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The Reinforcing and Rewarding Effects of Methylone, a Synthetic Cathinone Commonly Found in "Bath Salts"

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Abstract

Methylone is a member of the designer drug class known as synthetic cathinones which have become increasingly popular drugs of abuse in recent years. Commonly referred to as "bath salts", these amphetamine-like compounds are sold as "legal" alternatives to illicit drugs such as cocaine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA, ecstasy). Following their dramatic rise in popularity along with numerous reports of toxicity and death, several of these drugs were classified as Schedule I drugs in the United States in 2012. Despite these bans, these drugs and other new structurally similar analogues continue to be abused. Currently, however, it is unknown whether these compounds possess the potential for compulsive use and addiction. The present study sought to determine the relative abuse liability of methylone by employing intravenous self-administration (IVSA) and intracranial self-stimulation (ICSS) paradigms in rats. We demonstrate that methylone (0.05, 0.1, 0.2, and 0.5 mg/kg/infusion) dose-dependently functions as a reinforcer, and that there is a significant positive relationship between methylone dose and reinforcer efficacy. Furthermore, responding during short access sessions (ShA, 2 hr/day) appeared more robust than previous IVSA studies with MDMA. However, unlike previous findings with abused stimulants such as cocaine or methamphetamine, long access sessions (LgA, 6 hr/day) did not lead to escalated drug intake or increased reinforcer efficacy. Finally, methylone produced a dose-dependent, but statistically non-significant, trend towards reductions in ICSS thresholds. Together these results reveal that methylone may possess an addiction potential similar to or greater than MDMA, yet patterns of self-administration and effects on brain reward function suggest that this drug may have a lower potential for abuse and compulsive use than prototypical psychostimulants.

Keywords: Methylone; Self-administration; Intracranial self-stimulation; Reward; Reinforcement; Monoamine; Stimulant

Introduction

Methylone (3,4-methylenedioxymethcathinone (MDMC), 2-methylamino-1-(3,4- methylenedioxyphenyl)propan-1-one, or *bk*-MDMA) is a member of the designer drug class known as synthetic cathinones. These emerging drugs of abuse are derivatives of cathinone, a beta-ketone amphetamine with known abuse potential [1] and the primary active alkaloid of the *Catha edulis* (Khat) plant [2]. In recent years, synthetic cathinones have become increasingly popular as "legal highs" due to online marketing, media coverage, and availability in convenience stores, head shops, and the internet [3]. While most commonly sold as "bath salts", these drugs have been falsely sold as many different commercial products such as "plant food", "room odorizer", and "iPod cleaner", and typically contain labels stating "not for human consumption" as a means of evading regulatory controls [4]. Desired effects of these drugs include euphoria, appetite suppression, and increases in energy, focus, libido, and empathy [5]. However, an increasing number of calls to national poison control centers [6] and numerous reports of toxicity [5], adverse psychological and behavioral effects [7], and death [8-10] have been reported. While many synthetic cathinone analogues have been discovered in drug seizures, the three most common are methylenedioxypyrovalerone (MDPV), methylone, and mephedrone [3]. In October 2011, these three substances were temporarily classified as Schedule I substances in the United States [11]. Interestingly, only mephedrone and MDPV were *permanently* classified as Schedule I substances with the Synthetic Drug Abuse Prevention Act in July 2012 [12] while the *temporary* schedule I status of methylone was extended until April, 2013 [13]. Despite these new regulatory controls, U.S. Poison Control Centers continue to receive calls regarding "bath salts" [6], likely from continued abuse of mephedrone, MDPV, and methylone along with unscheduled structurally similar analogues.

While the rise in abuse of synthetic cathinones is now well documented, little information exists about the relative abuse liability of these compounds and whether consumption patterns are primarily *episodic* (i.e., recreational) or *compulsive* (i.e., characteristic of addiction). Given recent permanent scheduling for only mephedrone and MDPV, it is not surprising that most investigations of abuse potential have focused on these two synthetic cathinones, and relatively little attention has been given to methylone. We have recently shown that rats will dose-dependently maintain intravenous MDPV self-administration in short access (ShA, 2 hr/day) intravenous self-administration (IVSA) sessions. We also demonstrated significant dose effects for reinforcer efficacy (i.e., breakpoints) between each of the doses tested (0.05, 0.1, and 0.2 mg/kg/infusion) on a progressive ratio schedule of reinforcement. Finally, under long access (LgA, 6 hr/day) conditions, rats in the two highest dose groups also displayed escalated MDPV intake suggesting the potential for compulsive use in humans. The reinforcing effects of MDPV were complemented with significant dose-dependent reductions in ICSS thresholds, indicative of hedonic and rewarding properties [14]. With regards to mephedrone, studies by other investigators have shown that rats will self-administer

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mephedrone intravenously under ShA conditions [15], and in mice mephedrone elicits conditioned place preference (CPP) and increases in locomotor activity [16], leads to locomotor sensitization [17], and lowers ICSS thresholds [18].

The existing behavioral and neurochemical data suggest that methylone may possess the potential for compulsive use. Behavioral studies have shown that methylone elicits CPP at doses of 2.5 mg/kg or higher in mice [19] and substitutes for 3,4-methylenedioxymethamphetamine (MDMA) in a drug-discrimination paradigm [20]. Furthermore, methylone possesses psychomotor stimulant effects in mice, but to a lesser extent compared to methamphetamine [20,21].

As mentioned above, synthetic cathinones are similar in chemical structure to amphetamines. Methylone is a benzylic ketone analog of MDMA and, not surprisingly, has been shown to have similar neurochemical effects on monoamine transporters. Uptake inhibition studies have reported that methylone blocks the reuptake of norepinephrine, dopamine, and serotonin plasma membrane transporters (NET, DAT, and SERT, respectively) with a profile similar to that of methamphetamine and MDMA, but with greater potency than methamphetamine for SERT, and three-fold less potency for SERT compared to MDMA [22-24]. Methylone has also been shown to be a less potent at inhibiting the vesicular monoamine transporter 2 (VMAT2) compared to methamphetamine, MDMA [23], and mephedrone [22]. However, while uptake assays suggest that methylone functions as a transporter blocker, these assays are unable to discern between drugs that are transporter blockers versus those that are monoamine releasing agents, as tissue accumulation of radiolabeled transmitters is decreased by both drug types [25]. However, additional studies have clarified these discrepancies and reveal that methylone is a non-selective monoamine releaser with properties similar to MDMA [24,26]. Also, in comparison to MDMA, methylone produces qualitatively similar, but less potent, increases in extracellular monoamine levels in the nucleus accumbens [26].

These neurochemical effects, along with the few behavioral studies outlined above, suggest that methylone may possess the potential for compulsive use. However, to our knowledge, there are no published reports showing that laboratory animals will acquire intravenous self-administration of methylone or if extended access to methylone (i.e., 6 hr/day) leads to escalated drug intake, a consumption pattern predictive of compulsive use in humans [27]. The present study examined whether methylone would support IVSA at doses of 0.05, 0.1, 0.2, or 0.5 (mg/kg/infusion) under short (ShA, 2 hr/day) and long (LgA, 6 hr/day) access conditions. A separate group of animals was tested for effects of methylone (0.1-10 mg/kg i.p.) on current intensity thresholds for ICSS.

Methods and Materials

Subjects

All experimental procedures were conducted with the approval of the Institutional Animal Care and Use Committee at Arizona State University and according to the Guide for Care and Use of Laboratory Animals as adopted by the National Institutes of Health. Male Sprague-Dawley rats (n=48), weighing approximately 250 g upon arrival, were implanted with jugular vein catheters at Harlan Laboratories (Livermore, CA, USA) and used for intravenous self-administration procedures. An additional 4 non-catheterized male Sprague-Dawley rats, weighing approximately 250 g (Harlan Laboratories) were used for ICSS procedures. Upon arrival, all rats were individually housed on a 12-hour light-dark cycle and provided *ad libitum* access to food and water during all procedures, except during surgical and behavioral testing procedures. All experimental procedures were conducted during the dark phase with the exception of 16 hr overnight progressive ratio tests which began at approximately 4:00 pm and ended the following morning at approximately 8:00 am.

Drugs

Methylone was synthesized by the Department of Discovery and Analytical Sciences at Research Triangle Institute (RTI) International (Research Triangle Park, NC, USA). Methylone was dissolved in sterile physiological saline for intravenous self-administration and intraperitoneal administration.

Experiment 1: IVSA procedures

Surgical procedures: Following one day of acclimation to housing conditions, rats were anesthetized with isoflurane (2% v/v) vaporized oxygen at a flow rate of 2 l/min. A 2.5-cm longitudinal incision was made between the scapulae for implantation of a threaded vascular access port (Plastics One, Roanoke, VA, USA). A mesh collar attached to the port was sutured underneath the surrounding tissue within the incision. Access ports were sealed with a piece of Tygon tubing and protective cap. Rats received one week of post-operative care including daily infusions of 0.4 ml Timentin (66.6 mg/ml, in 70 U/ml heparinized saline) to protect against infection and ensure catheter patency. Meloxicam (2.5 mg/kg, s.c.) was administered for the first 3 days following surgery procedures to provide relief from post-surgical discomfort. Rats also received approximately 8–10 pieces of a sweetened cereal in their home cage each day during the recovery period to minimize post-surgical weight loss.

Apparatus: Operant drug self-administration sessions were conducted in modular self-administration chambers (ENV-008, Med Associates, St. Albans, VT, USA). All self-administration chambers were located inside sound-attenuating cubicles containing a house light and exhaust fan designed to mask external noise and odours, and were interfaced to a personal computer. Chambers contained two stainless steel response levers located on one wall with a 4.2×5 cm food pellet receptacle placed between the levers. Response levers were located approximately 7 cm above the grid floor and positioned above each lever was a 2.5 cm diameter white stimulus light. Located near the top of the chambers was a Sonalert speaker that provided an auditory stimulus during drug delivery. Syringe pumps were located outside each chamber, interfaced to a PC computer, and delivered methylone solution via a single-channel liquid swivel mounted atop the chambers via polyethylene tubing.

Experimental design: IVSA procedures: Following recovery from surgical procedures, rats began experimental sessions and were allowed to spontaneously acquire intravenous self-administration in 2 hour daily (ShA) sessions for 21 days. IVSA procedures were conducted 7 days a week as described elsewhere [13,27]. Briefly, active lever presses delivered the drug reinforcer on an FR1 schedule of reinforcement. Methylone was delivered to the vascular access port by polyethylene tubing housed in a stainless steel spring tether that was attached to a liquid swivel. Reinforcers were accompanied by activation of a stimulus light and tone complex for 2 sec, followed by a 20 sec timeout period during which additional lever presses were recorded but produced no consequences. Inactive lever presses were also recorded, but produced no programmed responses at any time during the experiment. Rats were randomly assigned to one of four groups based upon methylone dose (0.05, 0.1, 0.2, or 0.5 mg/kg per infusion). Each drug infusion was delivered in a volume of 0.06 ml. Both before and after each IVSA

session, access ports were flushed with 0.2 ml Timentin (66.6 mg/ml, in 70 U/ml heparinized saline) to protect against infection and ensure catheter patency.

Following 21 days of ShA IVSA, rats were placed in a 16 hr overnight progressive ratio (PR) sessions. During the PR session, methylone was delivered on a schedule determined by the following equation: responses per reinforcer delivery $=5 \times e^{(\text{injection number} - 0.2)} - 5$ (i.e. 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, etc.) [28,29]. Breakpoints were considered to be obtained when rats did not emit any active lever presses for 2 hr. Following PR tests, all rats were placed into 6 hr LgA sessions on a FR1 schedule for 10 additional days to assess escalation of drug intake. Finally, following 10 days of LgA sessions, rats were placed into an additional PR session to assess any changes in reinforcer efficacy following extended access. For both PR and LgA sessions, all aspects of IVSA sessions were identical except for session length and number of lever presses required for an infusion.

Based on earlier MDMA self-administration studies [30], methylone was considered to function as a reinforcer for individual responding greater on the active lever exceeded 10 lever presses per session. Figure 2 shows the percentage of rats for each dose group that responding greater than 10 times on the active lever for each experimental session.

Experiment 2: ICSS procedures

Surgical procedures: Rats were anesthetized with isoflurane (2% v/v) vaporized oxygen at a flow rate of 2 l/min and placed into a stereotaxic frame. A twisted stainless steel bipolar electrode (PlasticsOne, Roanoke, VA, USA; 2 mm diameter, insulated except at the ventral tip) was implanted into the medial forebrain bundle (anterior-posterior -0.5 mm; medial-lateral, 1.7 mm, dorsal-ventral, -8.3 mm from dura and bregma). Four skull screws and dental cement were used to permanently secure electrodes to the skull. To counterbalance for any hemispheric differences, half of the animals received electrodes in the left hemisphere and the other in the right hemisphere. Following surgery, the rats were given 7 days of recovery prior to commencement of ICSS procedures, during which they received daily injections of 2.5 mg/ml meloxicam (0.15 ml volume) to minimize post-surgical discomfort.

Apparatus: All ICSS testing was conducted in modular chambers (ENV-007CT; Med Associates). Chambers were housed inside sound-attenuating cubicles equipped with an exhaust fan to mask external noise and odors. Chambers contained front wall mounted nose-poke aperture with light-emitting diode (LED) stimulus lights located inside the access hole (ENV-114M; Med Associates). The nose poke aperture was 2.5 cm in diameter, located 5 cm above the stainless steel grid floor, and contained an infrared detector placed 0.64 cm from the front edge of the panel for recording responses. Located outside the chamber was a dual programmable ICSS stimulator (PHM-150B/2; Med Associates) that was interfaced to a PC which delivered electrical current to the electrode. MED-PC IV software was used to control all stimulation parameters, test functions, and data collection.

Experimental design: ICSS procedures: The procedures for determination of ICSS thresholds was a modified version of the discrete trials current-threshold method [31,32]. Briefly, following acquisition procedures, reward threshold training commenced and rats were tested for a minimum of 10 days until stable baseline levels of reward thresholds were achieved (defined as when the average of thresholds for the last 4 days minus the first 4 days of an 8-day window was less than 10% of the average of the full 8 days). Rats continued to undergo baseline (i.e., no drug administration) testing throughout the course of experiments every three days. Rats received vehicle injections 20 min prior to ICSS threshold determination procedures every 3 days. Methylone doses (0.1, 0.5, 1, 3, 5, and 10 mg/kg, i.p.) were assigned randomly and injections given 20 min prior to threshold determination procedures every three days. All rats received 4 to 5 threshold determinations at each dose of methylone and at least 10 threshold determinations following administration of saline vehicle.

Statistical Analysis

All statistical analyses were conducted using SPSS version 20 (Armonk, NY, USA). All data points represent the mean ± standard error of the mean (SEM). A significance criterion of $p<0.05$ was used for all analyses. For Experiment 1 during the initial 21 days of self-administration procedures, individual methylone doses were analyzed by a mixed analysis of variance (ANOVA) with lever (active versus inactive) as between measures factors and session number (1-21) as the repeated measures factor. Post-hoc one-way ANOVAs were conducted to determine when successful lever discrimination occurred. The total number of infusions obtained during experimental sessions was also analyzed with a mixed ANOVA with methylone dose (0.05, 0.1, 0.2, and 0.5 mg/kg) as between measures factors and session number (1-21) as the repeated measures factor. Holm-Sidak post-hoc tests further analyzed dose effects for each session. The total number of infusions obtained during PR tests was analyzed in a mixed ANOVA with dose as the between measures and PR tests (before and after LgA) as the repeated measures with Holm-Sidak post-hoc tests. For LgA sessions, the total number of infusions obtained during experimental sessions was analyzed with a mixed ANOVA with methylone dose and session number (1-10) as the repeated measures factor. Furthermore, one-way repeated measures ANOVAs were conducted for each dose separately to analyze for escalation of drug intake across experimental sessions. Data from rats removed from the study due to overdose or loss of catheter patency were removed from statistical analyses. For Experiment 2, raw ICSS current intensity thresholds (in μA) obtained following all doses and vehicle were converted to scores reflecting the percent change from mean baseline scores obtained following stabilization for each rat. Threshold measures following baseline days were calculated by averaging ICSS thresholds obtained across all baseline days following initial stabilization. Percentage change scores were analyzed by one-way repeated measures ANOVA.

Results

Lever discrimination during ShA

Throughout the course of the study, 3 of 48 rats were removed from experimental procedures due to catheter patency failure. Also, 2 additional rats in the 0.5 mg/kg/infusion group died on LgA days 7 and 10, respectively, presumably due to overdose. For the 0.05 mg/kg dose group (Figure 1A), significant main effects of lever ($F_{1,21}=8.54$, $p<0.01$) and session number ($F_{20,420}=2.07$, $p<0.01$) were observed, as well as a significant lever X session number interaction ($F_{20,420}=2.73$, $p<0.001$). Presses on the active lever were significantly greater than on the inactive lever for sessions 3–21 ($p<0.05$) indicating that rats in the 0.05 mg/kg dose group successfully discriminated between the active and inactive levers after 3 experimental sessions.

For the 0.1 mg/kg dose group (Figure 1B), significant main effects of lever ($F_{1,20}=8.59$, $p<0.01$) and session number ($F_{20,400}=2.15$, $p<0.01$) were observed, as well as a significant lever X session number interaction ($F_{20,400}=2.48$, $p<0.001$). Presses on the active lever were significantly greater than on the inactive lever for sessions 6–21 ($p<0.05$) indicating that rats in the 0.1 mg/kg dose group successfully discriminated

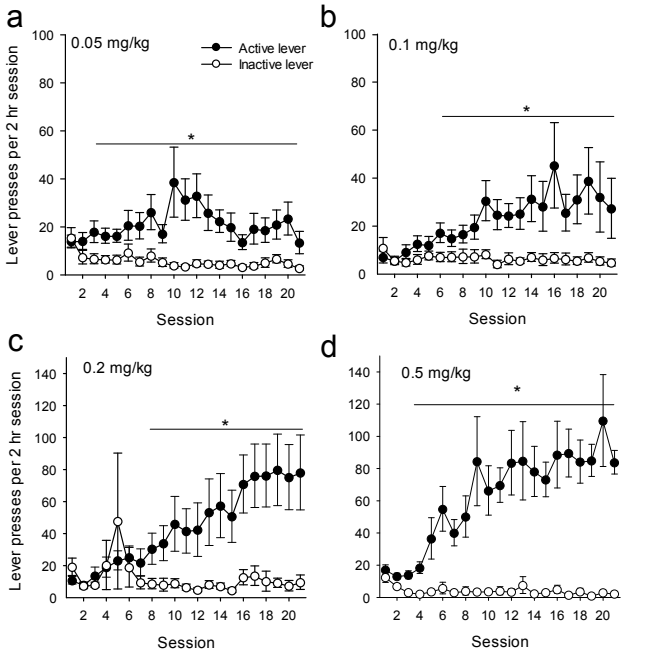

Figure 1: Intravenous self-administration (IVSA) of methylone. Data presented are active and inactive lever presses across the first 21 days of IVSA sessions for the (a) 0.05 (b) 0.1 (c) 0.2 and (d) 0.5 mg/kg/infusion groups (n = 12 for 0.05 and 0.5 mg/kg/infusion groups; n = 11 for the 0.1 and 0.2 mg/kg/infusion groups). *p<0.05 between active and inactive lever presses.

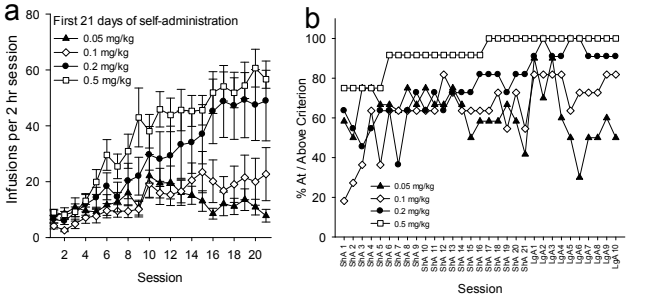

Figure 2: (a) Total number of infusions obtained during the first 21 days of 2 hr daily access sessions for each dose of methylone tested (n=12 for 0.05 and 0.5 mg/kg/infusion groups; n = 11 for the 0.1 and 0.2 mg/kg/infusion groups). (b) Percent of animals at or above criterion (10 active lever presses per session) for each experimental session.

between the active and inactive levers after 6 experimental sessions.

For the 0.2 mg/kg dose group (Figure 1C), significant main effects of lever ($F_{1,20}$=6.07, p<0.05) and session number ($F_{20,400}$=3.03, p<0.001) were observed, as well as a significant lever X session number interaction ($F_{20,400}$=4.49, p<0.001). Presses on the active lever were significantly greater than on the inactive lever for sessions 8–21 (p<0.05) indicating that rats in the 0.2 mg/kg dose group successfully discriminated between the active and inactive levers after 8 experimental sessions.

For the 0.5 mg/kg dose group (Figure 1D), significant main effects of lever ($F_{1,22}$=30.42, p<0.05) and session number ($F_{20,440}$=6.25, p<0.001) were observed, as well as a significant lever X session number interaction ($F_{20,440}$=7.14, p<0.001). Presses on the active lever were significantly greater than on the inactive lever for sessions 2–21 (p<0.05) indicating that rats in the 0.1 mg/kg dose group successfully discriminated between the active and inactive levers after 2 experimental sessions.

Infusions during ShA

For overall methylone intake (as determined from the total number of drug infusions obtained, figure 2) significant main effects of methylone dose ($F_{3,41}$=6.477, p<0.001) and session ($F_{20,820}$=25.67, p<0.001) were observed, along with a significant dose X sessions interaction ($F_{60,820}$=4.579, p<0.001). The overall number of methylone infusions obtained per 2 hr session across all 21 sessions was significantly greater in the 0.5 mg/kg group versus the 0.05 mg/kg group (p<0.01) and the 0.1 mg/kg group (p<0.01). Post-hoc tests revealed a greater number of infusions obtained at the 0.5 mg/kg dose versus the 0.05 and 0.1 mg/kg dose group for days 11–21 (p<0.05).

Progressive ratio tests

Analysis of breakpoints (Figure 3A) during PR sessions revealed significant main effects of methylone dose ($F_{3,37}$=9.209, p<0.001) and PR session ($F_{1,37}$=34.691, p<0.001). However, a significant dose X PR session interaction was not observed ($F_{3,37}$=1.166, p>0.05). For all doses tested, breakpoints decreased significantly from the first PR test (5.93 ± 0.52, mean ± SEM) to the PR test following LgA (3.34 ± 0.33, mean ± SEM). Post-hoc tests revealed that the total number of infusions obtained in the 0.5 mg/kg dose group was significantly greater than that of the 0.05 mg/kg (p<0.001), 0.1 mg/kg (p<0.001), and 0.2 mg/kg doses (p<0.01). While there were no significant differences observed among the three lower doses, there did appear to be a positive relationship between methylone dose and breakpoints.

Assessment of escalated intake during LgA

Analysis of the total number of infusions obtained during LgA sessions (Figure 3B) revealed a significant main effect of dose ($F_{3,38}$=7.035, p<0.001). However, there was no significant main effect of session (p>0.05), and a dose X session interaction only revealed a trend towards significance ($F_{27,3421}$=1.466, p=0.06). Pairwise comparisons revealed significant overall differences between the 0.05 mg/kg vs. the 0.2 and 0.5 mg/kg doses (p<0.05 and 0.001, respectively). No other pairwise comparisons between doses were significant. Analysis of escalation for each dose independently did not reveal escalated intake across experimental sessions for the 0.1 mg/kg and 0.2 mg/kg doses (p>0.05). Significance was obtained for both the 0.5 mg/kg ($F_{9,81}$=2.315, p<0.05) and 0.05 mg/kg doses ($F_{9,81}$=4.829, p<0.05). However this occurred as a result of reduced numbers of infusions across the 10

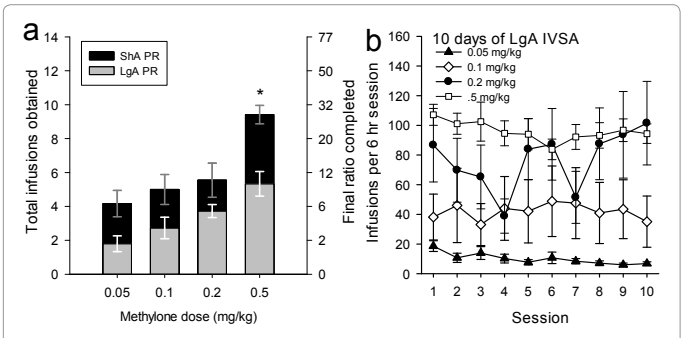

Figure 3: Total number of infusions earned during progressive ratio (PR) tests following 21 days of ShA sessions (ShA PR) and 10 days of LgA sessions (LgA PR) for the 0.05, 0.1, 0.2, and 0.5 mg/kg/infusion groups (n = 12 for 0.05 and 0.5 mg/kg/infusion groups; n = 11 for the 0.1 and 0.2 mg/kg/infusion groups). *p<0.05 compared to the 0.05, 0.1, and 0.2 mg/kg/infusion dose groups. (b) Total number of infusions obtained during the 10 days of LgA IVSA sessions for each dose of methylone tested (n=10 for 0.05 and 0.5 mg/kg/infusion groups; n = 11 for the 0.1 and 0.2 mg/kg/infusion groups).

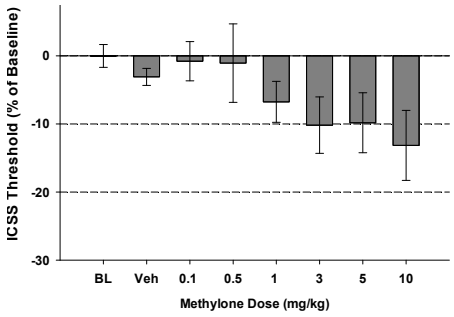

Figure 4: Effects of saline vehicle and methylone (0.1, 0.5, 1, 3, 5, and 10 mg/kg, i.p.) on intracranial self-stimulation (ICSS) current-intensity thresholds (n=4).

LgA sessions. For the 0.5 mg/kg dose group, pairwise comparisons did not reveal significant differences between individual sessions. For the 0.05 mg/kg group, pairwise comparisons revealed that the significance occurred only between day 1 and day 2 ($p<0.01$). No other pairwise comparisons were significant.

Assessment of ICSS thresholds

Repeated measures ANOVA did not reveal a significant effect of methylone dose on ICSS thresholds, however a trend was observed ($F_{7,163}=1.783$, $p=0.09$) (Figure 4).

Evidence of toxicity

In addition to the IVSA and ICSS results outlined above, it is also important to mention that during LgA sessions, a number of adverse effects of methylone self-administration were observed. The most common adverse effects were porphyrin staining and foaming at the mouth that typically began during sessions 3-4 of LgA conditions. These effects were observed in nearly all animals in the 0.5 mg/kg and roughly half of the 0.2 mg/kg group during the course of LgA procedures and, once manifested, typically continued until completion of the experiment. Additionally, two rats in the 0.5 mg/kg group self-administered methylone to the point of seizure (after 114 and 138 total infusions each), and despite being immediately removed from the self-administration chamber, died within 20 minutes of removal.

Discussion

The present study revealed that methylone serves as a reinforcer as rats dose-dependently acquired IVSA of methylone through spontaneous acquisition procedures. In Experiment 1, during 21 days of 2 hr daily access sessions, orderly dose-dependent differences in overall drug intake were observed across groups and rats successfully discriminated between active and inactive levers by days 3, 6, 8, and 2 for the 0.05, 0.1, 0.2, and 0.5 mg/kg per infusion groups, respectively. These findings indicate that responding occurred due to the reinforcing effects of methylone and not from any non-specific response-enhancing effects of methylone. This study further revealed a positive dose-dependent relationship between methylone dose and reinforcer efficacy as measured by breakpoints obtained during PR sessions both prior to and following LgA. Furthermore, while methylone intake was greater in LgA when compared to asymptotic responding during ShA sessions, none of the dose groups displayed escalated drug intake across experimental sessions. Finally, Experiment 2 revealed that methylone did not significantly decrease ICSS thresholds, suggesting a lack of effect on brain reward function.

To our knowledge, this study is the first to systematically verify that methylone serves as a reinforcer in the IVSA paradigm in drug-naïve animals. To date, discussions about reinforcing effects and abuse liability of synthetic cathinones have largely come from its comparison to amphetamine-type stimulants such as methamphetamine and MDMA. Most often, methylone has been compared to MDMA due to its similar chemical structure, similar *in vitro* binding and *in vivo* neurochemical data, and the early reports that methylone produced subjective effects similar to MDMA, but lacked the "unique magic" produced by MDMA [33]. Given this precedent, a comparison of the current results to previous work with MDMA serves as a logical starting point. However, it is important to state from the outset that comparisons of the present results with earlier findings must be interpreted with caution, as each of these studies employed somewhat different experimental procedures. Initial MDMA IVSA experiments by multiple investigators that revealed that MDMA functions as a reinforcer in rats. However, inconsistent and low response rates indicated that MDMA was a weak-to-moderate reinforcer since only a subset of animals acquired self-administration [34,35]. Additional IVSA studies with rhesus monkeys and baboons also revealed similar weak-to-moderate reinforcing properties [36,37]. Later studies by Schenk et al. found that in a subset of rats, MDMA could support higher rates of self-administration than those observed in earlier reports [30,38,39], corroborating reports in humans that compulsive use is possible in certain individuals [40]. When compared to the collective results from these studies of MDMA self-administration, methylone appears to support more robust self-administration responding than does MDMA, albeit with a rightward shift in the inverted dose-effect curve. All methylone doses tested in the present study supported IVSA, and lever-discrimination occurred for all rats on days 3, 6, 8, and 2 for the 0.05, 0.1, 0.2, and 0.5 mg/kg/infusion groups, respectively. Furthermore, as revealed in figure 3B, while only about 40-60% of rats pressed the active lever more than 10 times a session for the 0.05 mg/kg group between sessions 15-21, the 0.1, 0.2, and 0.5 mg/kg/infusion groups demonstrated group acquisition percentages that were approximately 60, 80, and 100%, respectively. Thus, at the higher doses, a larger percentage of rats acquired methylone IVSA in 2 hr daily sessions than rats self-administering MDMA in 6 hr daily access sessions (i.e., 60% for both the 0.25 mg/kg/infusion and 1 mg/kg/infusion MDMA dose groups) using nearly identical acquisition criterion (>10 lever presses per session) [30]. More recent work by Schenk and colleagues revealed that across 25 days of 2 hr IVSA sessions MDMA (1.0 mg/kg/infusion), only 49% (63 of 128 rats) acquired a total of ≥ 90 infusions across experimental sessions [39]. The present study revealed that only 5 rats failed to accumulate ≥ 90 infusions by the end of session 21, with 3 of those rats being in the 0.05 mg/kg group, 1 in the 0.1 mg/kg group, 1 in the 0.2 mg/kg group, and 0 in the 0.5 mg/kg group (data not shown). Together, these results are also consistent with previous studies showing that lower doses of methylone (≥ 2.5 mg/kg/i.p.) vs. MDMA (≥ 9 mg/kg/i.p.) elicit conditioned place preference in mice [19,41-43].

In addition, it is also important to mention differences in lever pressing behavior for methylone observed in the present study as compared to our previous findings with MDPV [14], as these are the first two published studies to establish initial dose-effect curves for IVSA of these two synthetic cathinones. Specifically, the highest methylone dose tested in the present study (0.5 mg/kg/infusion) lead to a maximum number of lever presses of approximately 100 after roughly twenty 2 hr IVSA sessions. In our previous MDPV study, the lowest dose tested (0.05 mg/kg/infusion) lead to approximately 200 active lever presses after only seven 2 hr IVSA sessions. Thus, while future studies must establish full IVSA dose-effect curves before direct comparisons can be

made between methylone and MDPV, our initial results suggest that MDPV is a much more potent reinforcer than methylone.

While our 2 hr IVSA acquisition data suggest stronger reinforcing properties of methylone compared to MDMA, our PR data appear similar to those obtained from previous studies on PR responding for MDMA. For example, the total number of infusions obtained for MDMA doses of 0.25 and 1.0 mg/kg/infusion were approximately 4.5 and 12.5, respectively [30], whereas our present methylone results with (0.2 and 0.5 mg/kg/infusion) revealed similar breakpoints with approximately 5.5 and 9.5 infusions, respectively. When compared to previous results with MDPV and prototypical stimulants d-amphetamine and methamphetamine, and using an identical PR procedures and doses (0.05, 0.1, and 0.2, mg/kg/infusion), methylone breakpoints in the present study were comparatively much lower [14,28,29]. Specifically, methylone breakpoints for these doses were approximately 4, 5, and 5.5, respectively, whereas our MDPV breakpoints were approximately 8, 10, and 15, respectively. Thus, the reinforcer efficacy of methylone appears to be significantly lower than that of MDPV. In addition to the initial progressive ratio tests following ShA procedures, the PR tests following extended access revealed similar dose effects, but compared to initial PR tests, the overall reinforcing efficacy was lower during the second test. This apparent decease in motivation to seek methylone following LgA is in contrast to previous work with cocaine [44] and methamphetamine [45] which have been shown to elicit greater PR responding following extended access. To our knowledge, PR data following LgA has not been reported for MDMA. These results suggest that methylone likely possesses a reinforcer efficacy that more closely resembles MDMA and is similarly weaker compared to other prototypic stimulants [27].

In addition to the results obtained during ShA and PR procedures, LgA sessions did not lead to escalated drug intake across experimental sessions. Our previous findings of responding for MDPV reinforcement under extended access conditions revealed escalated intake across LgA sessions [14], similar to previous findings with cocaine and methamphetamine [46,47]. While others have found evidence of escalated MDMA intake [48], this phenomenon only occurred with extended testing, and to our knowledge, there are no reports of escalated MDMA intake across experimental LgA following prior asymptotic responding on ShA. While none of the doses of methylone tested here led to escalated intake, it is possible that escalation of intake might occur with higher doses of methylone (i.e., 1.0 mg/kg/infusion), as we have shown that only higher doses of the MDPV produce escalation of intake [14]. Furthermore, while these data suggest that the potential for *compulsive* use of methylone in humans appears less likely than prototypic stimulants, replication of these results with additional animal experiments, as well as human studies, are ultimately needed before conclusions about abuse liability can be made.

Despite our non-significant ICSS results, a trend towards dose-dependent threshold decreases suggest that methylone may possess hedonic properties, corroborating reports of euphoric subjective effects in humans [7,10]. Furthermore, while it could be argued that higher doses and/or greater experimental power (observed power in the present study was 0.326) may have yielded significance, the decrease in reward thresholds produced by methylone here appear similar, but slightly weaker in magnitude, to those previously reported for MDMA [49,50], and are much less robust than decreases reported for cocaine, d-amphetamine, methamphetamine, and MDPV [14,51]. In the present study, the highest dose of methylone (10 mg/kg) produced threshold reductions that were smaller (13%) than the lowest dose (0.1 mg/kg) of MDPV (16%) previously tested under identical ICSS procedures [14]. Thus, while our self-administration data suggests that methylone functions as a stronger reinforcer than MDMA, our ICSS data suggest similar or weaker rewarding properties compared to MDMA. This effect is somewhat surprising in light of the more robust self-administration and stronger rewarding effects of methylone, as revealed in CPP studies mentioned above, as compared to MDMA. Thus, replication of these findings is needed before definitive conclusions can be reached.

In addition to the aforementioned measures of abuse liability, rats in the two higher dose groups showed signs of toxicity including porphyrin staining, foaming at the mouth, and death. For the two rats in the 0.5 mg/kg/infusion group which self-administered methylone to the point seizure and death, the total infusions obtained during this session were 114 and 138. Interestingly, both of these subjects had previously obtained a higher number of infusions in earlier LgA sessions, the highest being 214 and 198, respectively. Thus, these fatalities appear to be the result of repeated methylone self-administration and not necessarily the acute effects of a single intake session. These observations reveal the need for further studies regarding the toxic effects of methylone that may provide additional information about various reports of toxicity and death associated with methylone use in humans [10,52,53].

Overall, these results fit with previous research showing that the ratio of dopamine-serotonin release induced by psychostimulants is positively correlated with self-administration patterns, ICSS threshold-lowering ability, and addiction liability [31,54-56]. The *in vitro* release data from Baumann revealed a DAT/SERT transporter mediated release for methylone (1.82) to be similar to MDMA (0.97), along with qualitatively similar microdialysis release data. In contrast, methamphetamine and d-amphetamine DAT/SERT ratios are 152.0 and 219.5, respectively [25,54]. While our results generally conform to this hypothesis, the results here also demonstrate the importance of behavioral experiments in assessing pharmacological nuances not explicitly revealed in neurochemical assays. Prior to the current study, methylone was primarily compared to MDMA and predicted to exert similar effects. However, our data revealed more robust self-administration during 2 hr sessions than previously shown for MDMA, predictive of a greater addiction liability and suggestive of other possible neurochemical differences between methylone and MDMA not accounted for in previous monoamine assays. Furthermore, given the lack of escalation in LgA, relatively weak PR responding, and weak variable ICSS results, our study demonstrates the importance of testing beyond basic self-administration. The lack of escalation during LgA and weak variable ICSS effects may be reflective of lower dopamine-serotonin ratios and more indicative of lower compulsive use liability (episodic vs. compulsive use).

Finally, it is also important to mention some limitations of the current study. The primary limitation of the current study is a relatively small number of subjects in both the IVSA experiments (n=48) and ICSS experiments (n=4). One of the main conclusions made from the current study is that methylone possesses a relatively low abuse liability given the lack of escalation in LgA. While it does not appear likely that any dose group would display significant escalated intake, it is possible that with additional subjects, escalated intake might have been observed in a subset of animals. Further studies are needed to evaluate this possibility. In addition, ICSS experiments were performed with only 4 rats, and it is possible that additional subjects would have yielded statistical significance, as only a trend towards significance (p=0.09) was observed. Another limitation of the current study is that it was conducted with drug-naive animals. While demographic information regarding methylone users is scarce, it is possible that individuals with previous experience with illicit stimulants may be more sensitized to the reinforcing properties methylone. These possibilities warrant further

investigation. Finally, it is important to reiterate that while our results suggest more potent reinforcing properties of methylone as compared to MDMA, and weaker reinforcing properties compared to MDPV and other prototypic stimulants, our study is the first to demonstrate methylone IVSA. Thus, replication of our initial IVSA results, as well as additional studies directly comparing methylone to MDMA and other psychostimulants, is needed before definitive conclusions can be made.

In general, the IVSA results from the present study reveal that MDMA functions as a moderate reinforcer that appears stronger than MDMA given the more rapid rate and greater percentage of rats acquiring self-administration compared to previous MDMA self-administration studies. However, the weak PR responding and lack of escalated methylone intake in LgA indicate that methylone is weaker than prototypic stimulants. These results are complimented by our ICSS results which reveal a trend towards lowering ICSS thresholds similar to previous studies on MDMA. These results provide initial evidence which suggests that methylone possesses an abuse liability similar to or slightly greater than MDMA, but significantly lower other prototypic stimulants. In humans, MDMA is generally considered to have a low *addiction* liability as consumption patterns are generally intermittent rather than compulsive [57]. This is not without exception, however, as methylone dependence has been reported in some individuals [40]. Extrapolating from our results, one would predict that methylone dependence may be possible in a subset of individuals, but that consumption patterns would also generally stay intermittent and typically not advance to compulsive use. However, this conjecture requires validation from additional human experimental and epidemiological research, and definitive conclusions about human consumption patterns cannot be made at this time. Nonetheless, our findings provide an initial behavioral characterization of the reinforcing and rewarding effects of methylone and have important implications for future synthetic cathinone research, treatment specialists, and the development of appropriate regulatory policies.

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