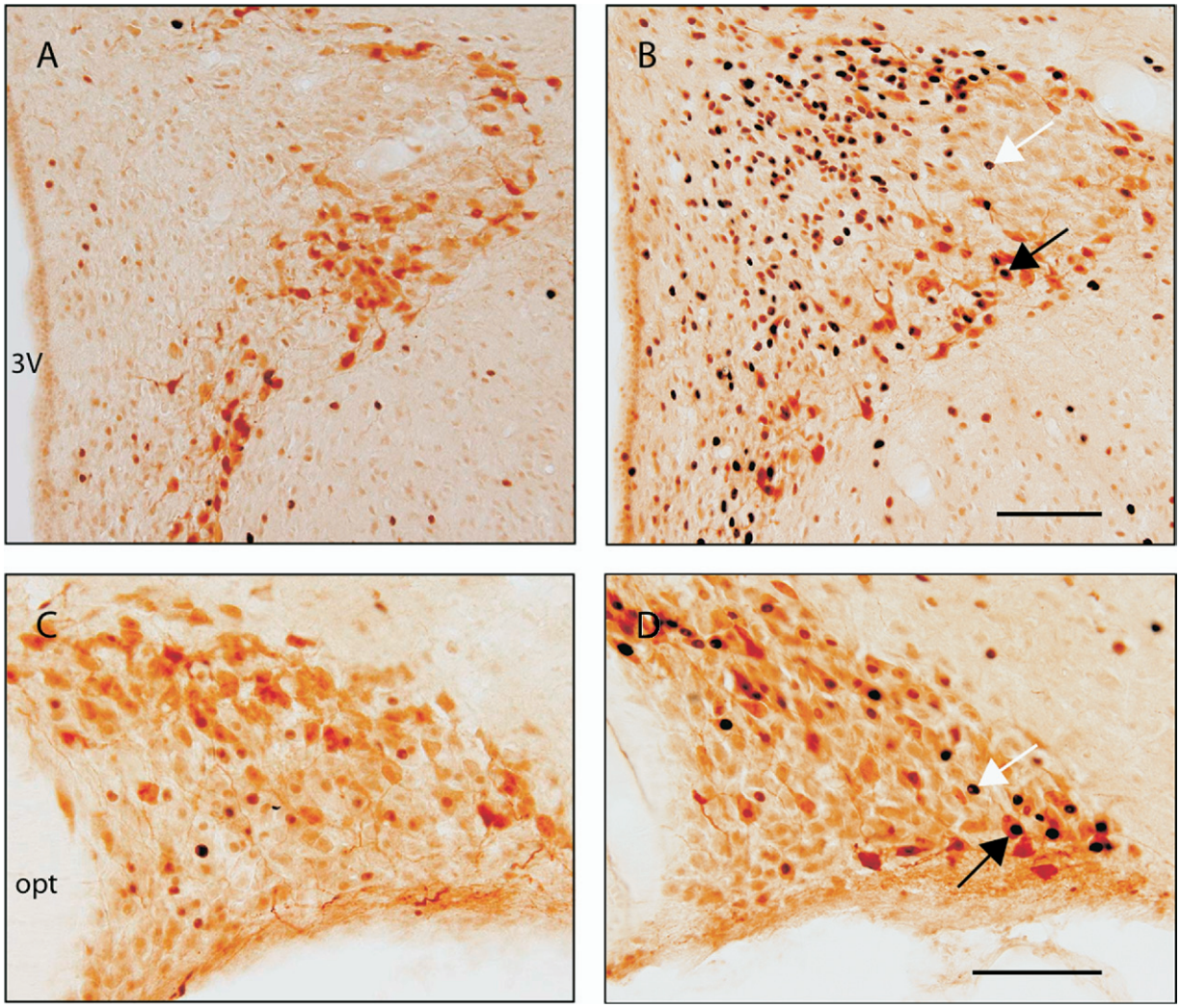

Fig. 1. Representative photomicrographs showing Fos (black, nuclear) and oxytocin (brown, cytoplasmic) labeling in the PVN (A, vehicle; B, MDMA) and the SON (C, vehicle; D, MDMA). White arrows in panels B and D show examples of cells expressing Fos only while the black arrows show examples of double-labeled (Fos and oxytocin) cells. 3V, third ventricle; opt, optic tract. Scale bar=100 μm.

All data were analyzed using Prism 4 for Macintosh (Graphpad Software, San Diego, CA, USA), with significance levels set at 0.05 for all tests.

RESULTS

Experiment 1 revealed that MDMA (5 mg/kg) increased Fos expression in both the SON ($F_{1,12}$=18.40, P<0.01) and PVN ($F_{1,12}$=13.17, P<0.01). Cells double labeled for Fos and oxytocin were also significantly increased by MDMA in the SON ($F_{1,12}$=24.71, P<0.001) and PVN ($F_{1,12}$=18.50, P<0.001) (Fig. 1 and Table 1).

The results of experiment 2 are shown in Fig. 2. A significant overall effect of treatment group was observed ($F_{3,30}$=3.95, P<0.05). Post hoc analysis using Newman-Keuls tests revealed that rats from the VEH/MDMA treatment group had significantly higher plasma oxytocin levels than the VEH/VEH (P<0.05), WAY/VEH (P<0.05) or WAY/MDMA (P<0.05) groups. No other significant between-group differences were observed.

The results of experiment 3 are presented in Table 2. A significant difference between treatment groups was observed in total social interaction ($F_{3,27}$=10.31, P<0.0001), adjacent lying ($F_{3,27}$=27.23, P<0.0001),

Table 1. Average counts for Fos positive and double-labeled (Fos+oxytocin) immunoreactive cells after MDMA (5 mg/kg) administration

Region	Vehicle (n=7)	MDMA (n=7)
Supraoptic nucleus		
Fos only	0.36±0.14	2.18±0.40**
Fos+oxytocin	0.57±0.18	6.18±1.11***
PVN		
Fos only	4.86±2.00	33.04±7.51**
Fos+oxytocin	0.36±0.36	10.84±2.52***

Data represent Mean±S.E.M.
** P<0.01 relative to vehicle group.
*** P<0.001 relative to vehicle group.

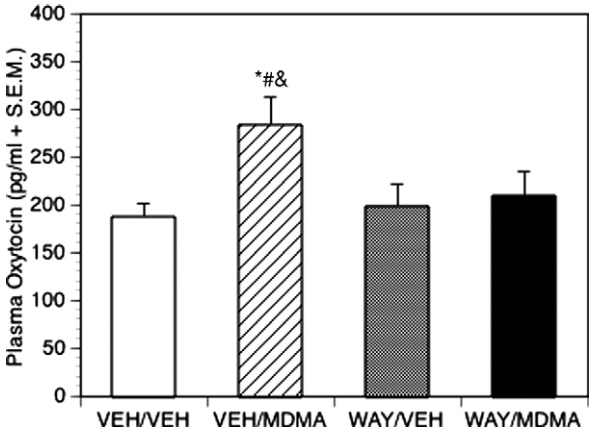

Fig. 2. Effect of MDMA and the 5-HT_{1A} antagonist WAY 100,635 on plasma oxytocin levels. * $P<0.05$ compared with VEH/VEH rats. # $P<0.05$ compared with WAY/VEH rats. & $P<0.05$ compared with WAY/MDMA rats.

anogenital investigation ($F_{3,27}=16.23$, $P<0.0001$) and rearing ($F_{3,27}=25.84$, $P<0.0001$). However no significant treatment effects were observed for general investigation ($F_{3,27}=1.01$, $P>0.05$).

Post hoc Newman-Keuls tests revealed that tocinoic acid attenuated the effects of MDMA on adjacent lying and total social interaction with a significant difference observed between the VEH/MDMA and TOC/MDMA groups on these measures. Tocinoic acid did not modulate MDMA effects on anogenital investigation or rearing. Tocinoic acid itself had no effects on social behavior, with no significant differences between the VEH/VEH and the TOC/VEH groups on any of the behaviors investigated.

The results of experiment 4 are shown in Table 3. A significant difference between treatment groups was observed in total social interaction ($F_{3,20}=4.40$, $P<0.05$), general investigation ($F_{3,20}=3.24$, $P<0.05$), adjacent lying ($F_{3,20}=8.63$, $P<0.001$), anogenital investigation ($F_{3,20}=4.33$, $P<0.05$) and rearing ($F_{3,20}=31.35$, $P<0.0001$). Post hoc analysis revealed that 8-OH-DPAT had very similar effects to MDMA on social behavior, with an increase in total Social Interaction and adjacent lying and a decrease in anogenital investigation and rearing in the VEH/DPAT group relative to the VEH/VEH group.

As with MDMA, tocinoic acid significantly attenuated key effects of 8-OH DPAT on social behavior. Thus, post hoc Newman-Keuls analysis showed a significant difference between the VEH/DPAT and TOC/DPAT groups for adjacent lying ($P<0.05$) and total social interaction ($P<0.05$). Post hoc analysis also revealed that the reduction in anogenital investigation caused by 8-OH-DPAT was not affected by tocinoic acid. Tocinoic acid administration alone had no significant effect, with no difference between the VEH/VEH and TOC/VEH groups on any variables.

DISCUSSION

The current results show a modest dose of MDMA produces clear activation of both the PVN and SON. MDMA predominantly activates oxytocin-labeled cells in the SON with approximately 75% of all Fos-labeled cells in this region also labeled for oxytocin. In contrast, the proportion of activated oxytocinergic cells was not as marked in the PVN, with approximately 25% of all Fos-labeled cells also oxytocin positive. We have recently shown that MDMA-induced Fos induction in the SON is augmented by high ambient temperature to a greater extent than in the PVN and this may account for the higher proportion of double-labeled cells in the SON seen here (Hargreaves et al., 2007). Furthermore, we have observed elevated levels of social interaction when MDMA is administered at high temperatures (Cornish et al., 2003): thus activation of oxytocinergic cells in the SON may be a key mechanism underlying this prosocial effect although further characterization of this process is required.

MDMA at the same modest dose (5 mg/kg) that activates oxytocin positive cells in the PVN and SON, also served to significantly increase plasma oxytocin levels. To the best of our knowledge this is the first report of *in vivo* MDMA-induced oxytocin release in the rat, and is consistent with previous *in vitro* findings (Forsling et al., 2002) and a recent study in human MDMA users at a dance party (Wolff et al., 2006). We also show here that MDMA-induced oxytocin release can be blocked by pretreatment with the 5-$HT_{1A,}$ antagonist WAY 100,635, which as other studies have shown (Vicentic et al., 1998; Galfi et al., 2005) had no effect on plasma oxytocin levels by itself.

The further key finding in the present study is that oxytocin release plays a role in the social behaviors stimulated by both MDMA and 8-OH-DPAT. Thus the oxytocin antagonist tocinoic acid, at doses that did not affect baseline social behaviors, reduced both MDMA and 8-OH-

Table 2. Social behavior following MDMA and/or tocinoic acid

Behavior (s)	VEH/VEH	TOC/VEH	VEH/MDMA	TOC/MDMA
Total social interaction	108.2±3.2	136.1±15.3	194.5±11.4[ab]	123.0±12.1[c]
Adjacent lying	9.6±2.1	13.0±2.3	122.4±15.0[ab]	58±12.2[abc]
General investigation	58.8±6.9	78.7±11.8	70.0±10.9	60.9±3.6
Anogenital investigation	39.8±7.3	44.4±8.5	2.1±1.0[ab]	4.1±2.1[ab]
Rearing	157.1±24.9	136.9±16.7	11.3±2.3[ab]	22.8±8.2[ab]

Data represent mean±S.E.M. for eight pairs of rats per condition. Total social interaction is the sum of the adjacent lying, general investigation, and anogenital investigation.

[a] $P<0.05$ relative to VEH/VEH group.

[b] $P<0.05$ relative to TOC/VEH group.

[c] $P<0.05$ relative to VEH/MDMA group. Student-Newman-Keuls test.

Table 3. Social behavior following 8-OH-DPAT and/or tocinoic acid

Behavior (s)	VEH/VEH	TOC/VEH	VEH/DPAT	TOC/DPAT
Total social interaction	119.0±13.9	130.3±12.4	207.2±26.0[ab]	125.5±23.2[c]
Adjacent lying	47.1±11.4	64.2±7.4	167.1±25.5[ab]	97.4±21.7[c]
General investigation	50.9±3.1	53.4±5.8	34.1±12.2	25.0±6.0[ab]
Anogenital investigation	21.0±5.4	12.8±3.1	6.0±4.1[a]	3.1±1.7[a]
Rearing	190.3±29.1	215.6±12.5	28.8±10.5[ab]	31.2±13.0[ab]

Data represent mean±S.E.M. for six pairs of rats per condition. Total social interaction is the sum of the general investigation, adjacent lying and anogenital investigation.

[a] $P<0.05$ relative to VEH/VEH group.

[b] $P<0.05$ relative to TOC/VEH group.

[c] $P<0.05$ relative to VEH/DPAT group, Student-Newman-Keuls test.

DPAT increases in total social interaction and adjacent lying. Interestingly, a complete reversal of all MDMA and 8-OH-DPAT-induced behaviors was not observed with tocinoic acid. Reductions in anogenital investigation and rearing caused by both drugs were not reversed suggesting a non-oxytocinergic mechanism underlying these behavioral effects of MDMA.

MDMA and 8-OH-DPAT had very similar effects on social interaction with a large increase in adjacent lying and a reduction in general investigation, anogenital investigation and rearing. This is consistent with our previous report that the prosocial effects of MDMA are reversed by pre-treatment with the 5-HT_{1A} antagonist WAY 100,635 (Morley et al., 2005). Previous studies showing facilitatory effects of 8-OH-DPAT on social behavior (for review see File and Seth, 2003) have not explicitly reported on the subtypes of social behavior that are affected by the drug. The present results clearly show that 8-OH-DPAT increases the passive social behavior of adjacent lying, in a similar manner to MDMA.

Taken together the present results suggest a mechanism whereby MDMA stimulates postsynaptic 5-HT_{1A} receptors in the hypothalamus to promote oxytocin release, which then triggers a strong prosocial effect, particularly with respect to adjacent lying behavior. However, important questions remain. Firstly, the key neural circuits involved in the prosocial effects of MDMA remain uncertain: oxytocin released via the PVN and SON affects many key limbic regions involved in emotional and social behavior and MDMA has widespread activating effects at many of these sites (Stephenson et al., 1999; Hargreaves et al., 2007). The present study did not measure central levels of oxytocin following MDMA, although increased central oxytocin levels would also appear likely. However, this hypothesis remains to be tested as the relationship between central and peripheral oxytocin levels is not well understood. SON- and PVN-mediated oxytocin release from the posterior pituitary into the peripheral circulation is unlikely to re-enter the brain, although extensive SON- and PVN-mediated oxytocin release occurs within the brain via somatodendritic mechanisms and via hypothalamic oxytocinergic projections to various brain regions (Landgraf and Neumann, 2004). Future studies will hopefully advance the present findings by identifying MDMA-induced central oxytocin release in key brain regions that regulate social behavior and emotion.

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REFERENCES

Cornish JL, Shahnawaz Z, Thompson MR, Wong S, Morley KC, Hunt GE, McGregor IS (2003) Heat increases 3,4-methylenedioxymethamphetamine self-administration and social effects in rats. Eur J Pharmacol 482:339–341.

Emanuele E, Arra M, Pesenti S (2006) Vasopressin and oxytocin as neurohormonal mediators of MDMA (ecstasy) sociosexual behavioural effects. Med Hypotheses 67:1250–1251.

File SE, Seth P (2003) A review of 25 years of the social interaction test. Eur J Pharmacol 463:35–53.

Forsling ML, Fallon JK, Shah D, Tilbrook GS, Cowan DA, Kicman AT, Hutt AJ (2002) The effect of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") and its metabolites on neurohypophysial hormone release from the isolated rat hypothalamus. Br J Pharmacol 135:649–656.

Galfi M, Radacs M, Juhasz A, Laszlo F, Molnar A, Laszlo FA (2005) Serotonin-induced enhancement of vasopressin and oxytocin secretion in rat neurohypophyseal tissue culture. Regul Pept 127:225–231.

Greer G, Tolbert R (1986) Subjective reports of the effects of MDMA in a clinical setting. J Psychoactive Drugs 18:319–327.

Hargreaves GA, Hunt GE, Cornish JL, McGregor IS (2007) High ambient temperature increases MDMA ("ecstasy")-induced Fos expression in a region specific manner. Neuroscience 145: 764–774.

Jorgensen H, Riis M, Knigge U, Kjaer A, Warberg J (2003) Serotonin receptors involved in vasopressin and oxytocin secretion. J Neuroendocrinol 15:242–249.

Landgraf R, Neumann ID (2004) Vasopressin and oxytocin release within the brain: a dynamic concept of multiple and variable modes of neuropeptide communication. Front Neuroendocrinol 25:150–176.

Lim MM, Young LJ (2006) Neuropeptidergic regulation of affiliative behavior and social bonding in animals. Horm Behav 50:506–517.

Morley KC, Arnold JC, McGregor IS (2005) Serotonin (1A) receptor involvement in acute 3,4-methylenedioxymethamphetamine (MDMA) facilitation of social interaction in the rat. Prog Neuropsychopharmacol Biol Psychiatry 29:648–657.

Morley KC, McGregor IS (2000) (+/−)-3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") increases social interaction in rats. Eur J Pharmacol 408:41–49.

Paxinos G, Watson C (1998) The rat brain in stereotaxic coordinates. New York: Academic Press.

Picazo O, Lopez-Rubalcava C, Fernandez-Guasti A (1995) Anxiolytic effect of the 5-HT1A compounds 8-hydroxy-2-(di-n-propylamino) tetralin and ipsapirone in the social interaction paradigm: evidence of a presynaptic action. Brain Res Bull 37:169–175.

Solowij N, Hall W, Lee N (1992) Recreational MDMA use in Sydney: a profile of "ecstacy" [sic] users and their experiences with the drug. Br J Addict 87:1161–1172.

Stephenson CP, Hunt GE, Topple AN, McGregor IS (1999) The distribution of 3,4-methylenedioxymethamphetamine "ecstasy"-induced c-fos expression in rat brain. Neuroscience 92:1011–1023.

Verty AN, McFarlane JR, McGregor IS, Mallet PE (2004) Evidence for an interaction between CB1 cannabinoid and oxytocin receptors in food and water intake. Neuropharmacology 47:593–603.

Vicentic A, Li Q, Battaglia G, Van de Kar LD (1998) WAY-100635 inhibits 8-OH-DPAT-stimulated oxytocin, ACTH and corticosterone, but not prolactin secretion. Eur J Pharmacol 346:261–266.

Vollenweider FX, Gamma A, Liechti M, Huber T (1998) Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naive healthy volunteers. Neuropsychopharmacology 19:241–251.

Wolff K, Tsapakis EM, Winstock AR, Hartley D, Holt D, Forsling ML, Aitchison KJ (2006) Vasopressin and oxytocin secretion in response to the consumption of ecstasy in a clubbing population. J Psychopharmacol 20:400–410.

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