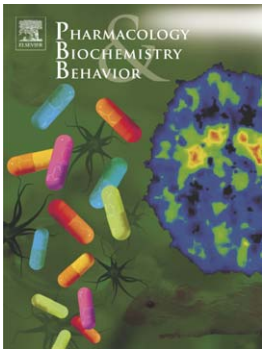

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PII: S0091-3057(16)30101-0
DOI: doi: 10.1016/j.pbb.2016.06.002
Reference: PBB 72371

To appear in: *Pharmacology, Biochemistry and Behavior*

Received date: 29 February 2016
Revised date: 24 May 2016
Accepted date: 1 June 2016

Please cite this article as: Schenk Susan, Foote Jason, Aronsen Dane, Bukholt Natasha, Highgate Quenten, Van de Wetering Ross, Webster Jeremy, Serotonin antagonists fail to alter MDMA self-administration in rats, *Pharmacology, Biochemistry and Behavior* (2016), doi: 10.1016/j.pbb.2016.06.002

Serotonin antagonists fail to alter MDMA self-administration in rats

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Abstract

Acute exposure to ±3,4-methylenedioxymethamphetamine (MDMA) preferentially increases release of serotonin (5-HT), and a role of 5-HT in many of the behavioral effects of acute exposure to MDMA has been demonstrated. A role of 5-HT in MDMA self-administration in rats has not, however, been adequately determined. Therefore, the present study measured the effect of pharmacological manipulation of some 5-HT receptor subtypes on self-administration of MDMA. Rats received extensive experience with self-administered MDMA prior to tests with 5-HT ligands. Doses of the 5-HT_{1A} antagonist, WAY 100635 (0.1-1.0 mg/kg), 5-HT_{1B} antagonist, GR 127935 (1.0-3.0 mg/kg), and the 5-HT_{2A} antagonist, ketanserin (1.0-3.0 mg/kg) that have previously been shown to decrease self-administration of other psychostimulants and that decreased MDMA-produced hyperactivity in the present study did not alter MDMA self-administration. Experimenter-administered injections of MDMA (10.0 mg/kg, ip) reinstated extinguished drug-taking behaviour, but this also was not decreased by any of the antagonists. In contrast, both WAY 100635 and ketanserin, but not GR 127935, decreased cocaine-produced drug seeking in rats that had been trained to self-administered cocaine. The 5-HT_{1A} agonist, 8-OH-DPAT (0.1-1.0 mg/kg), but not the 5-$HT_{1B/1A}$ agonist, RU 24969 (0.3-3.0 mg/kg), decreased drug-seeking produced by the reintroduction of a light stimulus that had been paired with self-administered MDMA infusions. These findings suggest a limited role of activation of 5-HT_{1A}, 5-HT_{1B} or 5-HT_2 receptor mechanisms in MDMA self-administration or in MDMA-produced drug-seeking following extinction. The data suggest, however, that 5-HT_{1A} agonists inhibit cue-induced drug-seeking following extinction of MDMA self-administration and might, therefore, be useful adjuncts to therapies to limit relapse to MDMA use.

Introduction

The principle psychoactive component of "Ecstasy", or "Molly", is ±3,4-methylenedioxymethamphetamine (MDMA), an amphetamine analogue that is being used recreationally by young people across the globe. Several studies have documented a dependence syndrome in some users, based on DSM IV criteria (Degenhardt et al., 2010, Cottler et al., 2009). In the more recent DSM V, many symptoms that are used to define a substance use disorder (SUD) also apply to some "ecstasy" users (Parrott, 2013);(Hopper et al., 2006); (Cottler et al., 2009, Yen and Hsu, 2007); (Yen and Hsu, 2007, Parrott, 2005, Kirkpatrick et al., 2014, Peroutka et al., 1988, McKetin et al., 2014).

The potential to develop an SUD might appear to be somewhat of a puzzle given the pharmacology of MDMA. MDMA preferentially increases synaptic serotonin (5-HT), and produces smaller increases in synaptic dopamine (DA) (Green et al., 2003). It is well-accepted that DAergic mechanisms mediate the positive effects of drugs of abuse (Di Chiara and Imperato, 1988). In contrast, selective 5-HT uptake inhibitors (Lichtigfeld and Gillman, 1998) are not abused and the releasing stimulant fenfluramine did not maintain self-administration in rats trained to self-administer amphetamine (Gotestam and Andersson, 1975). Further, the reinforcing potency of amphetamine analogues was negatively correlated with affinity for the 5-HT transporter (Ritz and Kuhar, 1989). Increasing synaptic 5-HT by addition of the releasing stimulant, fenfluramine, decreased amphetamine self-administration by primates (Wee and Woolverton, 2006) supporting the idea that 5-HT releasing stimulants are not reinforcing and also that non-selective activation of 5-HT receptors is inhibitory to psychostimulant-produced reward. Why then, do some ecstasy users develop an SUD?

There is substantial evidence of alterations in 5-HT and DA neurochemistry following repeated exposure to MDMA, and we have suggested that some of these underlie the development of MDMA self-administration and drug-seeking, consistent with an SUD (Schenk, 2011). In particular, the density of 5-HT transporters was decreased in ecstasy users (McCann et al., 2008) and in rats and non-human primates that were exposed to MDMA (Ricaurte et al., 2000, Schenk et al., 2007). MDMA, like other psychostimulant drugs of abuse, increased DA preferentially in the shell of the nucleus accumbens in rats (Cadoni et al., 2005) and this neurochemical effect became sensitized following repeated exposure (Kalivas et al., 1998). Acute exposure to MDMA produced hyperactivity that also became sensitized following repeated exposure (Bradbury et al., 2012, Schenk and Bradbury, 2015, Ball et al., 2009) even in 5-HT transporter knock-out rats (Lizarraga et al., 2014). The locomotor activating effects of MDMA have been shown to be dependent upon

DA activation (Daniela et al., 2004), and we have shown cross-sensitization to hyperlocomotion produced by amphetamine or the DA $D_{2/3}$ agonist, quinpirole, following repeated exposure to MDMA (Bradbury et al., 2012).

The acute effects of MDMA have been attributed to both 5-HT and DA mechanisms (McCreary et al., 1999, Ball and Rebec, 2005) but the reinforcing effects have often been attributed to DAergic effects (Tancer and Johanson, 2003, Liechti et al., 2000, Johanson et al., 2006, Kirkpatrick et al., 2012). Consistent with the idea that the positive effects of MDMA are mediated by dopaminergic mechanisms, MDMA self-administration (Daniela et al., 2004) and drug-seeking (Schenk et al., 2011), were attenuated by pretreatment with DA antagonists. Importantly, extinguished drug-taking behavior was reinstated following extensive exposure to MDMA self-administration in rats was produced by DAergic, but not 5-HTergic, direct and indirect agonists (Schenk et al., 2011). All of these studies point to a prominent role of DA in the maintenance of MDMA-taking and drug-seeking but a potential role of 5-HT has not been adequately addressed. The reinforcing effects of other drugs and drug-seeking following extinction of self-administration of other drugs are often decreased by selective 5-HT agonists as well as antagonists (Burmeister et al., 2004, Ruedi-Bettschen et al., 2015, Nic Dhonnchadha et al., 2009, Neisewander and Acosta, 2007, Peltier and Schenk, 1993). Therefore, the present study optimized conditions for observing decreases in MDMA self-administration and reinstatement of drug-seeking following administration of some 5-HT agonists and antagonists.

Methods

Animals

All procedures were approved by the Animal Ethics Committee of Victoria University of Wellington. Male Sprague-Dawley rats bred at Victoria University of Wellington, New Zealand were used for testing. They were housed 4 to a cage in hanging polycarbonate cages until weights of 300 gm were achieved (2 – 3 months) at which time they were housed in isolation for 7 days before experimental procedures commenced. The colony room was temperature- (19-21 ºC) and humidity- (55%) controlled and maintained on a 12-hour day-night cycle, with the light cycle commencing at 0700 hr. Self-administration testing took place within the light cycle, between 10:00 and 4:00 each day and locomotor activity testing took place between 10:00 and 2:00. Food and water were available *ad libitum* except during the testing sessions.

Apparatus

Self-administration testing was conducted in standard operant chambers equipped with two levers (Med Associated Inc, USA; model ENV-001). Responses on the active lever resulted in a

100 µl infusion of MDMA delivered over a period of 12 seconds and the concurrent illumination of a light located above the lever. Responses on the inactive lever were recorded but produced no programmed consequence. A 20 ml syringe housed in a mechanical pump (Med Associated Inc, USA; model – PHM-100A) was connected through a swivel apparatus to a length of microbore tubing that was connected to the exposed portion of the intravenous catheter. Drug delivery and data acquisition were controlled by Med PC software. Testing was conducted within a temperature- (19-21^{o}C) and humidity- (55%) controlled dark room. Once weekly, catheters were infused with sodium pentobarbital (20.0 mg/kg, iv). An immediate loss of the righting reflex confirmed patency.

Procedures

Surgery. Deep anesthesia was produced by an intraperitoneal injection of a solution combining ketamine (90.0 mg/kg, PhoenixPharm, Auckland, New Zealand) and xylazine (9.0 mg/kg, Provet, Palmerston North, New Zealand) followed by a subcutaneous (sc) injection of the anti-inflammatory analgesic, Carprofen (5mg/kg, Pfizer Animal Health, Auckland, New Zealand). The jugular vein was isolated, the anterior end was tied off with a length of surgical suture, and a silastic catheter was inserted. The distal end of the catheter was attached to a length of 22 ga stainless steel tubing which was threaded subcutaneously and mounted on the scalp using four jeweler's screws embedded in dental acrylic. Post-surgical care consisted of administration of Hartmann's solution (2 × 6 mL, sc) to restore electrolyte balance. For two days following surgery daily Carprofen injections (5.0 mg/kg, sc) were administered. The catheter was flushed daily with 0.2 ml of sterile 0.9% saline solution containing heparin (30 IU/ml) and penicillin (250 000 IU/ml) to prevent blood coagulation and infection.

Acquisition of self-administration. Every session began with an experimenter-delivered infusion of drug to clear the line of the saline solution. Thereafter, each depression of the active lever resulted in an automatic infusion of MDMA (1.0 mg/kg per infusion) or cocaine (0.5 mg/kg/infusion) paired with the illumination of a stimulus light located directly above the active lever.

Initial training for MDMA self-administration consisted of daily 2 hr sessions during which lever presses were reinforced with MDMA infusions (1.0 mg/kg) according to an FR1 schedule. This initial phase continued until a total of 90.0 infusions had been self-administered, or 25 test sessions, whichever came first. Rats that failed to meet this initial criterion (about 50%, as per our previous studies (Schenk, 2012, Schenk et al., 2011) were not tested further. For those that met the criterion (n=45), the dose of MDMA was decreased to 0.5 mg/kg until an additional 520

infusions had been delivered (total of 350.0 mg/kg). The reinforcement schedule was then increased to FR2 for a minimum of 5 days and then FR5 for at least 7 days prior to further testing. Separate groups of rats were then randomly assigned to determine the effects of 5-HT ligands on either MDMA-self-administration or reinstatement of drug-seeking. Cocaine self-administration proceeded in the same manner except that the dose of 0.5 mg/kg/infusion was available throughout the training period (n=16).

Self-administration tests. Effects of the 5-HT_{1A} antagonist, WAY 100635 (0.0, 0.1, 0.3 or 1.0 mg/kg, sc; n=5), the 5-HT_{1B} antagonist, GR 127935 (0.0, 1.0 or 3.0 mg/kg, sc; n=5) or the 5-HT_{2A} antagonist, ketanserin (0.0, 1.0 or 3.0 mg/kg, ip; n=4) on MDMA self-administration (0.5 mg/kg/infusion) were determined in separate groups of rats during a recurring series of 2 hr daily tests. This dose of MDMA was chosen because it produces a moderate level of responding; lower doses led to increased responding and higher doses led to decreased responding (Schenk et al., 2003). Therefore, both increases and decreases in responding maintained by MDMA and produced by the various drugs would be expected to be observed following administration of effective antagonists. Between the tests of effects of the individual doses there was at least 2 days of self-administration. Tests of each dose occurred once there was less than 20% variability in responses during these baseline tests. Separate groups were tested with each of the antagonists. All rats within each test drug group received all doses of the test drug, administered in random order. GR 127935 (n=5) was administered 30 minutes prior to the session, WAY 100635(n=5) was administered 15 min prior to the session and ketanserin (n=4) was administered immediately prior to the session.

Reinstatement of extinguished drug-taking behavior. Daily sessions were increased to 6 hr for some additional groups of rats. Drug-seeking tests were conducted during a recurring series comprising baseline (Phase 1; FR5), extinction (ext; Phase 2), and reinstatement (Phase 3) phases, as previously reported (Schenk et al., 2008; 2011). Phase 1 consisted of at least two days of responding that was reinforced according to an FR5 schedule by an infusion of MDMA or cocaine (0.5 mg/kg/infusion) and the illumination of the drug-associated light stimulus. Once there was less than 20% variability in responding, Phase 2 commenced. During Phase 2, the drug solution was replaced with vehicle (3U heparinized saline) and the light stimulus that had been paired with self-administered infusions was omitted. Once less than 20% of baseline responding was produced for 2 consecutive days, Phase 3 commenced. During this phase, responding maintained by infusions of the vehicle and the light stimulus during the ensuing 6-hr session was measured. To

determine whether 5-HT antagonists would decrease the potentiated drug-seeking response produced by MDMA, WAY 100635 (0.0, 0.1, 0.3, 1.0mg/kg, sc; n=8), GR 127935 (0.0, 1.0, 3.0mg/kg, sc; n=7) or ketanserin (0, 1.0 or 3.0 mg/kg, ip; n=8) were administered to separate groups of rats prior to an injection of MDMA (10.0 mg/kg, ip). Separate groups of rats were tested with each of the antagonists and all rats in each group received all doses of each drug, administered in random order.

To determine whether the antagonists would decrease cocaine-produced cocaine-seeking, groups of rats that received cocaine self-administration were tested in a manner identical to testing of the MDMA-trained groups. Separate groups of rats received WAY 100635 (n=6), GR 127935 (n=5) or ketanserin (n=5) prior to an injection of cocaine (10.0 mg/kg, IP). As with the MDMA-trained groups, all rats in each group received all doses of each drug, administered in random order.

To determine whether selective 5-HT agonists would decrease MDMA-seeking, different groups received the 5-$HT_{1B/1A}$ agonist, RU 24969 (0.0, 0.3, 1.0, 3.0mg/kg, sc, n=4), or the 5-HT_{1A} agonist, 8-OH-DPAT (0.0, 0.1, 0.3, 1.0mg/kg, sc, n=4), 15 min prior to the start of Phase 3.

Locomotor activity testing. In order to ensure that the doses used in the MDMA self-administration and drug-seeking experiments were behaviorally relevant and to get an indication of time-course for the effects of the antagonists, effects on MDMA-produced hyperactivity were measured. Separate groups of rats (n=6-8) received WAY 100635 (0.0 or 1.0 mg/kg) immediately prior to being placed in the activity chambers, GR 127935 (0.0 or 3.0 mg/kg) 15 min after being placed in the activity chambers and ketanserin (0.0 or 3.0 mg/kg) 30 min after being placed in the activity chambers. MDMA (10.0 mg/kg, IP) was administered 30 min after WAY 100635, 15 min after GR 127935 and immediately after ketanserin. Locomotor activity was measured for the 30 min prior to, and 60 min following, the MDMA injection.

Statistical analysis

Data were analyzed using repeated measures ANOVAs using SPSS version 20. Significance was set at $p<0.05$. The effects of each of the antagonists on responding maintained by MDMA were determined using separate 2-way repeated measures ANOVAs on lever responses (Dose antagonist X Lever). Effects of the various drugs on reinstatement of extinguished drug-taking behavior were measured using 2-way repeated measures ANOVAs on lever responses (Dose Antagonist/Agonist X Lever).

Materials

All antagonists were obtained from Tocris Bioscience, NZ. GR 127935, dissolved in distilled water, was administered 30 minutes prior to the test, WAY 100635, dissolved in saline, was administered 15 min prior to the test and ketanserin, dissolved in saline, and was administered immediately prior to the test. RU 24969 and 8-OH-DPAT, dissolved in saline, were administered 15 min prior to the MDMA injection during drug-seeking tests. +/- MDMA HCl and cocaine HCl, dissolved in 3U heperanized saline for self-administration and in saline for IP injections, were obtained from ESR (Porirua, NZ)

Results

Figure 1 shows the effect of various doses of the antagonists on responding maintained by 0.5 mg/kg MDMA reinforced according to the FR5 schedule of reinforcement. During these 2 hr tests, MDMA-maintained responding was high whereas inactive lever responding was low. Separate 2-way repeated measures ANOVA on data from each of the antagonists revealed significant main effects of lever (WAY 100635, $F(1,4) = 99.77$); GR 127935, $F(1,3) = 35.769$; ketanserin, $F(1,3) = 129.74$) but failed to reveal any significant effect of drug dose or a significant interaction between drug dose and lever.

Figure 2 shows the effects of the antagonists on reinstatement of drug-taking behavior following extinction of MDMA self-administration. Responding was high during the baseline self-administration tests (FR5) and decreased during the extinction trials (ext). MDMA (10.0 mg/kg) reinstated extinguished responding (0.0 dose for each drug condition), as we have previously reported (Schenk et al., 2011). ANOVAs on the responses produced following pretreatment with the antagonists failed to reveal any significant effect of the pretreatment on MDMA-produced drug-seeking.

Figure 3 shows the effects of the antagonists on drug-seeking following extinction of cocaine self-administration. Responding was high during the baseline self-administration tests (FR5) and decreased during the extinction trials (ext). Cocaine reinstated extinguished responding (0.0 dose for each drug condition), as we have previously reported (Schenk, 2000). ANOVAs on the responses produced following pretreatment with the antagonists revealed a significant interaction between Lever and WAY 100635 Dose ($F(1,5) = 7.393$). There was a significant decrease in active lever responses following administration of 1.0 mg/kg. There was a main effect of ketanserin Dose ($F(1,4)=7.916$) and the active lever responses following both 1.0 and 3.0 mg/kg were significantly decreased. There was no effect of GR 127935 Dose or an interaction between Lever and GR 127935 Dose.

Figure 4 shows the average number of responses during extinction for the 8 rats that subsequently received the 5-HT agonists, 8 OHDPAT and RU 24969. During extinction testing neither the light stimulus or MDMA infusions reinforced lever pressing and during the drug-seeking test, responses were reinforced by the presentation of the light stimulus that had been paired with self-administered infusions and a vehicle infusion (0.0 mg/kg). Reintroduction of the light stimulus produced drug-seeking, as indicated by a significant increase in responding relative to the extinction day. There was a significant interaction between Test Day (ext versus 0.0 mg/kg) and lever ($F(1,7) = 8.954$), and post-hoc tests confirmed that active lever responding increased when the light stimulus was reintroduced.

Figure 5 shows the effects of the 5-HT agonists, RU 24969 and 8-OH-DPAT, on drug-seeking produced by the light stimulus that had been paired with MDMA infusions. 8-OH-DPAT, but not RU 24969, significantly decreased the reinstatement of drug-seeking produced by the light stimulus.

Figure 6 shows the effect of the highest dose of the antagonists used in the self-administration experiments on MDMA-produced hyperactivity. All of the antagonists decreased this response to MDMA. ANOVA on the data from the WAY 100635 groups revealed main effects of Time ($F(11,154) = 4.923$) and Dose ($F(1,14) = 40.318$) but no interaction. ANOVA on the data from the GR 127935 groups revealed main effects of Time ($F(11,132)=3.889$), Dose ($F(1,12)=6.766$) and an interaction ($F(11,132)=3.629$). Tukey post-hoc tests revealed a significant decrease in MDMA-produced hyperactivity from 35 min following the MDMA injection. ANOVA on the data from the ketanserin groups revealed a main effect of Dose ($F(1,13)=5.322$), Time ($F(11,143)=5.943$) and an interaction ($F(11,143)=4.689$). Post hoc tests confirmed a significant decrease in MDMA-produced hyperactivity from 25 min following the MDMA injection.

Discussion

Results show that 5-HT_{1A}, 5-$HT_{1B,}$ or 5-HT_{2A} receptor antagonists failed to alter the maintenance of MDMA self-administration. Interpretation of drug effects on self-administration of a single dose of a drug can be problematic, particularly if the dose used is at either the high or low end of the dose-response curve. Because a moderate dose of MDMA was used for self-administration, both increases and decreases in responding would have been observable. Thus, it is unlikely that the use of a single dose precluded the ability to observe changes in responding.

The antagonists also failed to decrease the potentiated drug-seeking response produced by a priming injection of MDMA. Reinstatement of extinguished drug-taking behavior produced by a priming injection of MDMA was not altered by the 5-HT_{1A} antagonist, WAY 100635, the 5-HT_{1B} antagonist, GR 127935 or the 5-HT_{2A} antagonist, ketanserin. Doses of the antagonists used were pharmacologically effective, attenuated other drug-produced behaviors (Aronsen et al., 2014) and attenuated MDMA-produced hyperactivity (present results). Some of the antagonists also decreased cocaine-produced drug-seeking (present results). Therefore, it is unlikely that the failure to alter drug-seeking was due to inadequate dosing.

It is possible that the failure to observe effects of the serotonin antagonists on MDMA-produced drug-seeking reflects differences in the elimination half-life. Thus, if the antagonist half-life was substantially shorter than the half-life of MDMA, a potential effect might have been obscured due to the long (6 hr) sessions. Unfortunately, time course data for the reinstatement tests that would directly assess this possibility were not available. Of importance, however, the elimination half-life of ketanserin and GR127935 are long (Persson et al., 1987, Skingle et al., 1996) compared to the half-life of MDMA (Kalant, 2001), and doses of each drug were high, suggesting that if a decrease in drug-seeking was produced, it would have been observed even when total responding during the 6 hr session was measured. The elimination half-life of WAY 100635 is, however, quite short (Zuideveld et al., 2002) relative to MDMA which raises the possibility that the failure to observe an effect of this drug was due to pharmacokinetic factors. This possibility is unlikely, however, since the elimination half-life of SCH 23390 (Bourne, 2001) and eticlopride (Norman et al., 2011) are also short relative to MDMA and both of these drugs significantly attenuated MDMA-produced reinstatement of drug-seeking (Schenk et al., 2011).

We have suggested that MDMA self-administration and drug-seeking following extinction of responding is due to a decrease in MDMA-produced 5-HT and an increase in MDMA-produced DA (Schenk, 2011). In our studies that have examined maintenance of MDMA self-administration, we have provided extensive self-administration experience to the rats that meet an initial criterion. This extensive experience produced decreases in tissue levels of 5-HT (Do and Schenk, 2013) and decreased 5-HT transporter binding (Schenk et al., 2007). In our experience, drug-seeking is not produced without extensive experience with self-administered MDMA, an effect also indicated in results from another laboratory (Ball et al., 2007). Thus, we suggest that the deficits in 5-HT are a necessary prerequisite to both the development of reliable and high levels of MDMA self-administration and for drug-seeking following extinction of responding (Schenk, 2011).

It is noteworthy that responding maintained by the rats in our studies generally reaches about 15-30 mg/kg in a 2 hr session, as in the present study, but this is achieved only following an extended acquisition period, and only in a subset of rats. Results from other laboratories generally indicate more modest MDMA self-administration, although results from Dalley's laboratory (Dalley et al., 2007) indicated self-administration that was comparable to rates achieved during the same protocol of amphetamine self-administration. Other studies have tended to report that MDMA is a less efficacious reinforcer than most other psychostimulant drugs. While the basis for the differences across laboratories is not understood, they might reflect procedural variables. For example, our studies employ a relatively long infusion interval of 12 sec, whereas many others employ an infusion interval typically of 4 sec or less (Dalley et al., 2007, Ball et al., 2007). Many studies also employ a time-out period of up to 30 sec following an infusion to prevent accidental overdose (Vandewater et al., 2015, Ball et al., 2007) or limit the number of MDMA infusions (Dalley et al., 2007). In our studies we do not have a time-out. Our studies persist for up to 25 days during acquisition and then for additional days of maintenance to bring total exposure up to at least 350 mg/kg prior to tests of agonists/antagonists whereas most others are conducted for much shorter periods (Reveron et al., 2010, De La Garza et al., 2007, Aarde et al., 2015, Ball and Slane, 2014, Ball and Slane, 2012). The impact of these differences is not currently known but, as discussed by De la Garza (De La Garza et al., 2007), they might not be trivial. A further examination of the impact of these variables on the acquisition and maintenance of MDMA self-administration would help to determine what the differences across laboratories might be attributed to.

Our previous study showed that 5-HT_2 agonists, DOI, mCPP failed to alter drug-seeking and that the uptake inhibitor, clomipramine, decreased drug-seeking following extinction of MDMA self-administration (Schenk et al., 2011). The failure of the selective 5-HT_2 antagonist, ketanserin, to decrease MDMA-produced drug-seeking is consistent with the idea that this receptor mechanism is not critical for this behavioral effect of MDMA. These findings were extended in the present study and the 5-HT agonist, 8-OH-DPAT, but not RU 24969, decreased drug-seeking produced by reintroduction of the light stimulus that had been paired with MDMA infusions. On the basis of these findings, it might have been expected that the 5-HT antagonist, WAY 100635, would have increased MDMA-produced drug-seeking. Because the dose of MDMA used in this study was relatively high (10.0 mg/kg), a potentiated response might not have been observed due to a ceiling effect (Schenk et al., 2008). Alternatively, the failure to observe an

effect of the antagonists might reflect differential effects of 5-HT agonists and antagonists on DA release.

DAergic mechanisms of MDMA self-administration and drug-seeking have been demonstrated. For example, DA antagonists decreased MDMA-produced drug-seeking (Brennan et al., 2009) and self-administration (Daniela et al., 2004) and direct and indirect DA agonists potentiated drug-seeking produced by reintroduction of the light stimulus that had been paired with self-administered MDMA infusions (Schenk et al., 2011). An interaction between 5-HT_1 and DA mechanisms might underlie the decrease in drug-seeking produced following 5-HT_1 agonists, since these drugs have been reported to decrease DA overflow produced by psychostimulants, whereas the antagonists are generally ineffective in altering psychostimulant-produced increases in DA (Hayes and Greenshaw, 2011, Muller and Homberg, 2015).

Other studies have indicated a role of some 5-HT receptor mechanisms in drug self-administration. For example, 5-HT_{1B} antagonists dose-dependently decreased cocaine- and amphetamine-self-administration (Miszkiel and Przegalinski, 2013), 8 OHDPAT decreased cocaine self-administration (Peltier and Schenk, 1993) and WAY 100635 and ketanserin attenuated some aspects of drug-seeking (Burmeister et al., 2004) (present results). In rhesus monkeys self-administration of S(+) or R(-) MDMA was attenuated following administration of some doses of ketanserin or MDL100907, but the magnitude of the effect was much greater for self-administration of the R(-) isomer (Fantegrossi et al., 2002). These findings might reflect the higher affinity of the S(+) enantiomer for the DA transporter (Steele et al., 1987). Unfortunately, effects on self-administration of racemic MDMA were not obtained. In monkeys trained to self-administer amphetamine, +/- MDMA also reinstated extinguished responding and this effect was attenuated by fluoxetine, suggesting an important role of the 5-HT transporter in these effects (McClung et al., 2010). It would be interesting to determine whether the more selective 5-HT compounds similarly impacted this effect of MDMA in primates.

Drug-self-administration procedures are widely used to determine neurobiological mechanisms that underlie compulsive drug-taking so that effective pharmacotherapies can be developed. In many studies, 5-HT manipulations have been demonstrated as effective in decreasing either self-administration and/or drug-seeking and, on the basis of these findings, it has been suggested that selective ligands might be useful therapeutic interventions (Cunningham and Anastasio, 2014, Howell and Cunningham, 2015, Paris and Cunningham, 1992). The present findings fail to support the idea that 5-$HT_{1A,}$ 5-HT_{1B} or 5-HT_{2A} antagonists would be effective therapeutics for MDMA dependence. Rather, the data support the idea that some serotonin

agonists might be more useful in the treatment of drug-seeking elicited by exposure to cues that had been associated with self-administered MDMA.

Acknowledgements

The authors gratefully acknowledge the technical assistance of Michael Roberts. Funding for these studies was provided by the School of Psychology at Victoria University of Wellington and by a grant from the Wellington Medical Research Foundation.

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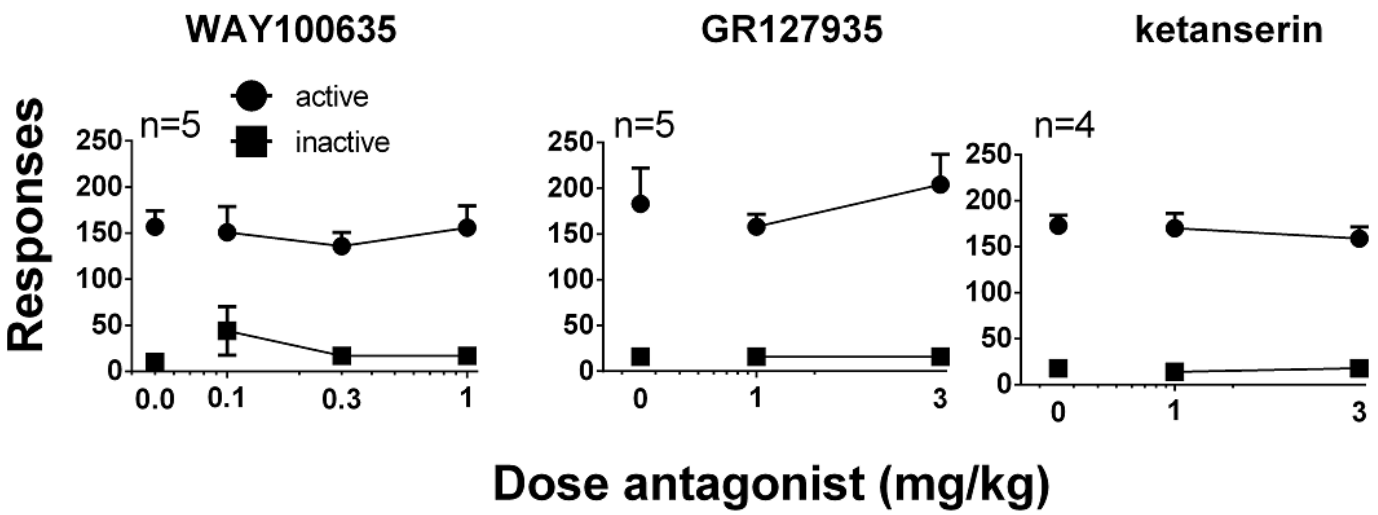

Figure 1 Effect of 5-HT antagonists on MDMA (0.5 mg/kg/infusion) self-administration. Symbols represent mean responses (+SEM) reinforced according to an FR5 schedule.

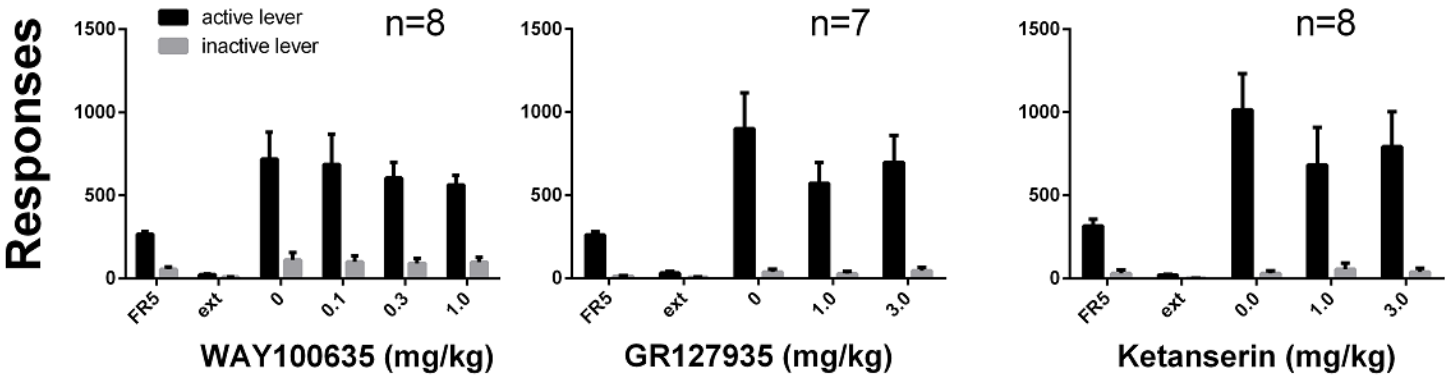

Figure 2 Effect of 5-HT antagonists on reinstatement of extinguished drug-taking behavior produced by MDMA (10.0 mg/kg). Bars represent the mean number of response (+SEM). During FR5 phase, active lever responses were reinforced with the delivery of MDMA (0.5 mg/kg./infusion) plus a stimulus light. During the ext phase, responses were reinforced by a vehicle infusion only; the light stimulus was omitted. During the final phase, antagonists were administered prior to the test (see Methods for details) and responses on the active lever were reinforced by the presentation of the light stimulus that had been paired with self-administered infusions of MDMA and a vehicle infusion.

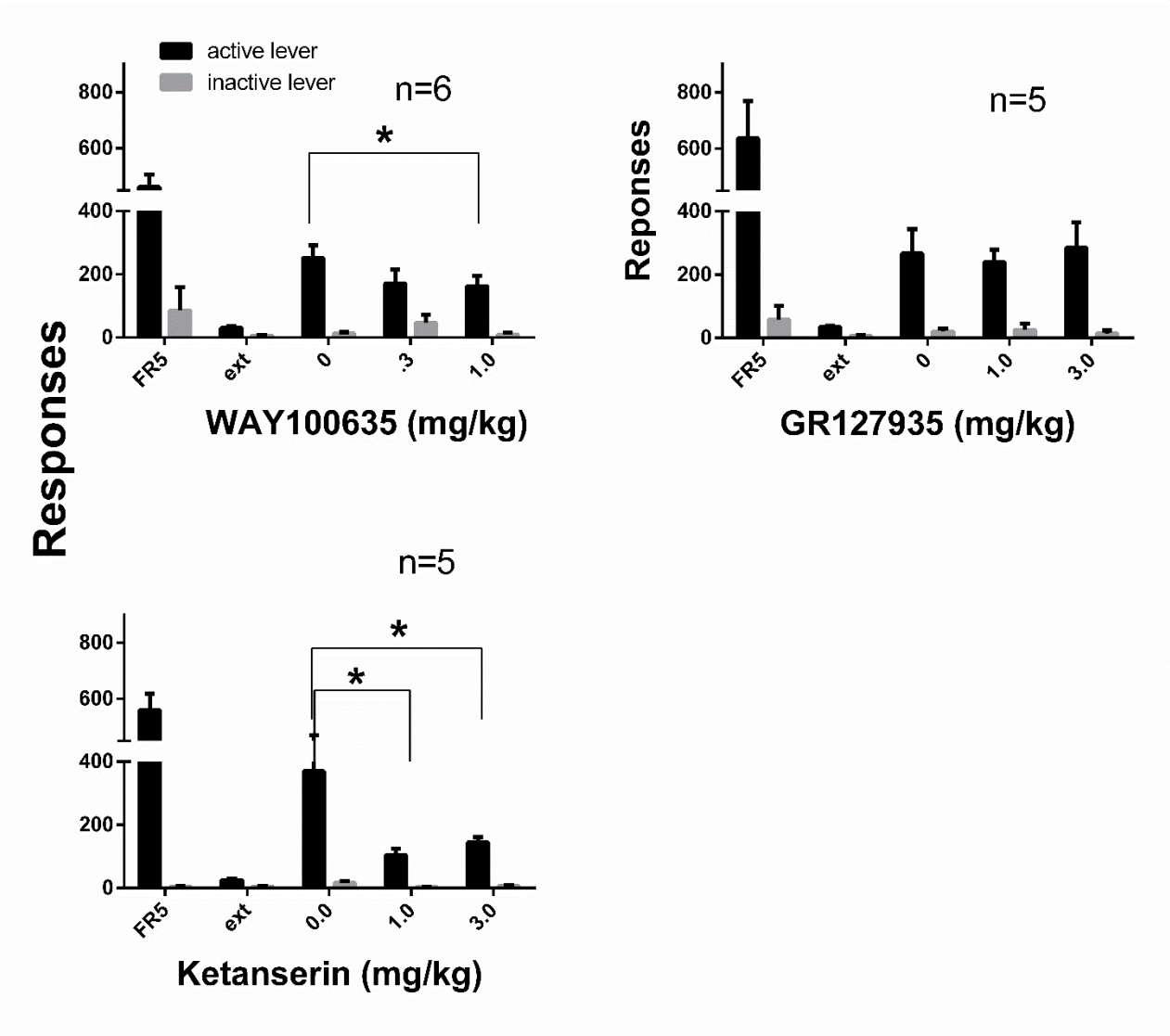

Figure 3 Effect of 5-HT antagonists on reinstatement of extinguished drug-taking behavior produced by cocaine (10.0 mg/kg). Bars represent the mean number of response (+SEM). During FR5 phase, active lever responses were reinforced with the delivery of cocaine (0.5 mg/kg./infusion) plus a stimulus light. During the ext phase, responses were reinforced by a vehicle infusion only; the light stimulus was omitted. During the final phase, antagonists were administered prior to the test (see Methods for details) and responses on the active lever were reinforced by the presentation of the light stimulus that had been paired with self-administered infusions of cocaine and a vehicle infusion. * $p<0.05$ compared to 0.0 dose

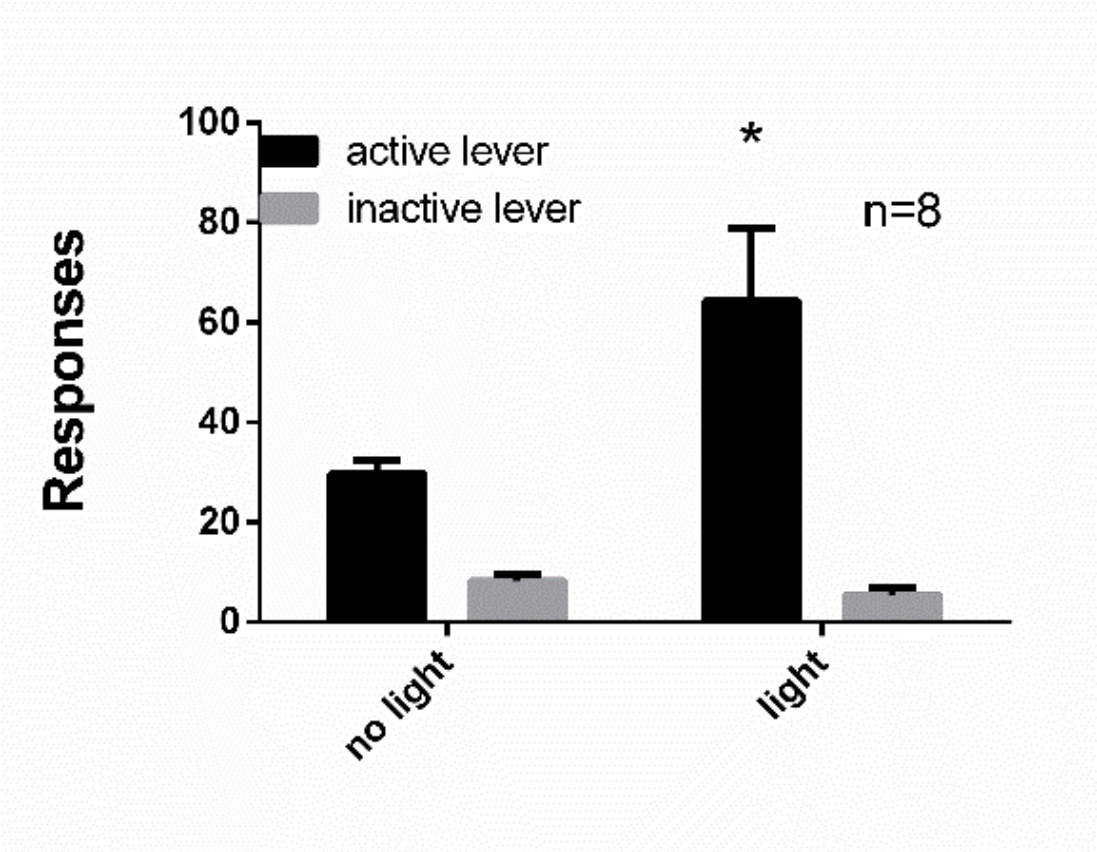

Figure 4 Responses produced during the last day of extinction testing when both the light and MDMA infusions were omitted (no light condition) and following reintroduction of the light stimulus that had been associated with self-administered MDMA infusions (light condition) and following an injection of vehicle (0.0 mg/kg). Bars=Mean +SEM, * $p<0.05$ compared to no light condition.

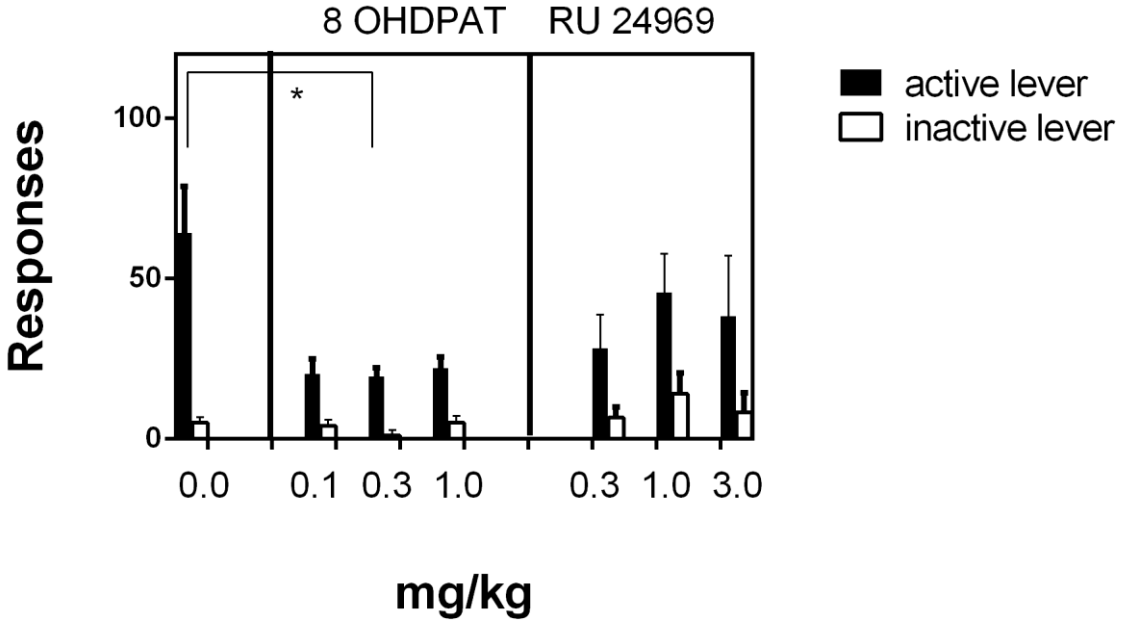

Figure 5 Effect of RU 24969 and 8 OHDPAT on the reinstatement of responding produced by reintroduction of the light stimulus that had been associated with self-administered MDMA. * $p<0.05$ compared to 0.0 mg/kg condition.

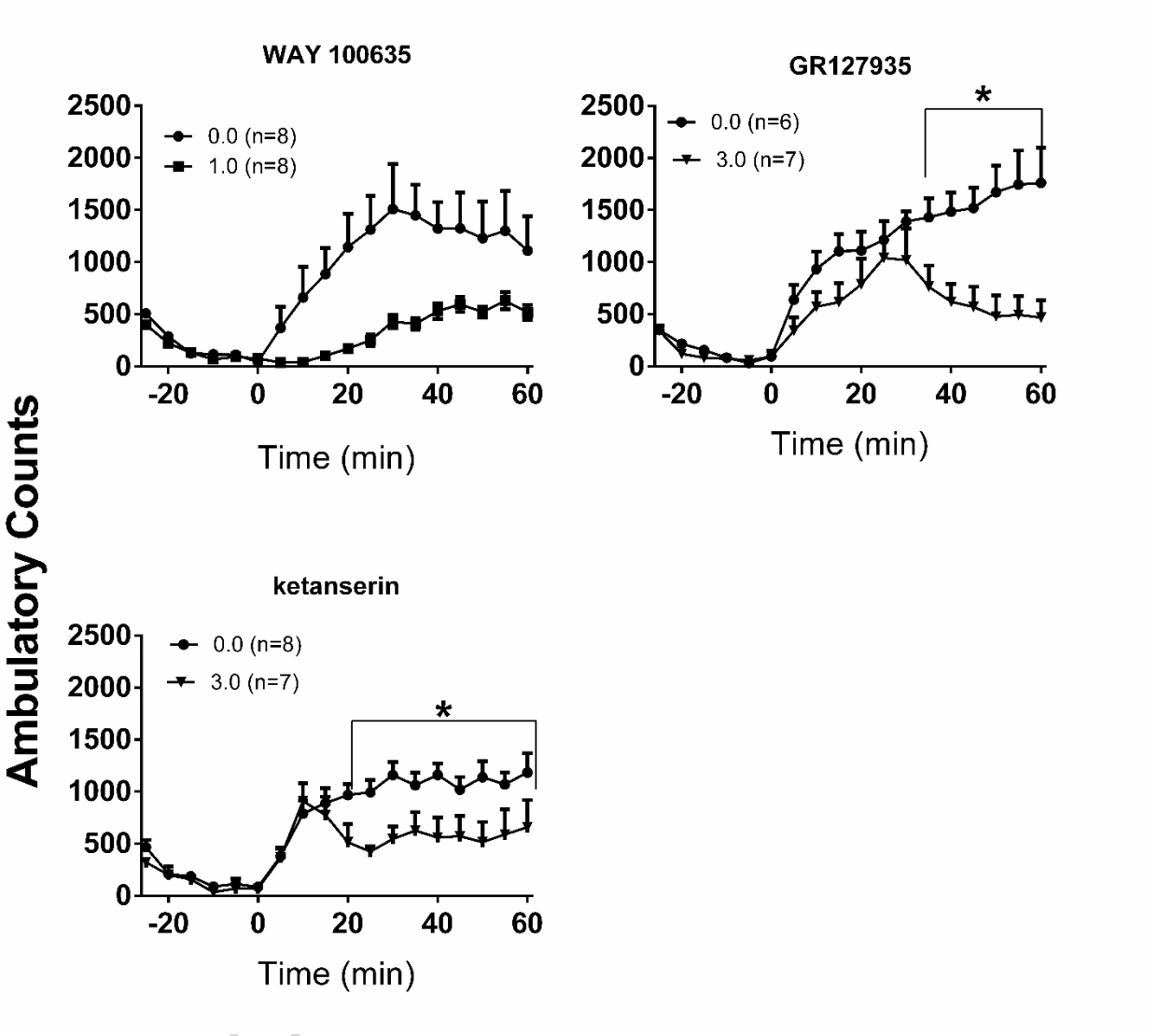

Figure 6 Effects of the highest doses of the antagonists on MDMA-produced hyperactivity. MDMA (10.0 mg/kg) was administered at time=0. Way100635 produced a decrease in MDMA-produced hyperactivity (main effect of Drug Dose) and interactions between Drug dose and Time were produced for the other 2 drugs. * $p<0.05$

Highlights:

- MDMA self-administration was not decreased by several 5-HT antagonists
- MDMA-seeking was not decreased by several 5-HT antagonists
- MDMA-produced hyperactivity was decreased by 5-HT antagonists
- Cocaine-seeking was attenuated by some 5-HT antagonists
- MDMA-seeking was decreased by pretreatment with a 5-HT_{1A} agonist