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Effects of acute doses of prosocial drugs methamphetamine and alcohol on plasma oxytocin levels

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Abstract

Many drugs, including alcohol and stimulants, demonstrably increase sociability and verbal interaction and are recreationally consumed in social settings. One drug, 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”), appears to produce its prosocial effects by increasing plasma oxytocin levels, and the oxytocin system has been implicated in responses to several other drugs of abuse. Here, we sought to investigate the effects of two other “social” drugs on plasma oxytocin levels: methamphetamine and alcohol. Based on their shared capacity to enhance sociability, we hypothesized that both methamphetamine and alcohol would increase plasma oxytocin. In Study 1, 11 healthy adult volunteers attended three sessions during which they received methamphetamine (10mg or 20mg) or placebo under double blind conditions. Subjective drug effects, cardiovascular effects, and plasma oxytocin were measured at regular intervals throughout the sessions. In Study 2, 8 healthy adult volunteers attended a single session during which they received one beverage containing placebo, and then a beverage containing alcohol (0.8 g/kg). Subjective effects, breath alcohol levels, and plasma oxytocin were measured at regular intervals. Both methamphetamine and alcohol produced their expected physiological and subjective effects, but neither drug increased plasma oxytocin levels. The neurobiological mechanisms mediating the prosocial effects of drugs such as alcohol and methamphetamine remain to be identified.

Keywords

methamphetamine; alcohol; oxytocin; social behavior

Introduction

Many drugs, including alcohol and stimulants, are used in social contexts, perhaps because they enhance prosocial behaviors such as social bonding, talking, and empathy.^{1,2} Recent evidence from animal and human laboratories indicates that the club drug 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”) increases central and peripheral

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concentrations of oxytocin, a neuropeptide involved in social bonding and affiliative behavior³⁻⁷. In rats, oxytocin receptor antagonists prevent the prosocial effects of MDMA.³ These observations have led to the suggestion that oxytocin may mediate the drug's acute prosocial effects. Indeed, McGregor and Bowen⁸ take this idea further, proposing that oxytocin-mediated prosocial effects form the basis of the reinforcing effects of many drugs, noting also that oxytocin itself can induce conditioned place preference, a common measure of reinforcement, in animals.⁹ Despite evidence suggesting a role for oxytocin in the acute effects of MDMA in humans,^{6,7,10} it is not known whether oxytocin is involved in producing the prosocial effects of other drugs, such as alcohol or other stimulants.

Both alcohol and methamphetamine increase verbal interaction and other social behaviors.^{1,2,11} Although there is some evidence that chronic methamphetamine or alcohol can have long-lasting effects on oxytocinergic function in the brain in animals,^{12,13} it is not known whether they increase social behavior by increasing oxytocin. To our knowledge, the effects of alcohol on plasma oxytocin levels have only been tested in pregnant and lactating women^{14,15}. In these populations, for whom oxytocin plays an entirely different role in infant bonding, alcohol *decreased* plasma oxytocin levels. With regard to methamphetamine, one small study found no difference in plasma oxytocin levels in methamphetamine users and healthy controls¹⁶. However, the acute effects of the drug on oxytocin levels in humans have not been tested. Here, we examined for the first time the effects of acute doses of methamphetamine and alcohol on plasma oxytocin in healthy young adults.

Methods

Design

Two separate within-subject, placebo-controlled studies were conducted. In Study 1, healthy young adults received single doses of oral methamphetamine (0, 10, 20 mg) in randomized order over three sessions separated by at least 48 hours. In Study 2, participants completed one session, in which they first consumed a placebo beverage and one hour later an alcohol beverage (0.8 g/kg). Plasma oxytocin levels and drug effects were assessed at regular intervals during each session.

Participants

Healthy men and women were recruited via online advertisements, and then completed in-person psychiatric and medical evaluations. Inclusion criteria were a high school education, English fluency, and normal BMI. Exclusion criteria included smoking >10 cigarettes/day, or any significant medical condition or psychiatric illness, including substance dependence. Participants were told that they could receive a stimulant (e.g., methamphetamine), a sedative (e.g., Valium), alcohol or placebo. Both studies were approved by the University of Chicago IRB.

Study 1: N=11 healthy adults (5 men; 22.5±3.7 years). Women not using hormonal contraceptives were tested during the follicular phase (days 2–14) of the menstrual cycle to minimize the impact of hormonal fluctuations. Participants consumed an average of 8.6±9.3

alcoholic drinks/week and 2.2 ± 1.5 servings of caffeine/day. Six participants had used stimulants recreationally in the past, and four had used MDMA.

Study 2: N=8 healthy men (25.5 ± 3.3 years). Participants consumed an average of 17.1 ± 8.1 alcoholic drinks/week and 2.1 ± 0.6 servings of caffeine/day. Seven participants had used stimulants recreationally in the past, and four had used MDMA.

Procedure

Both studies were conducted in the Clinical Resource Center. Participants first provided breath and urine samples to confirm abstinence from alcohol, amphetamine, cocaine, marijuana, and opiates, and women were tested for pregnancy. An intravenous catheter was placed shortly after arrival to collect plasma oxytocin samples.

Study 1: Sessions were conducted between 9am–1:30pm. At 9:30am participants consumed a capsule (0, 10 or 20 mg methamphetamine). Measures of heart rate, blood pressure, plasma oxytocin and subjective effects were obtained at baseline and every 30 minutes post capsule administration. At 1:30pm, participants were discharged provided subjective and cardiovascular drug effects had returned to baseline.

Study 2: Sessions were conducted between 9am–2:30pm. Subjective effects, breath alcohol levels, and plasma oxytocin were obtained at baseline and every 30 minutes throughout the session. Participants were tested in pairs, and consumed a placebo beverage from 9:30–9:45 and an alcohol beverage from 11:00–11:45 am. At 2:30pm, participants were discharged provided they passed a field sobriety test and their breath alcohol levels were below 0.04 g/L.

Physiological measures

For the oxytocin assay, 10 ml blood was drawn into a pre-cooled tube containing disodium EDTA every 30 minutes, six times during each session. Samples were kept on ice and then centrifuged in a refrigerated 4 °C centrifuge (3000 rpm, for 15 min) at a consistent post-draw interval. Oxytocin assays were conducted by Dr. Toni Ziegler at the University of Wisconsin. Samples were analyzed by enzyme immunoassay (EIA) using the Assay Designs EIA kit, which has been validated in humans.¹⁷ In Study 2, breath alcohol level (BAL) was assessed every half hour using the Alco-sensor III (Intoximeters, St. Louis, MO).

Subjective effects

In both studies, participants completed the drug-effect questionnaire (DEQ), a visual analog questionnaire designed to assess the extent to which participants experienced acute drug effects, and visual analog scales consisting of adjectives describing several mood and prosocial effects (e.g., 'I feel sociable') every half hour at six time points throughout the sessions. Each item was presented with a 100-mm line labeled 'not at all' at one end and 'extremely' at the other. At the end of the sessions subjects completed a questionnaire asking what drug they thought they had received.

Study Drugs

Methamphetamine—Methamphetamine hydrochloride (Desoxyn®; 5 mg tablets) was encapsulated in size 00 capsules with dextrose filler. Placebo capsules contained dextrose only. These moderate methamphetamine doses (10, 20 mg) produce reliable behavioral and subjective effects, including increases in social behavior.¹⁸

Alcohol—The 0.8-g/kg alcohol dose was prepared in a 16% solution by volume with 95% alcohol and cranberry juice. The placebo beverage consisted of cranberry juice plus 1% alcohol added to mask the taste. Both beverages were prepared in a volume of 450 ml/70 kg and were divided into equal thirds (i.e., 150 ml/70 kg for each third), administered at 5-min intervals over 15 min. This alcohol dose was chosen because it reliably produces subjective and social effects in moderate alcohol users.¹

Statistical analysis

To characterize the effects of methamphetamine, plasma, subjective, and cardiovascular data were analyzed by calculating area under the curve (AUC) scores for each session. These scores were then compared with repeated measures analyses of variance (ANOVAs) with dose (0, 10, 20 mg methamphetamine) as a within-subject factor.

Similarly, to characterize the effects of alcohol, plasma and subjective data were analyzed by calculating area under the curve scores for the placebo time window (time points 1-3) and alcohol time window (time points 4-6). Placebo and alcohol AUC scores were compared using repeated measures ANOVAs with dose (alcohol versus placebo) as a within-subjects factor. For all analyses, *p* values were considered statistically significant at less than 0.05.

Results

Effects of methamphetamine

Methamphetamine produced its expected effects on cardiovascular and subjective measures. Subjects correctly guessed that they had received a stimulant drug 84% of the time. Methamphetamine dose-dependently increased heart rate (Table 1), and increased self-reported ratings of “Feel Drug” and “Stimulated”. It also tended to increase ratings of “Confident”, “Sociable”, and “Friendly”, though not significantly (Table 1). Methamphetamine did not affect plasma oxytocin levels.

While oxytocin levels were relatively stable in men, women varied markedly on this measure both between and within individuals. Among women, plasma oxytocin levels ranged from 4.3pg/ml to 590 pg/ml, and from 9.6pg/ml to 590pg/ml within one individual across multiple sessions. Most of these variations were not related to drug administration or to cycle phase. In women taking hormonal contraceptives, some of the variability may have been related to the types of hormonal contraceptives used.

Effects of alcohol

Alcohol produced its prototypic effects. It increased breath alcohol concentrations and increased ratings of “Feel Drug” compared to placebo (Table 1). Subjects correctly guessed

which drug they received 81% of the time. Alcohol also slightly increased ratings of “Friendly” and “Sociable”, and “Stimulated” compared to placebo. Alcohol did not alter plasma oxytocin levels.

Discussion

In the present study, both methamphetamine and alcohol produced expected subjective and physiological effects, which included measures of self-reported sociability. Yet, neither drug increased plasma oxytocin levels. These findings contrast with results from studies with MDMA, which increases circulating oxytocin while enhancing social behaviors⁵⁻⁷. Our results suggest the prosocial effects of some drugs may not be mediated by oxytocin.

In this study we failed to detect increases in plasma oxytocin after methamphetamine or alcohol administration, but it is possible that either drug affected central oxytocin levels without altering peripheral levels.¹⁹ Although central optogenetic stimulation increases oxytocin levels both in the brain and periphery in rats,²⁰ central levels of oxytocin are difficult to determine in human subjects. Peripheral oxytocin levels in humans coincide with social behaviors, such as parenting,²¹ suggesting that there is an accordance between circulating levels and behaviors; however, other studies have shown a lack of correspondence between oxytocin measured in the periphery and in the CNS.²² It is difficult, then, to determine whether the peripheral absence of increased oxytocin reflects a similar absence in the brain, and the possibility remains that the social effects of either alcohol or methamphetamine are mediated by central oxytocin.

Other neural mechanisms may generate the prosocial effects of alcohol or stimulant drugs. For example, alcohol may enhance social behaviors through its anxiolytic effects, possibly via GABAergic mechanisms,^{23,24} whereas stimulants such as methylphenidate may alter the HPA axis.²⁵ Alternatively, either drug may produce prosocial effects via the enhancement of dopamine concentrations in the ventral striatum.²⁶ The neural mechanisms underlying the social effects of drugs remain an important topic for future study.

In study 1, we found extreme variability in oxytocin levels among women regardless of methamphetamine administration. It is possible that subtle variations in levels of sex hormones, due to different types of hormonal contraceptives, may have contributed to these observed differences in oxytocin. Both testosterone and estrogen can affect oxytocin availability and receptor densities in the brain.²⁷ In rats, estrogen increases the number of oxytocin receptors in the ventromedial nucleus of the hypothalamus, while progesterone increases receptor densities in estrogen-primed females, but not males.²⁸ Thus, future studies should take into account differences in sex hormone levels.

The studies reported here have several limitations. First, we tested only two methamphetamine doses, and one alcohol dose. It is possible that higher doses of either of these drugs could produce increases in plasma oxytocin comparable to those seen with MDMA. Second, we tested a homogeneous sample of healthy young adults without symptoms of drug dependence. It is also possible that the environment in which the studies were conducted was not conducive to producing an increase in oxytocin. These drugs are

typically consumed in clubs or other social venues, and not in a sterile hospital laboratory. Finally, both studies were conducted with small samples sizes, and larger studies might be needed to detect subtle effects on plasma oxytocin levels.

Despite these limitations, the present results suggest that the prosocial effects of methamphetamine and alcohol may not be mediated by an increase in plasma oxytocin levels. Because numerous studies indicate oxytocin contributes to the prosocial effects of other drugs, such as MDMA, further exploration into the effect of these drugs on endogenous peripheral and central oxytocin is essential. In the future, the use of oxytocin receptor antagonists may allow for a more definitive exploration into the role of this hormone in brain mechanisms of sociability.

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Figure 1. The effects of methamphetamine on measures of a) heart rate, b) ratings of “feel drug”, c) plasma oxytocin, and d) ratings of “stimulated”

Women (N=6) are excluded from c) because extreme variability made the data uninterpretable. Symbols depict mean $\pm$ SEM (N=11). An * indicates significant difference between 20mg and placebo ($p<0.05$; ** = $p<0.001$). A # indicates significant difference between 10mg and placebo ($p<0.05$; ## = $p<0.001$). A + indicates significant difference between 20 mg and 10 mg ($p<0.05$).

Figure 2. The effects of alcohol on measures of a) breath alcohol level, b) ratings of “feel drug”, c) plasma oxytocin, and d) ratings of “sociable”
 One subject was excluded from c) due to extreme variability. Symbols depict mean $\pm$ SEM (N=8).

Table 1

Drug related mean (SEM) physiological and self report ratings calculated as area under the curve after change from baseline

	Study 1					Study 2				
	Placebo		10mg Methamphetamine			20mg Methamphetamine		Alcohol		
	Mean	(SEM)	Mean	(SEM)		Mean	(SEM)	Mean	(SEM)	<i>p</i>
<i>Physiological Measures</i>										
Breath Alcohol Level	-	-	-	-	-	-	-	0.09*	(0.01)	190.440 <0.001
Heart Rate	-4.4	(6.0)	18.6*	(5.0)	19.9*	(5.3)	7.642	0.003	-	-
Plasma Oxytocin	2.0	(4.4)	-7.9	(7.1)	3.8	(5.3)	0.924	0.413	(0.6)	1.581 0.255
<i>Self Report Ratings</i>										
Feel Drug	8.1	(3.5)	46.5*	(10.1)	52.6*	(11.1)	11.748	<0.001	5.7 (2.2)	29.544 <0.001
Friendly	-2.6	(7.2)	-2.5	(6.8)	15.6	(15.1)	1.835	0.186	-2.3 (3.6)	3.071 0.123
Sociable	-2.2	(8.9)	20.1	(7.4)	15.3	(15.7)	1.557	0.235	-4.8 (4.5)	3.493 0.104
Confident	1.1	(5.3)	0.5	(7.1)	22.0	(10.7)	4.223	0.030	-4.3 (3.8)	1.192 0.311
Stimulated	5.1	(7.6)	25.5	(8.7)	42.6*	(13.7)	6.568	0.006	-1.3 (2.0)	3.550 0.102

* Significantly different from placebo