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Modulatory effects of low-dose MDMA on cocaine-induced locomotor activity and place conditioning in rats

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ABSTRACT

Methylenedioxymethamphetamine (MDMA; "Ecstasy") is commonly abused by humans in environments such as nightclubs and rave parties where other drugs of abuse are readily available. Despite the popularity of polysubstance abuse among recreational MDMA users, relatively few controlled experimental studies have documented the neurobehavioral effects of MDMA in combination with other abused substances. This study employed conditioned place preference procedures (CPP) to assess the locomotor activating and place conditioning effects of acute concurrent administration of MDMA (1.5 or 3.0 mg/kg) and cocaine (10 or 20 mg/kg) in rats. Results indicate that low dose MDMA can enhance the locomotor and conditioned rewarding effects of cocaine. These findings may have important implications for understanding the contribution of serotonergic–dopaminergic interactions in the abuse liability of MDMA when used in combination with cocaine or other psychostimulant drugs.

1. Introduction

Recreational use of methylenedioxymethamphetamine (MDMA; "Ecstasy") commonly occurs in dance party or "rave" settings where other drugs of abuse are also readily available. Several studies have documented that recreational MDMA users tend to engage in polysubstance use (Scholey et al., 2004; Wish et al., 2006; Grov et al., 2009), with a particular propensity to use MDMA in combination with other psychostimulants (cocaine, amphetamine, methamphetamine) or the dissociative hallucinogen, ketamine (Grov et al., 2009). Based on an internet survey of experienced MDMA users and nonusers, Scholey et al. (2004) reported that cocaine use was more prevalent among the MDMA users compared to nonusers. In a survey of college students, Wish et al. (2006) found that MDMA users were more likely to have also used other illicit psychoactive drugs, including cocaine, heroin, LSD or other hallucinogens. Employing a time sampling method, Grov et al. (2009) interviewed club-going young adults in New York City between 2004 and 2006 and found that the most frequently used drugs in combination with other illicit substances were cocaine (85.7% of users) and MDMA (86.6% of users).

Despite the apparent prevalence of polysubstance abuse among MDMA users, few controlled experimental studies have investigated the neurobehavioral effects of MDMA in combination with other drugs of abuse. At the present time, preclinical investigations of the combined acute effects of MDMA and cocaine are limited to a few studies (Daza-Losada et al., 2009a; Diller et al., 2007; Panos and Baker, 2010). Although several studies have examined the effects of MDMA pretreatment on the behavioral effects of other drugs, most of these studies utilized relatively high or neurotoxic MDMA doses (e.g., 5, 10, or 20 mg/kg twice a day for 3 to 4 days). MDMA pretreatment enhances cocaine-induced locomotor activation (Kalivas et al., 1998) dopamine release in the nucleus accumbens (Morgan et al., 1997) and conditioned place preference (CPP) established by cocaine (Horan et al., 2000; Cole et al., 2003; Aberg et al., 2007; Daza-Losada et al., 2009b) or morphine (Daza-Losada et al., 2008), but appears to reduce ethanol CPP (Cole et al., 2003).

The acute effects of cocaine and MDMA on psychomotor stimulation and brain dopamine activity are well documented. MDMA has been demonstrated to increase dopamine efflux. The dopaminergic effects of MDMA are reviewed by Colado et al. (2004). Our laboratory has recently demonstrated that low dose MDMA/cocaine combinations produce significant activation of the motor system and greater dopamine release than either drug alone (Panos and Baker, 2010). Until now, the conditioned rewarding effects of low dose combinations of MDMA and cocaine have not been examined. The primary aim of the current study was to assess the locomotor and conditioned rewarding effects of low MDMA doses administered singly and in combination with cocaine in rats.

2. Method

2.1. Subjects

Adult male Sprague–Dawley rats (Charles River, Portage, MI) weighing approximately 175–250 g were used. All rats were housed

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individually throughout the experiment in facilities maintained on a 12 L:12 D cycle (lights on at 0700 h/lights off at 1900 h) and at constant temperature (20 °C) and humidity. Standard rat chow and water were available ad libitum in the home cages. The study protocol was reviewed and approved by the Institutional Animal Care and Use Committee of Western Michigan University.

2.2. Apparatus

The conditioned place preference apparatus consisted of a two-chambered compartment constructed of Plexiglas walls and aluminum and plastic floors. The apparatus was divided into two visually and tactually distinct chambers separated by removable sliding doors. Each chamber was situated within an Accuscan Instruments Versamax Activity Monitoring system (Accuscan Instruments, Columbus, OH). Versamax and Versadat software were used to record and analyze horizontal activity and time spent in each chamber as indexed by infrared sensor interruption.

2.3. Drugs

3,4-methylenedioxymethamphetamine (MDMA) and cocaine-hydrochloride were obtained from the National Institute on Drug Abuse (Rockville, MD). Drugs were dissolved in sterile 0.9% saline and administered by intraperitoneal (I.P.) injections. Doses were determined based on the weight of the salts.

2.4. Procedures

Rats were habituated to the place conditioning apparatus with the sliding doors removed for a 15 min period on two successive days. Habituation data were assessed for side preference prior to commencing place conditioning. Place conditioning trials began the day after habituation day 2 and were conducted one trial per day for six consecutive days (days 3–8). During conditioning trials, the sliding door was closed and rats had access to only one side of the apparatus. A biased procedure was used, such that the side in which each animal spent the least amount of time during habituation was paired with drug and the opposite side was paired with saline. Prior to drug conditioning trials, rats received I.P. injections of cocaine (10 or 20 mg/kg), MDMA (1.5 or 3.0 mg/kg), one of four possible cocaine/MDMA combinations (coc10/MDMA1.5, coc20/MDMA 1.5, coc10/MDMA 3.0, coc20/MDMA 3.0), or saline 5 min prior to being placed in one side of the CPP chambers for 30 min. On days 3, 5 and 7, experimental rats were administered the drug or drug combination paired with one side of the apparatus, on days 4, 6 and 8 rats were administered saline paired with the opposite side. The vehicle control group was administered saline injections on all six conditioning days. Horizontal activity was electronically recorded during conditioning trials. On day 9, rats were given no injections and were placed in the center doorway of the chamber with the sliding door removed. Horizontal activity and the time spent in each chamber of the apparatus were electronically recorded.

2.5. Statistical analysis

Horizontal activity during drug and saline conditioning trials were graphed for visual analysis. Horizontal activity during drug conditioning trials was analyzed using a two-factor repeated measures analysis of variance (ANOVA) with treatment group as a between subjects factor and conditioning trial as a within subjects factor using GraphPad Prism 4.0 (San Diego, CA). Additionally, averages were calculated for the three drug conditioning trials and a one way ANOVA followed by Tukey's multiple comparison tests were conducted to compare the three-day drug averages among the nine treatment groups. CPP test results were expressed as a difference score, which was calculated by subtracting the time spent in the saline-paired compartment from the time spent in the drug-paired compartment. Difference scores were also calculated for horizontal activity during the 15 min CPP test. These data were analyzed using a 3 (MDMA 0, 1.5, 3.0 mg/kg) × 3 (cocaine 0, 10, 20 mg/kg) design in MYSTAT (Systat Software Inc., Chicago IL). Graphical analyses were also conducted on these data to examine any possible trends.

3. Results

Fig. 1A displays horizontal activity during drug conditioning trials (left) and saline conditioning trials (right) for each treatment group. Saline administration produced similar levels of activity among all nine treatment groups, whereas MDMA and cocaine had differential effects on activity. A two factor (treatment group × conditioning trial) repeated measures ANOVA on horizontal activity during drug conditioning trials showed a statistically significant treatment group effect ($F(8, 86) = 11.65$, $p<0.0001$), but there was no statistically significant conditioning trial effect or group × trial interaction. Since there were no statistically or visually evident trends across the three drug conditioning days within treatment groups, averages were calculated for the three drug days and these data were analyzed using a one way ANOVA. These averages are depicted in Fig. 1B. The one way ANOVA on these averages was statistically significant ($F(8, 51) = 11.65$, $p<0.0001$). Tukey's multiple comparison tests on these data indicated that horizontal activity in animals administered either the 1.5 or 3.0 mg/kg dose of MDMA alone was not significantly different from the activity of animals administered saline. Animals administered either the 10 or 20 mg/kg dose of cocaine alone were significantly more active during drug conditioning days than the saline treated animals (COC 10 vs. saline; $p<0.01$; COC20 vs. saline, $p<0.01$). Animals that received COC20/MDMA1.5 ($p<0.001$) or COC20/MDMA3.0 ($p<0.001$) were also significantly more active than saline treated controls, but animals that received COC10/MDMA1.5 or COC10/MDMA3.0 were not significantly more active than saline treated animals or animals that received MDMA alone. Additionally, treatment groups that received COC 10, COC 20, COC20/MDMA 1.5, or COC20/MDMA 3.0 were significantly more active during drug conditioning trials than animals that received MDMA 1.5 alone (COC10 vs. MDMA 1.5, $p<0.05$; COC20 vs. MDMA 1.5, $p<0.01$; COC20/MDMA1.5 vs. MDMA 1.5, $p<0.001$; COC20/MDMA3.0 vs. MDMA 1.5, $p<0.001$). These four treatment groups were also significantly more active than animals that received only MDMA 3.0 during drug conditioning trials (COC10 vs. MDMA 3.0, $p<0.01$; COC20 vs. MDMA 3.0, $p<0.001$; COC20/MDMA1.5 vs. MDMA 3.0, $p<0.001$; COC20/MDMA3.0 vs. MDMA 3.0, $p<0.001$). None of the COC/MDMA combination groups were significantly more active than animals that received either dose of cocaine alone. However, the COC20/MDMA1.5 group was significantly more active than the COC10/MDMA1.5 ($p<0.05$) and the COC10/MDMA3.0 ($p<0.01$).

CPP test results are displayed in Fig. 2 as difference scores derived from time spent in the drug-paired compartment minus time spent in the saline-paired compartment. Neither dose of MDMA increased the amount of time spent on the drug-paired side following conditioning, whereas both cocaine doses induced a preference for the drug-paired side. The difference scores were analyzed using a 3 (MDMA 0, 1.5, 3.0 mg/kg) × 3 (cocaine 0, 10, 20 mg/kg) design. A significant main effect was found for cocaine ($F(2, 43) = 5.508$, $p<0.01$). No significant main effect was found for MDMA or for the MDMA × cocaine interaction. Non-significant trends were visible in the graphic analysis of different treatment groups, with the greatest amount of time spent in the drug-paired side by the COC20/MDMA3.0 treatment group.

Fig. 3 displays the horizontal activity on the test day. These results indicate a change in arousal in the drug-paired contextual environment in a drug-free state. Compared to the saline-treated control group and the MDMA-only treated groups, the cocaine-treated and the MDMA/cocaine combination groups engaged in more activity in the drug-paired chamber. Group differences in the amount of activity

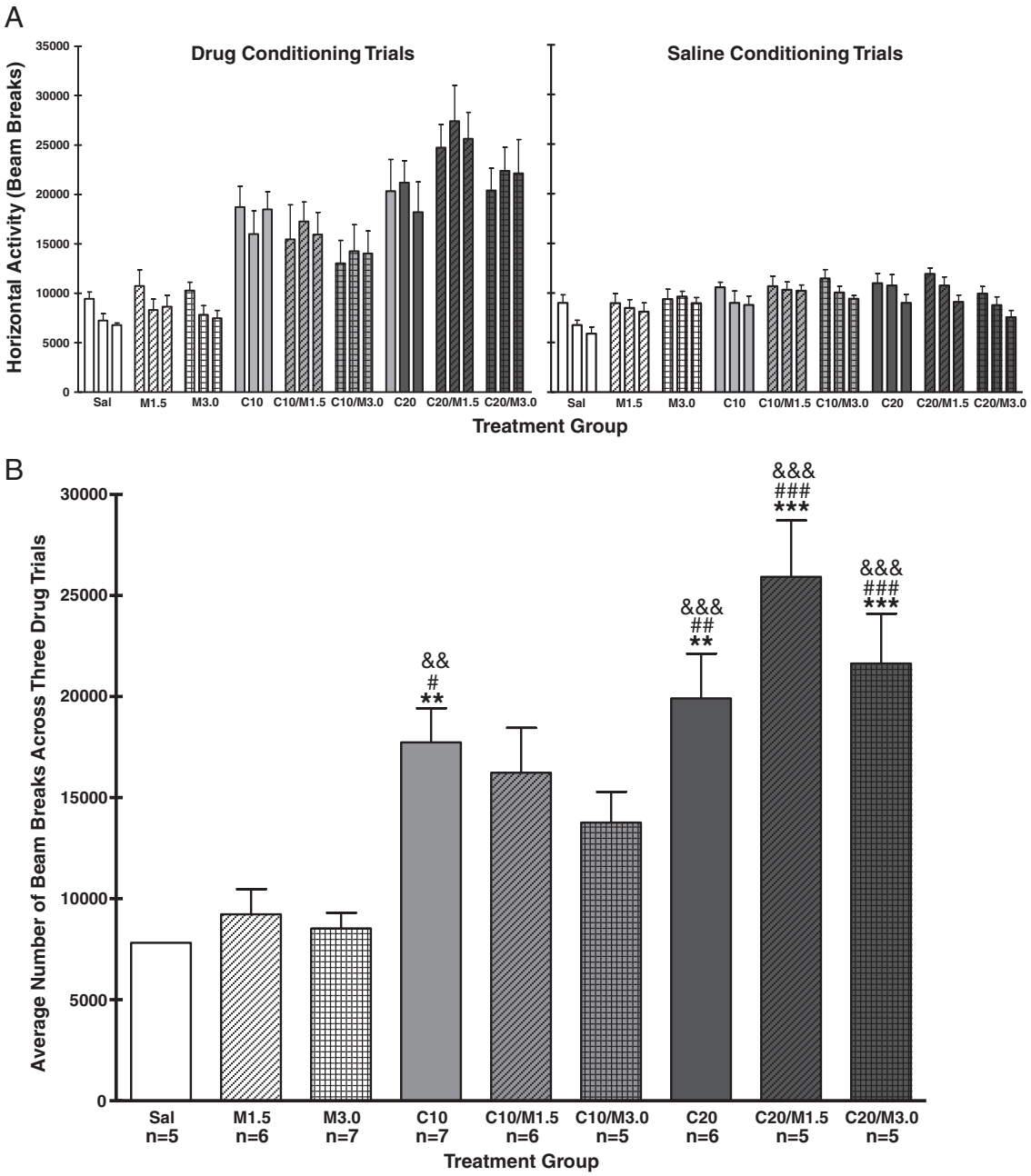

Fig. 1. A) Horizontal activity expressed as number of beam breaks during three 30 min drug conditioning trials (left) and three 30 min saline conditioning trials (right). Bars represent group means (±S.E.M.). B) Average horizontal activity for all three drug conditioning trials. Statistically significant Tukey post-tests are indicated by * for significantly different from saline, # for significantly different from MDMA 1.5 mg/kg, and & for significantly different from MDMA 3.0 mg/kg. (one symbol, $p<0.05$; two symbols, $p<0.01$; three symbols, $p<0.001$).

in the drug-paired side are consistent with the differences observed in time spent in the drug-paired side. A 3×3 analysis of the data in Fig. 3 showed a significant main effect for cocaine ($F(2, 43) = 6.658$, $p<0.005$), but no significant main effect was found for MDMA, nor was there a significant MDMA×cocaine interaction on horizontal activity during the assessment of place preference.

4. Discussion

The current findings indicate that low MDMA doses (1.5, 3.0 mg/kg) have little to no effect on locomotor activity and fail to establish conditioned place preference in adult male Sprague–Dawley rats following three conditioning trials. Although locomotor activity during MDMA conditioning trials was not significantly different from activity levels following saline injections, it should be noted that MDMA is behaviorally active at these low doses in rodents as indicated by numerous reports that rats can be trained to discriminate them from vehicle (Glennon and Higgs, 1992; Baker et al., 1997; Fantegrossi et al., 2009).

While MDMA alone failed to establish CPP, the concurrent administration of 20 mg/kg cocaine and 3.0 mg/kg MDMA showed a non significant trend towards establishing a CPP compared to either of these substances alone. Visual analysis of drug-induced locomotor activity during conditioning trials suggests MDMA may attenuate activity induced by 10 mg/kg cocaine, but enhance the locomotor activating effects of 20 mg/kg cocaine. These findings are consistent with previous reports from our laboratory based on in vivo microdialysis with simultaneous measures of locomotor activity. Using the same dosing regimen as in the present study, we found that concurrent administration

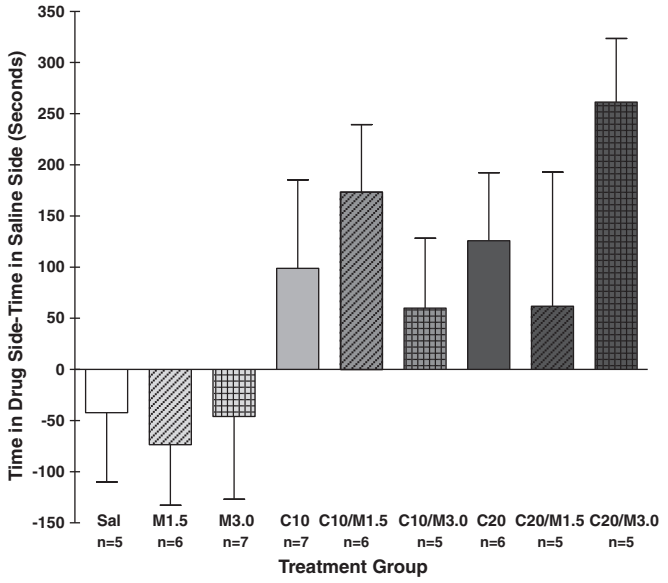

Fig. 2. CPP test results. Difference scores are expressed as time spent in drug-paired chamber minus the time spent in the saline-paired chamber. Bars represent treatment group means (±S.E.M.).

MDMA (3.0 mg/kg) and cocaine (20 mg/kg) enhanced dopamine efflux in the nucleus accumbens and increased locomotor activity to a greater extent than either of these drugs alone (Panos and Baker, 2010).

To our knowledge, the current study is the first to assess the combined acute effects of low dose MDMA and cocaine on place conditioning in rodents, although previous studies have examined the behavioral effects of slightly different dose combinations of these substances. Diller et al. (2007) demonstrated place preference with 5.0 mg/kg MDMA but not with 10.0 mg/kg MDMA. Furthermore, they reported that MDMA suppressed the conditioned rewarding

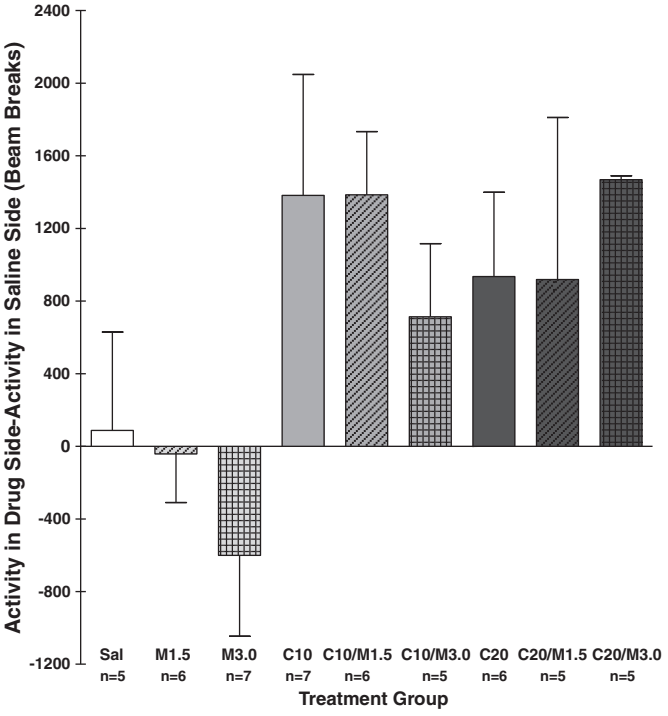

Fig. 3. Horizontal activity during CPP test. Difference scores are expressed as number of beam breaks in the drug-paired chamber minus number of beam breaks in the saline-paired chamber. Bars represent treatment group means (±S.E.M.).

effects of 5.0 mg/kg cocaine. Graphical analyses of the current findings indicate that a lower dose of MDMA (3.0 mg/kg) may enhance the conditioned rewarding effects of higher doses of cocaine (20 mg/kg). Besides different dosing regimens, other methodological differences between the current study and the Diller et al. (2007) study should be noted. They administered S.C. injections of MDMA 25 min prior to I.P. injections of cocaine in order to account for the slow onset of the effects of MDMA in comparison to cocaine (Diller et al., 2007), whereas the current study administered cocaine immediately following MDMA and both drugs were administered by I.P. injection. These methodological differences preclude direct comparisons between the outcomes of these studies.

Daza-Losada et al. (2009a) also assessed the behavioral effects of concurrent MDMA and cocaine administration. They examined the combined acute effects of MDMA (5, 10 or 20 mg/kg) and 25 mg/kg cocaine on locomotor activity, behavior in an elevated plus maze, and social contacts in mice. They reported that both MDMA and cocaine, administered alone or concurrently, produced hyperactivity and a decrease in social contacts, but only those animals administered with the drug combination showed an increase in time spent in open arms of an elevated plus maze.

The above-mentioned studies are the only preclinical assessments of the combined acute effects of MDMA and cocaine to date. Several other studies have examined the effects of MDMA pretreatment on cocaine induced-locomotor activity or CPP. As noted previously, pretreatment with a neurotoxic regimen of MDMA enhances cocaine-induced locomotor activity (Kalivas et al., 1998) and dopamine release in the nucleus accumbens (Morgan et al., 1997). MDMA pretreatment has also been reported to enhance CPP established by cocaine (Horan et al., 2000; Cole et al., 2003; Aberg et al., 2007; Daza-Losada et al., 2009b) or morphine (Daza-Losada et al., 2008) and reduce ethanol-induced CPP (Cole et al., 2003). Only the study by Aberg et al. (2007) examined pretreatment with low doses of MDMA. They compared the effects of MDMA pretreatment (2 or 5 mg/kg daily for 7 days) on cocaine CPP in adolescent and adult rats. Their results indicated that MDMA increased cocaine conditioned reward in adolescent rats, but decreased it in adult rats.

It is well established that psychostimulants exert their actions via a common dopaminergic pathway (Wise, 1978; Bozarth, 1986; Pierce and Kumaresan, 2006) and these actions are presumably important in mediating the neurobehavioral effects responsible for establishing conditioned place preference. Cocaine (Pettit et al., 1990; Zocchi et al., 2003; Panos and Baker, 2010) and MDMA (Koch and Galloway, 1997; Kankaanpaa et al., 1998; Bankson and Yamamoto, 2004) have both been shown to increase extracellular dopamine (DA) in the nucleus accumbens (NAc). Cocaine exerts its actions primarily through blocking DA re-uptake and increasing extracellular DA levels in the nucleus accumbens shell (David et al., 1998). MDMA acts at nerve terminals to modulate release and re-uptake mechanisms of DA and 5-HT (Bankson and Yamamoto, 2004). Furthermore, MDMA-induced NAc DA release appears to be modulated by 5-HT (Koch and Galloway, 1997; Fillip and Cunningham, 2002). Acute MDMA administration increases the release of both DA and 5-HT in awake-behaving rats (Gough et al., 1991; Hiramatsu and Cho, 1990; Kankaanpaa et al., 1998; Yamamoto and Spanos, 1988). Microdialysis studies have also shown that both systemic and local injections of cocaine increase synaptic 5-HT in the NAc (Teneud et al., 1996).

Ball and Rebec (2005) demonstrated a modulatory effect of 5-$HT_{2B/2C}$ receptors on striatal DA by 5 mg/kg MDMA. It has been suggested that the attenuation of DA release by the activation of 5-$HT_{2B/2C}$ receptors is mediated by ventral tegmental area (VTA) GABA (Bankson and Yamamoto, 2004). Furthermore, it has been hypothesized that increased 5-HT release may activate 5-HT_{2c} receptors to suppress the psychomotor effects of cocaine (Burmeister et al., 2004). Others have suggested that the suppression of the psychomotor effects by MDMA may be negated after DA efflux reaches a

threshold (Fletcher et al., 2006). Together with the reports from previous studies regarding the involvement of 5-HT_{2c} receptor activation on DA efflux (Broderick et al., 2004; Sasaki-Adams and Kelley, 2001; Yamamoto et al., 1995), the current locomotor activity findings appear to be consistent with 5-HT modulation of DA. With respect to establishing MDMA/cocaine-induced conditioned reward, expanded dose response profiles may be required along with substantially more subjects included in the design. Moreover, future studies targeting the activities of 5-HT_{2a} and 5-HT_{2c} receptors, either through pharmacological or genetic manipulations, may further elucidate significance of the current findings. Determining the importance of these receptor subtypes may have important implications for understanding the contribution of serotonergic–dopaminergic interactions in the abuse liability of MDMA when used in combination with cocaine or other psychostimulant drugs.

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