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Intravenous self-administration of entactogen-class stimulants in male rats

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Abstract

The intravenous self-administration (IVSA) of 3,4-methylenedioxymethamphetamine (MDMA) is inconsistent in rats, with up to half of subjects failing to acquire reliable drug intake. It is unknown if this changes under long-access conditions (6 h sessions) under which the IVSA of cocaine and methamphetamine escalates. The entactogen class cathinone stimulants which exhibit MDMA-like monoamine effects in the nucleus accumbens, mephedrone (4-methylmethcathione) and methylone (3,4-methylenedioxymethcathinone), may support more reliable IVSA but results have been mixed. This study was designed to directly compare the IVSA of these three compounds. Groups of male Wistar rats were trained to self-administer mephedrone, methylone or MDMA (0.5 mg/kg/inf) under a Fixed-Ratio (FR) 1 schedule of reinforcement for 14 sessions. Following the acquisition interval, animals were evaluated in FR (0.0, 0.125, 0.25, 0.5, 1.0, 2.5 mg/kg/inf) and Progressive Ratio (PR; 0.125, 1.0 mg/kg/inf) dose-substitution procedures. Long access conditions escalated MDMA intake over the 6 h session but not in the first 2 h. In short access, drug intake was significantly higher in mephedrone-trained rats compared with either the methylone-trained or MDMA-trained groups during acquisition. Mephedrone resulted in the highest intakes during FR and PR dose-substitution in MDMA- and mephedrone-trained groups. Overall it was found that mephedrone is a more effective reinforcer than methylone or MDMA and represents a higher risk for compulsive use.

Keywords

Drug addiction; bath salts; Ecstasy; reward; substance abuse

1. INTRODUCTION

Recreational use of cathinone derivative drugs has increased substantially since 2009 and continues to expand worldwide and in the USA. Use of these substances continues despite legal control efforts internationally, at the US federal level, within multiple US states and

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even the local US jurisdictions. In particular, the earliest appearing entities such as 4-methylmethcathinone (4-MMC; **Mephedrone**) and 3,4-methylenedioxymethcathinone (**Methylone**; beta keto-MDMA) remain highly popular (De Paoli et al. 2011; Deluca et al. 2012; Winstock et al. 2011) and appear to have joined established drugs such as 3,4-methylenedioxymethamphetamine (MDMA), methamphetamine or cocaine, rather than replacing them, in user populations (Moore et al. 2013). Although studies of dependence on these novel drugs are not available yet, a compulsive-use pattern is clear in many Case Reports of morbidity and user surveys point to use patterns and symptoms consistent with high potential for addiction and dependence (Dargan et al. 2010; Winstock et al. 2011). In addition, case reports of fatalities involving mephedrone or methylone are reminiscent of similar deaths attributed to MDMA (Lusthof et al. 2011; Patel et al. 2004; Pearson et al. 2012; Schifano 2004; Torrance and Cooper 2010). This motivates investigation of addiction liability in controlled animal models to determine the relative risks compared with more established recreational drugs.

The intravenous self-administration (IVSA) of MDMA has proven variable in rats (De La Garza et al. 2007; Feduccia et al. 2010), exhibits greater inter-subject variability than amphetamine (Dalley et al. 2007) and 40–50% of rats fail to meet acquisition criteria in some studies (Colussi-Mas et al. 2010; Oakly et al. 2014; Schenk et al. 2007). Furthermore, while long access (6 h daily sessions) to cocaine (Ahmed and Koob 1998; Larson et al. 2007) or methamphetamine (Kitamura et al. 2006; Schwendt et al. 2009) leads to escalation of drug intake relative to animals trained only in 1–2 h sessions, a report of MDMA IVSA using 6 h sessions reported no difference in *total session intake* between 6 h and 2 h groups over the first 11 sessions (Schenk et al. 2003). That lab also reported that only 60% of rats met *a priori* acquisition criteria for MDMA IVSA even when trained in 6 h sessions for 15 days (Schenk et al. 2007) and that escalated intake is a function of the cumulative number of sessions (>20) more so than the duration of those sessions (Schenk et al. 2008). The studies by Schenk et al were conducted in the rats' inactive period of the day which may explain why 6 h access did not result in many infusions past the first few hours and in addition, a relatively high per-infusion dose (1.0 mg/kg/inf) was used. One major goal of the present study was therefore to determine if 2 h and 6 h MDMA IVSA sessions result in identical intakes when rats are trained in their active part of the day, using a more moderate per-infusion dose (0.5 mg/kg/inf) as a reinforcer.

Pharmacologically, mephedrone and methylone have been found to serve as monoamine transporter substrates and monoamine releasers with enhanced effect on serotonin over dopamine systems (Baumann et al. 2012; Eshleman et al. 2013; Hadlock et al. 2011; Simmler et al. 2013), making them most similar to 3,4-methylenedioxymethamphetamine (MDMA) within the familiar amphetamine class substances. Mephedrone and methylone also both produce greater relative increases in nucleus accumbens serotonin compared with dopamine *in vivo* (Baumann et al. 2012; Kehr et al. 2011; Wright et al. 2012), which is a profile produced by MDMA (Baumann et al. 2008) but not amphetamine or methamphetamine. Thus it might be predicted that mephedrone and methylone would produce inconsistent IVSA such as has been described for MDMA. Evidence suggests, however, that mephedrone supports more consistent IVSA (Aarde et al. 2013a; Hadlock et

al. 2011; Motbey et al. 2013) and methylone has been reported to be readily self-administered by male Sprague-Dawley rats (Watterson et al. 2012) in one study. A prior report from this laboratory found the IVSA of methylone to be similar to MDMA and dissimilar to mephedrone in *female* Wistar rats (Creehan et al. 2015), therefore another major goal was to determine if the relative reinforcer efficacies of these three drugs was similar in male Wistar rats under short access conditions.

2. METHODS

2.1 Subjects

Male Wistar rats (Charles River, New York) were used for these investigations. Animals were housed in a humidity and temperature-controlled (23±1 °C) vivarium on 12:12 hour light:dark cycles. Animals entered the laboratory at 13–14 weeks of age and weighed an average of 383.1 (SEM: 6.3) grams at the start of the self-administration study. Animals had *ad libitum* access to food and water in their home cages. All procedures were conducted in the dark cycle, under protocols approved by the Institutional Care and Use Committees of The Scripps Research Institute and consistent with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2 Intravenous catheterization

Rats (MDMA Short Access, N = 18; MDMA Long Access, N = 12; mephedrone Short Access, N = 18; methylone Short Access, N=18) were anesthetized with an isoflurane/oxygen vapor mixture (isoflurane 5% induction, 1–3% maintenance) and prepared with chronic intravenous catheters as described previously (Aarde et al. 2013b; Aarde et al. 2015a; Miller et al. 2012). Briefly, the catheters consisted of an 14-cm length of polyurethane based tubing (Micro-Renathane®, Braintree Scientific, Inc, Braintree MA, USA) fitted to a guide cannula (Plastics One, Roanoke, VA) curved at an angle and encased in dental cement anchored to an ~3 cm circle of durable mesh. Catheter tubing was passed subcutaneously from the animal's back to the right jugular vein. Catheter tubing was inserted into the vein and tied gently with suture thread. A liquid tissue adhesive was used to close the incisions (3M™ Vetbond™ Tissue Adhesive; 1469SB).

A minimum of 4 days was allowed for surgical recovery prior to starting an experiment. For the first three days of the recovery period, an antibiotic (cephazolin) and an analgesic (flunixin) were administered daily. During testing and training, intravenous catheters were flushed with ~0.2–0.3 ml heparinized (166.7 USP/ml) saline before sessions and ~0.2–0.3 ml heparinized saline containing cefazolan (100 mg/mL) after sessions.

Catheter patency was assessed nearly once a week after the last session of the week via administration through the catheter of ~0.2 ml (10 mg/ml) of the ultra-short-acting barbiturate anesthetic Brevital sodium (1% methohexital sodium; Eli Lilly, Indianapolis, IN). Animals with patent catheters exhibit prominent signs of anesthesia (pronounced loss of muscle tone) within 3 sec after infusion. Animals that failed to display these signs were considered to have faulty catheters and were discontinued from the study. Data that was taken prior to failing this test and after the previous passing of this test were excluded from analysis.

2.3 Drugs

The racemic 4-methylmethcathinone (mephedrone) HCl used for this study was obtained from Fox Chase Chemical Diversity Center (Doylestown, PA). Racemic 3,4-methylenedioxymethamphetamine (MDMA) HCl was provided by the National Institute on Drug Abuse's Drug Supply Program. Racemic 3,4-methylenedioxymethcathinone (methylone) HCl was obtained from Cayman Chemical. All doses are expressed as the salt and were dissolved in physiological saline for injection.

2.4 Self-administration procedure

2.4.1 Acquisition—Drug self-administration was conducted in operant boxes (Med Associates) located inside sound-attenuating chambers located in an experimental room (ambient temperature 23 ± 1 °C; illuminated by red light) outside of the housing vivarium as in prior studies (Aarde et al. 2015b; Miller et al. 2015). To begin a session, the catheter fittings on the animals' backs were connected to polyethylene tubing contained inside a protective spring suspended into the operant chamber from a liquid swivel attached to a balance arm. Each operant session started with the extension of two retractable levers into the chamber. Following each completion of the response requirement (response ratio), a white stimulus light (located above the reinforced lever) signaled delivery of the reinforcer and remained on during a 20-sec post-infusion timeout, during which responses were recorded but had no scheduled consequences. Drug infusions were delivered via syringe pump. The training dose for all three drugs (0.5 mg/kg/infusion; ~0.1 ml/infusion) was selected from prior self-administration studies (Aarde et al. 2013a; Hadlock et al. 2011; Watterson et al. 2012) and comparison of mephedrone vs MDMA potency in locomotor and thermoregulatory studies (Aarde et al. 2013a; Huang et al. 2012; Miller et al. 2013; Wright et al. 2012) and confirmed in a prior study of IVSA in female rats (Creehan et al. 2015). Session duration for the normal (Short Access; ShA) acquisition and Fixed-Ratio dose-substitution sessions was 2 h, up to 3 h sessions were conducted for Progressive-Ratio dose substitution and the Long Access (LgA) training sessions were 6 h in duration.

2.4.2 Fixed- Ratio (FR) Dose-Response Testing—All groups were initially subjected to randomized dose-substitution conditions in which the per-infusion dose of their respective training drug differed (0.0, 0.125, 0.25, 0.5, 2.5 mg/kg/inf) on sequential sessions immediately following acquisition (see Figure 1). The MDMA ShA group was next evaluated with sequential substitution of doses of methylone and mephedrone. The MDMA LgA group was evaluated on methylone following the training drug. The methylone group was evaluated on mephedrone and then on MDMA. The mephedrone-trained group was evaluated on a MDMA dose substitution after their training drug dose-substitution. The individual treatment order within each drug series was balanced by Latin Square design.

2.4.3 Progressive- Ratio (PR) Dose-Response Testing—Following the FR evaluation, the animals in all four groups were subjected to randomized dose-substitution conditions in which different per-infusion doses (0.125, 1.0 mg/kg/inf) of MDMA, methylone or mephedrone were presented on sequential sessions as described previously (Creehan et al. 2015). The sequence of response ratios started with one response then progressed thru ratios determined by the following equation (rounded to the nearest integer):

Response Ratio = 5e^(injection number * j) − 5 (Richardson and Roberts 1996). The value of "j" for was 0.3 and was chosen so as to observe a "breakpoint" in ~3 hrs at 0.10 mg/kg/inf. The drug and dose order was balanced by Latin Square design (i.e., the 6 total conditions were randomized). The last ratio completed before the end of the session (1 h after the last response up to a maximum of 3 h sessions) was operationally defined as the breakpoint.

2.5 Data Analysis

Due to prior observations of significant individual differences in the acquisition of MDMA IVSA (Colussi-Mas et al. 2010; Oakly et al. 2014; Schenk et al. 2007), the primary analysis of the acquisition data in Short Access (ShA) groups included the discrimination ratio (drug associated lever / all lever responses) as a dependent variable and a secondary median split analysis were also conducted for the ShA groups. The Long Access group drug intake was analyzed for the first 2 h of the session as well as for the entire 6 h session. The data were analyzed with repeated-measures Analysis of Variance (rmANOVA) with dose and session number as within-subjects factors and Access duration, drug identity and intake preference subgroup (median split) as between-subjects factors as appropriate. In dose-substitution analyses the number of rats included in a given dose-series varied slightly depending on whether it was a repeated-measures analysis (i.e. multiple sequential FR series across a group) or between-subjects (i.e., the first FR substitution across groups) design; the latter did not require an animal to remain patent through all of the dose-series conducted. Any significant rmANOVA main effects were followed with post-hoc analysis using Tukey (within-subject) or Sidak (between-groups) correction for all possible comparisons. Analyses were conducted using Prism 6 for Windows (v. 6.02; GraphPad Software, Inc, San Diego CA). Graphs were generated with Excel (Microsoft, Redmond WA) and figures created in Canvas (v.12; ACD Systems of America, Inc, Seattle, WA)

3. RESULTS

3.1 MALE RAT IVSA ACQUISITION

The mean number of infusions for the groups of Short Access male rats that remained patent through the 14 session acquisition phase while being trained on 0.5 mg/kg/inf of MDMA (N=17), Methylone (N=14) and Mephedrone (N=15) are shown in Figure 2. The ANOVA confirmed significant effects of Session [$F(13, 559) = 16.53$; $P < 0.0001$], of training Drug [$F(2, 43) = 5.072$; $P = 0.0105$] and the interaction [$F(26, 559) = 2.165$; $P = 0.0008$] for infusions obtained. The post hoc test confirmed that the mephedrone group obtained more infusions than the MDMA group (Sessions 6–14) and the methylone group (Session 14); the latter two groups did not differ significantly. The post hoc test also confirmed increased drug intake over the first session in the mephedrone (Sessions 5–14) and methylone (Sessions 10–13) groups. A second ANOVA analysis confirmed that the drug-associated lever discrimination ratio (Figure 2) was significantly affected by training Session [$F(13, 559) = 10.82$; $P < 0.0001$] and by training Drug [$F(2, 43) = 7.10$; $P < 0.005$] but not by the interaction [$F(26, 559) = 0.93$; $P = 0.57$]. The post hoc test confirmed that lever discrimination was significantly higher than the first session for the mephedrone (Sessions 7,9), MDMA (Sessions 12–14) and methylone (Sessions 7–14) groups. The post hoc test

also confirmed that mephedrone trained animals exhibited higher discrimination ratios than the MDMA (Sessions 2, 4, 6–10) and methylone (Sessions 5–6) trained animals.

3.2 FIXED RATIO DOSE SUBSTITUTION

The first analysis of infusions earned in the FR dose substitution (Figure 3) focused on a median split due to the *a priori* recognition of significant inter-subject differences when it comes to MDMA self-administration. (The male overall group means are presented in Supplemental Figure S3 in the sex-comparison analysis.) Analysis was between-Group for drug-identity / median split and within-group for Dose. Treating drug-identity as a between-subjects factor permitted the retention of individuals who completed at least one FR series in the analysis of a given drug.

3.2.1 MDMA-trained rats—The number of individuals completing the MDMA and methylone dose-substitution series was N=17 (9 upper half) and the number completing the mephedrone series was N=14 (6 upper half). The ANOVA confirmed that there was a significant effect of Dose [$F(4, 168) = 11.23$; $P < 0.0001$], of the Group [$F(5, 42) = 5.59$; $P < 0.001$] and of the interaction of factors [$F(20, 168) = 2.89$; $P < 0.0005$] on infusions obtained. The post hoc test confirmed significantly more infusions of mephedrone were obtained by the Upper preference group at the 0.125 mg/kg/inf dose relative to either MDMA or methylone at the same dose. See Figure 3 for additional within-group differences. There were no dose-related or drug-identity-associated differences in intake within the Lower preference MDMA-trained group.

3.2.2 Methylone-trained rats—The number of individuals who completed the methylone and mephedrone dose-response series was N=14 (7 upper half) and the number which completed the MDMA dose-response series was N=11 (5 upper half). There was a main effect of Dose [$F(4, 132) = 20.39$; $P < 0.0001$], of the Group [$F(5, 33) = 5.47$; $P < 0.001$] and an interaction [$F(20, 132) = 2.80$; $P < 0.0005$]. The post hoc test did not confirm any significant differences between drugs at any dose within Upper or Lower preference groups. There were no significant dose-related differences within the Lower preference group confirmed. Within the Upper preference group, significant dose related effects on intake were confirmed in all three dose-substitution series. Under methylone, the post hoc test confirmed significant differences relative to the 2.5 mg/kg/inf condition (0.0–0.25 mg/kg doses) and relative to the 0.125 mg/kg/inf dose (0.5–2.5 mg/kg/inf doses). In the mephedrone dose-substitution, the post hoc test confirmed significant differences relative to the 2.5 mg/kg/inf condition (0.0–0.25 mg/kg doses) and relative to the 0.125 mg/kg/inf dose (0.25–2.5 mg/kg/inf doses). In the MDMA dose-substitution, the post hoc test confirmed significant differences relative to the 2.5 mg/kg/inf condition (0.0–0.25 mg/kg doses) and relative to the 0.125 mg/kg/inf dose (0.0, 0.25–2.5 mg/kg/inf doses). Post hoc testing also confirmed significant differences between Upper and Lower preference groups both within and between a drug identity in the 0.125 mg/kg/inf condition. Saline infusions also differed across some groups, i.e., the Lower preference group differed from the Upper group when both were on the mephedrone series. Differences were also confirmed when the Lower group was on the MDMA series versus the Upper group on mephedrone or methylone series

and when the Lower group was on the methylone series versus the Upper group on the methylone or mephedrone series.

3.2.3 Mephedrone-trained rats—The number of mephedrone-trained males which completed the mephedrone and MDMA dose-response series was N=14 (N=7 upper half). There was a main effect of Dose [F (4, 96) = 25.13; P < 0.0001], of the Group [F (3, 24) = 11.51; P < 0.0001] and an interaction [F (12, 96) = 5.54; P < 0.0001]. The post hoc test confirmed a significant difference between MDMA and mephedrone intake at the 0.25 mg/kg/inf dose within the Upper preference group. See Figure 3 for additional within-group differences. There were no dose-related or drug-identity-associated differences in intake within the Lower preference group.

3.3 PROGRESSIVE RATIO DOSE SUBSTITUTION

The statistical analysis initially compared the breakpoints achieved under six different dosing conditions within training group, including a median split division of the groups into upper and lower preference halves based on the Acquisition phase (Figure 4). Dose was treated as a repeated-measures factor and preference group (median split) X drug identity treated as a between-Groups factor. The ANOVA for the *MDMA-trained* (N=12; 6 upper) animals confirmed significant effects of Dose [F (1, 68) = 8.11; P < 0.01], Drug [F (5, 68) = 5.43; P < 0.0005] and the interaction [F (5, 68) = 2.37; P < 0.05]; the post hoc test confirmed a significantly higher breakpoint was achieved for the 1.0 mg/kg/inf versus the 0.125 mg/kg/inf dose of mephedrone in Upper half animals only. The ANOVAs for the male *mephedrone-trained* (N=13; 7 upper) and the male *methylone-trained* (N=7; 4 upper) groups did not confirm significant effects of Group or Dose. A follow up ANOVA compared breakpoints achieved by the upper-half animals from each training Group with all six drug/dose conditions treated as a single repeated Dose factor. There was a significant main effect of Dose F (5, 70) = 2.62; P < 0.05. The post hoc test further confirmed that across groups a higher breakpoint was achieved in the 1.0 mg/kg/inf mephedrone condition vs the 0.125 mg/kg/inf condition for mephedrone, MDMA and methylone. (A similar ANOVA on the Lower-half animals' breakpoints did not confirm any significant differences.)

3.4 LONG ACCESS

A group of male Wistar rats (N=12; N=9 survived with patent catheters through 35 sessions of acquisition) were trained to self-administer MDMA (0.5 mg/kg/inf) in 6 h daily sessions. The infusions in the first 2 h of the first 14 sessions were initially compared with the short access (2 h) animals described above (Figure 5). The ANOVA did not confirm any significant difference in MDMA infusions obtained by the ShA group and by LgA rats (first 2h) during the first 14 days, but there were significant effects of Session [F (13, 312) = 2.49; P < 0.01] and the interaction of Session with Group [F (13, 312) = 2.284; P < 0.01]. The post hoc test confirmed that ShA rats earned more infusions on sessions 10 and 12 compared to *each* of their first four sessions in this two-group analysis but no differences were confirmed in the first 2 h infusions within the LgA group.

The repeated measures analysis for the MDMA infusions earned for the entire acquisition interval within the LgA group confirmed significant effects of Session [F (34, 272) = 2.63; P

< 0.0001], of Interval (first 2 h versus the entire 6 h) [F (1, 8) = 68.93; P < 0.0001] and the interaction of factors [F (34, 272) = 2.08; P < 0.001]. The post hoc test confirmed that within the first 2 h of long access significantly increased infusions were obtained in Sessions 33 (vs 2,5,9, 17, 22, 30 or 35), 31 (vs 5, 17, 22, 30 or 35) and 16 (vs Sessions 5 or 17). There were other significant differences in first-2h-intake confirmed between sessions but overall there were no sustained trends for escalated intake at the end of training. In contrast, the 6 h intake was significantly higher in Sessions 16, 21, 23, 25, 26, 29, 31, 33 and 34 compared with *each* of the first five sessions and significantly higher in Sessions 21, 25 and 31 compared with each of Sessions 7–11.

In terms of apparent outlier sessions of decreased intake, sessions 30 and 35 were Fridays during a full 5-day week, Session 17 occurred on the day after Session 16 which followed a 2 day weekend break and Session 24 was the first after a 4 day interval of no testing. For the sessions of elevated intake relative to prior sessions, a five day interval of no behavioral testing preceded Sessions 6 and 16 due to holiday schedules, but session 31 followed a normal two day weekend. The post hoc test furthermore confirmed that significantly higher total infusions were obtained in the full 6 h session compared with the first 2 h of each session in all 35 sessions.

In the analysis of 5 session blocks, the ANOVA confirmed effects of Session Block [F (4, 64) = 5.77; P < 0.001] and of Interval (2h vs 6 h totals within the session) [F (1, 16) = 19.95; P < 0.0005] but not of the Interaction [F (4, 64) = 1.73; P = 0.154]; The post-hoc confirmed significantly greater 6 h totals from sessions 10–14 through 31–35. The post-hoc test also confirmed significant escalation compared with the first five sessions in the blocks of Sessions 20–24, 26–30, 31–35 of 6 h. No escalation in the first-2 h totals was confirmed in this analysis.

The long access group underwent dose-substitution under FR (as for the ShA groups, above) for first MDMA and then methylone after the 35 session long-access interval (Figure 6); N=8 completed this phase with patent catheters. For the dose-substitution phase all sessions were 2 h in length. The ANOVA therefore included factors for Drug/Access condition and Dose. The ANOVA confirmed a significant effect of Dose [F (4, 184) = 19.16; P < 0.0001] and an interaction of Dose with Drug Identity/Access condition [F (12, 184) = 3.79; P < 0.0001]. The post hoc test confirmed that there were significant differences between the Access groups in dose-substitution only for 0.125–0.25 methylone challenge; the LgA group also self-administered significantly more infusions of 0.125–0.25 methylone compared to the ShA groups' intake of *MDMA* at those respective doses. There were no differences between the groups on the MDMA dose substitution confirmed. Additional significant differences attributable to dose within the treatment groups and drug identity are as depicted in Figure 6.

4. DISCUSSION

This investigation confirmed that male Wistar rats will obtain more infusions of MDMA (0.5 m/gkg/inf) in intravenous self-administration (IVSA) when trained in Long Access (LgA; 6 h) sessions compared with their own initial 2 h intake, or with the intake of a 2 h

session-only Short Access (ShA) group. Furthermore, the daily intake of LgA animals escalated over the first 21 sessions of training, consistent with prior reports of escalated intake of the more typical stimulant methamphetamine (Anker et al. 2012; Jang et al. 2013; Kitamura et al. 2006; Schwendt et al. 2009). Thus, a prior report that 6 h access led to no difference in total session MDMA intake relative to animals trained in 2 h sessions (Schenk et al. 2003) may have depended on a relatively high per-infusion dose (1.0 mg/kg/inf) and / or training animals in the inactive (light) cycle. The ShA and LgA rats in this study did not differ in responding for MDMA in the initial FR dose-substitution but the LgA rats did respond significantly more for methylone, potentially revealing an altered liability for some, but not all, of these entactogen-class stimulants in LgA animals.

The limited escalation of drug seeking in the LgA group is perhaps unexpected. Decreasing serotonergic effects of different dopamine-potentiating drugs has previously been associated with increased reinforcing or rewarding effect (Roberts et al. 1999; Wee et al. 2005; Wee and Woolverton 2006) and prior treatment of rats with the serotonergic neurotoxin 5,7-dihydroxytryptamine sped the acquisition of MDMA IVSA (Bradbury et al. 2014). The LgA animals in this study self-administered a similar number of cumulative MDMA infusions as rats did in a 2 h short access IVSA procedure which resulted in significant serotonin reductions two weeks after the cessation of self-administration (Do and Schenk 2013). The relatively modest escalation observed for the LgA animals in this study suggests, however, that serotonergic neurotoxicity was not a contributing factor.

The present study also made a comparison of the abuse liability of entactogen-class stimulant drugs (i.e., those that enhance serotonin more than dopamine accumulation in nucleus accumbens) and showed directly for the first time in male rats that mephedrone is more effective as a reinforcer than either MDMA or methylone. This was indexed during initial acquisition, in the FR dose-substitution between training groups and in the within-training group comparison across drugs for the MDMA- and mephedrone-trained groups. Mephedrone also dose-dependently increased breakpoints in the Progressive-Ratio procedure most consistently. Although prior studies of the intravenous self-administration (IVSA) of mephedrone (Aarde et al. 2013a; Hadlock et al. 2011; Motbey et al. 2013) suggested indirectly that it is a more effective reinforcer than MDMA (Ball et al. 2007; Dalley et al. 2007; De La Garza et al. 2007; Feduccia et al. 2010; Schenk et al. 2012; Schenk et al. 2007) in male rats, the present *direct* comparison provides more compelling evidence. The result for methylone IVSA under short access training conditions contrasts with the finding of a prior study in male Sprague-Dawley rats (Watterson et al. 2012) but is consistent with a prior report for female Wistar rats from this laboratory (Creehan et al. 2015). The results for males in this study was in fact very similar to those previously reported for female rats (Creehan et al. 2015) during the initial acquisition phase. Significant sex differences during acquisition were only confirmed for the MDMA-trained groups; the analysis is reported in the Supplemental Materials (Figure S1, S2). The increased preference of the female animals for MDMA is consistent with prior demonstrations that female rats self-administer more cocaine or methamphetamine but it is puzzling why no sex differences were observed for the more efficacious training drugs during the Acquisition phase. Significantly more infusions were obtained by female versus male animals during the initial

FR dose-substitution with the respective training drug for all three training drugs (Figure S3) and in the PR MDMA and methylone dose-substitution for mephedrone-trained groups (Figure S4).

The median split analysis of the FR dose-substitutions within the male rats identified mephedrone as a more-effective reinforcer of behavior in each of the MDMA-trained and mephedrone-trained groups. No differences were observed in the animals initially trained on methylone, however. This differs from our previous finding in female rats in which mephedrone- and methylone-trained rats exhibited tremendous similarity of potency and efficacy across the three drugs; results were somewhat more equivocal for the MDMA-trained group. It is possible that the failure to divide the female groups by initial preference in our original study obscured effects similar to what is reported here for the males, but the median split analysis of the FR data (see Supplemental Materials Table S2) for those female groups does not strongly support this supposition.

It is unclear at present what mechanisms may explain the differences in outcome for the three drugs. We previously described how the known pharmacological differences do not satisfyingly explain these IVSA results in our prior study of female animals (Creehan et al. 2015). To summarize briefly, pharmacological evidence of DAT/SERT ratio on transporter inhibition, DAT inhibition potency and monoamine release mediated by the DAT or SERT (Baumann et al. 2012; Baumann et al. 2013; Simmler et al. 2013; Simmler et al. 2014) all fail to explain the outcome of this IVSA assessment of these three drugs. Potential explanations may lie in a relatively rapid brain entry of mephedrone (Simmler et al. 2013) or a slightly earlier elevation of dopamine compared with serotonin in the nucleus accumbens (Kehr et al. 2011). Another potential explanation may be the well-established reductions in serotonergic markers produced by repeated MDMA exposure in rats (Malberg and Seiden 1998) and nonhuman primates (Taffe et al. 2002; Taffe et al. 2003). Similar serotonergic alterations have been reported for mephedrone under high ambient-temperature conditions (Hadlock et al. 2011) and for methylone (den Hollander et al. 2013; Lopez-Arnau et al. 2014). Conversely, the den Hollander et al. (2013) study failed to detect any serotonin neurotoxicity following repeated mephedrone and Baumann et al. (2012) failed to detect any neurotoxic effect of repeated methylone. Differences in outcome are likely related to the precise dosing regimens used and factors of ambient temperature and housing conditions which are so important to the body temperature response which governs toxic effects of MDMA (Dafters 1994; Fantegrossi et al. 2003; Malberg and Seiden 1998). Mephedrone is also much less toxic than MDMA to dopaminergic neurons in mouse models (Angoa-Perez et al. 2013; Angoa-Pérez et al. 2012; Granado et al. 2008). Overall, it appears to be the case that the potential for lasting serotonergic neurotoxicity after repeated mephedrone or methylone exposure is likely no greater than after repeated MDMA and may perhaps be lesser. It thus appears unlikely that the present results are explained by differential lasting/neurotoxic modulation of the serotonergic systems based on IVSA of the three entactogen compounds.

In summary this study found that MDMA IVSA intakes in 6 h sessions are greater than in 2 h sessions for male rats and furthermore that such long-access conditions support gradual escalation of daily drug intake. Thus, MDMA does not differ from traditional stimulants

such as methamphetamine or cocaine in Short/Long access conditions to the extent that was suggested by one prior report in which 2 h and 6 h intakes were identical (Schenk et al. 2012). There was, however, no escalation of the initial 2 h intake in the Long Access group which is discordant with the most canonical interpretations of escalated stimulant self-administration (Ahmed and Koob 1998; Kitamura et al. 2006; Larson et al. 2007; Schwendt et al. 2009). The study also further confirms our prior conclusion, based on direct comparisons between the drugs in female rats, that mephedrone has relatively high abuse liability in comparison with either methylone or MDMA. This further questions assertions that mephedrone has lower abuse liability which followed from a study of intra-cranial self-stimulation reward (Bonano et al. 2014). The present results are also dissimilar to a prior report that methylone supports robust IVSA under short access conditions (Watterson et al. 2012); additional experiments will be required to identify possible methodological contributions to the differing results. Finally, we show that male rats self-administer MDMA less consistently than female rats and that this is mostly attributable to the lower half of the respective preference distributions. This suggests that women may be at increased risk of developing compulsive use of MDMA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Intravenous self-administration of MDMA is inconsistent
- Long-access to MDMA led to escalated 6 h intake but not 2 h intake
- Mephedrone was a more effective reinforcer than MDMA or methylone
- Male rats self-administer at slightly lower rates than female rats

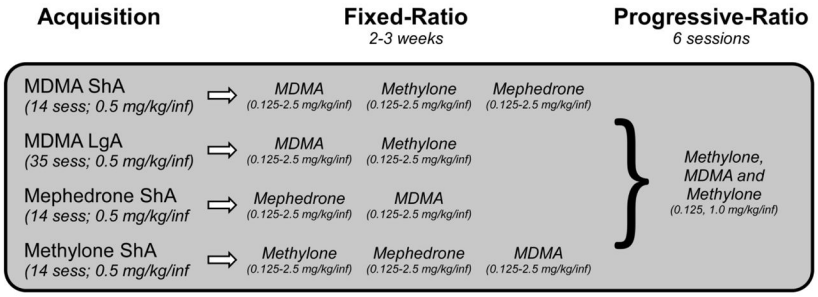

Figure 1.

A schematic depicting the sequential treatment phases for the experimental groups originally trained to self-administer MDMA, Mephedrone and Methylone. ShA: Short Access (2 h session); LgA: Long Access (6 h session).

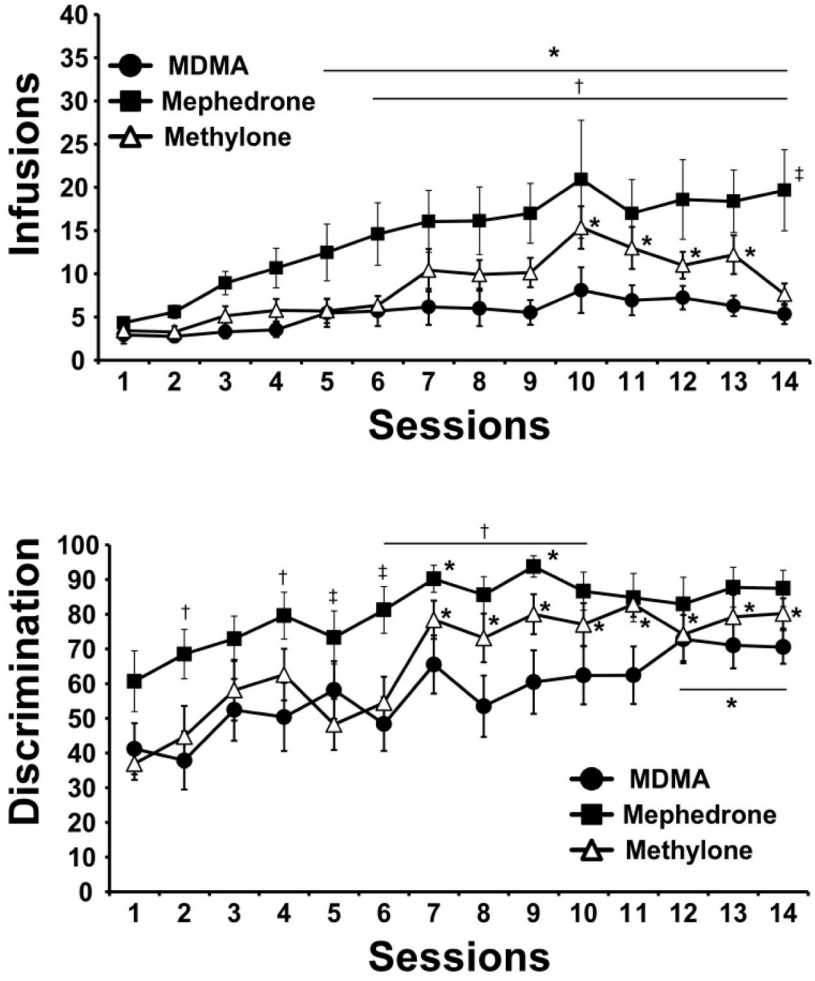

Figure 2.

Mean (±SEM) infusions (upper panel) and drug-associated lever discrimination ratios (lower panel) obtained during acquisition for groups of male rats trained to self-administer MDMA (N=17), Methylone (N=14) or Mephedrone (N=15). Significant differences from the first session within group are indicated by *, differences between mephedrone and both other groups by #, differences from methylone by ‡ and differences from MDMA by †.

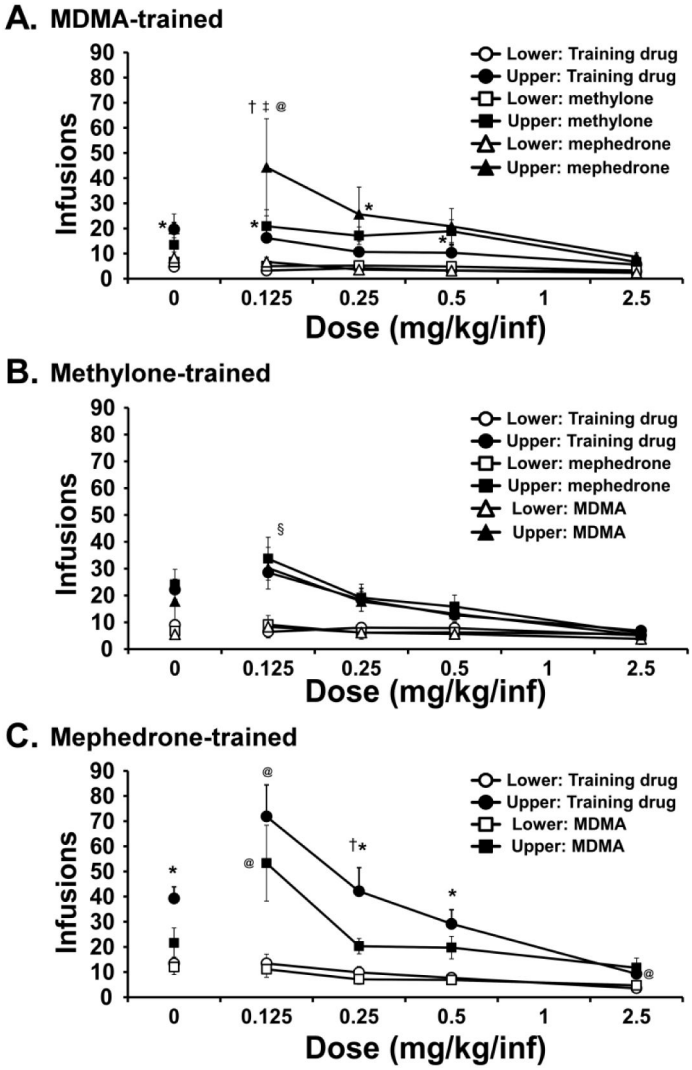

Figure 3.

Mean (±SEM) infusions obtained during the dose-substitution studies under a Fixed-Ratio 1 schedule of reinforcement in the Upper and Lower half of male rats originally trained on A) MDMA, B) Methylone or C) Mephedrone. Analyses included only the doses that were matched across the sex groups within a given training drug. Significant differences from MDMA, within a preference-group are indicated with †. Significant differences within-group from all other conditions are indicated with @, from both the 0.5 and 2.5 mg/kg/inf condition by §, from the 2.5 mg/kg/inf condition by * and from the 0.5 mg/kg/inf condition by &. See text for additional significant differences.

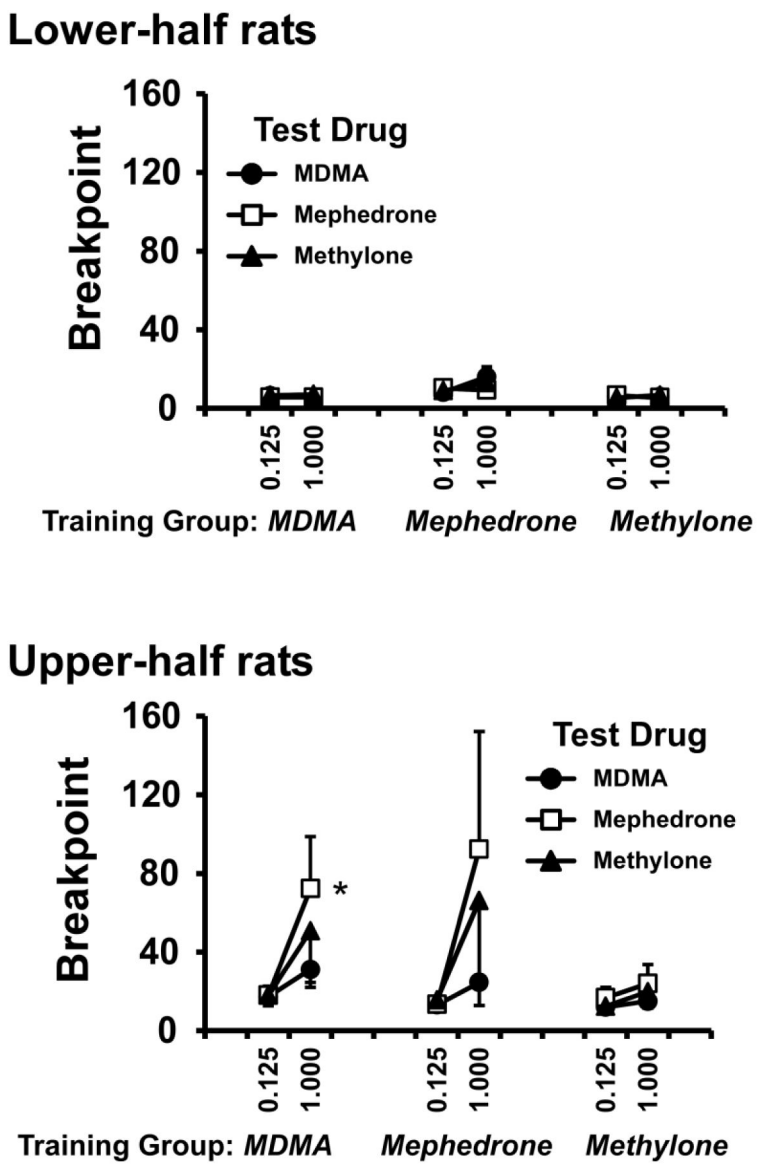

Figure 4.

Mean (±SEM) infusions obtained by the Lower-half (upper panel) and Upper-half (lower panel) subgroups of male rats originally trained on MDMA (N=12; 6 Upper-half) Mephedrone (N=13; 7 Upper-half) or Methylone (N=7; 4 Upper-half) during dose-substitution under a Progressive-Ratio schedule of reinforcement. Significant differences between doses, within drug, are indicated by *.

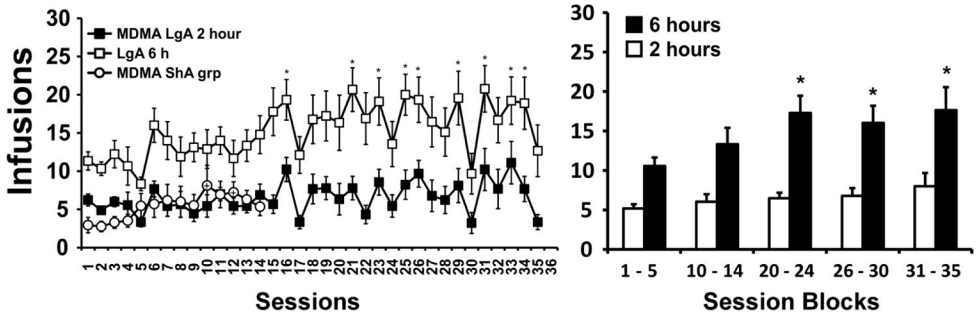

Figure 5.

Mean (N=9; ±SEM) infusions of MDMA obtained by a group trained in Long Access (6 h; LgA) sessions depicted by session (left panel) or 5 session averages (right panel). The left panel includes the data for the MDMA Short Access (ShA; N=13) group and LgA intakes are depicted for the first 2 h of the sessions as well as the entire 6 h totals in both panels. Significant differences from the first five sessions are indicated with * (LgA) and from the first four sessions by + (ShA).

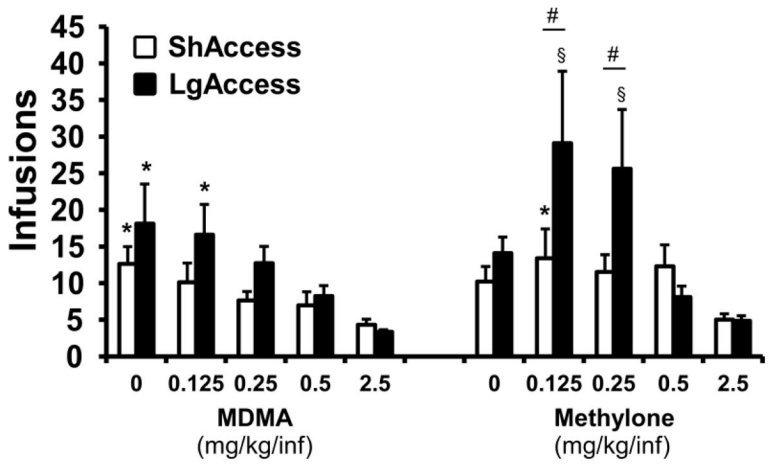

Figure 6.

Mean (±SEM) infusions obtained during the MDMA and Methylone dose-substitution studies under a Fixed-Ratio 1 schedule of reinforcement in the male rats originally trained to self-administer MDMA in Short Access (2 h; ShAccess) or Long Access (6 h; LgAcces) sessions. Significant differences between Access groups are indicated with #. Significant differences within-group and within-drug from the 2.5 mg/kg/inf dose are indicated by * and from both the 0.5 and 2.5 mg/kg/inf doses by §.