Binge-like Acquisition of α-pyrrolidinopentiophenone (α-PVP) Self-Administration in Female Rats

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Abstract

The synthetic cathinone α-pyrrolidinopentiophenone (α-PVP) recently drew attention due to reports of violent and/or bizarre public behavior in users. Association of such behavior with extended binges of drug use motivates additional investigation, particularly since a prior study found that half of male rats experience a binge of exceptionally high intake, followed by sustained lower levels of self-administration during the acquisition of intravenous self-administration (IVSA) of a related drug, 3,4-methylenedioxypyrovalerone. The pattern appeared to be novel for rat IVSA, thus the present study was designed to determine if this effect generalizes to IVSA of α-PVP in female rats.

Female Wistar rats were trained in IVSA of α-PVP (0.05 mg/kg/inf) in operant boxes that contained an activity wheel. Groups (N=12 per group) of animals were trained with the wheels fixed (No-Wheel group) or free to move (Wheel group). Following acquisition, the groups were subjected to a wheel-access switch and then all animals to dose-substitution (0.0125-0.3 mg/kg/inf) with the wheels alternately fixed and free to move.

Half of the rats initiated their IVSA pattern with a binge day of exceptionally high levels of drug intake, independent of wheel access condition. Wheel activity declined as acquisition progressed in the Wheel group and was much lower in the No-Wheel group in the wheel switch post-acquisition. Dose-effect curves were similar for binge/no binge subgroups and were not altered with wheel access during the dose-substitution. This confirms the high reinforcer efficacy of α-PVP in female rats and the accompanying devaluation of wheel activity as a naturalistic reward.

1. Introduction

The structurally related (see **Figure 1**) cathinone derivative psychostimulant drugs 3,4-methylenedioxypyrovalerone (MDPV) and α-pyrrolidinopentiophenone (α-PVP) are monoamine transporter inhibitors with high selectivity for dopamine over serotonin or norepinephrine transporters. These compounds are highly effective and potent reinforcers in male rats when assessed with the intravenous self-administration (IVSA) model (Aarde et al., 2013; Schindler et al., 2016; Watterson et al., 2014), and MDPV and α-PVP have been shown to be approximately equipotent when directly compared under a Progressive Ratio schedule of reinforcement in IVSA (Aarde et al., 2015a; Gannon et al., 2017), again in male rats. Although female rats will self-administer more cocaine (Roth, M. E. and Carroll, M. E., 2004; Smith et al., 2011) and more methamphetamine (Reichel et al., 2012; Roth, Megan E. and Carroll, Marilyn E., 2004) than male rats, the IVSA of entactogen stimulants such as mephedrone, methylone and 3,4-methylenedioxymethamphetamine (MDMA) does not differ substantially between male and female rats (Creehan et al., 2015; Vandewater et al., 2015). Other studies have failed to find any sex-difference in IVSA of cocaine in rats (Miller et al., 2017; Perry et al., 2013) or the oral self-administration of cocaine in mice (DePoy et al., 2016) and in some cases male rats may acquire cocaine IVSA more rapidly and in higher proportion compared with female rats (Swalve et al., 2016). These findings caution against simple assumptions about sex differences in drug IVSA and recommend investigation of the abuse liability of novel drugs in female as well as male rats to establish similarities and differences that might exist.

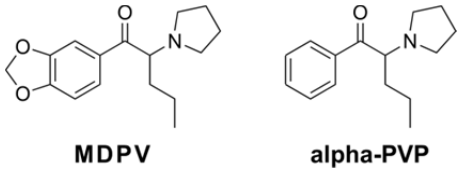

Figure 1: Chemical structures of MDPV and α-PVP.

A binge-like acquisition pattern of MDPV IVSA has been previously reported for male rats (Aarde et al., 2015b). In this pattern, a session was observed early in acquisition for about half of the individual rats wherein drug intake was particularly high on one day, but this was followed by a subsequent pattern of lower, but sustained intake for subsequent sessions. This binge-like pattern has not been reported for the acquisition of IVSA of other psychostimulants, but it is unclear if such individual patterns have simply been overlooked in typical group-mean analysis or if such patterns do not typically occur with other

drugs. The present study was therefore designed to determine if the binge-like acquisition would occur in female rats during acquisition of α-PVP IVSA.

Prior studies have also shown that provision of an activity wheel in the home cage reduces IVSA of cocaine, methamphetamine, MDMA or mephedrone on the following session (Aarde et al., 2015c; Smith and Witte, 2012). Wheel access provided concurrently with the IVSA session reduced intake of methamphetamine in male rats previously trained to press the lever for food reward (Miller et al., 2012) and cocaine IVSA in female rats with previous wheel experience (Cosgrove et al., 2002). Concurrent wheel access did not affect the acquisition of MDPV IVSA in behaviorally naïve male rats (Aarde et al., 2015b), however the ongoing IVSA of MDPV was accompanied by a gradual group mean decrease in wheel activity, similarly to male Wistar and Sprague-Dawley rats allowed to IVSA methamphetamine (Miller et al., 2012). Furthermore, the group mean trend for the MDPV study obscured the essentially immediate transition within-animal whereby IVSA of MDPV supplanted wheel activity within a single session for many of the subjects. One major goal of this study was to determine if a similar co-option of wheel reinforcement would generalize to female rats trained to IVSA α-PVP, further confirming the conclusion that the restricted transporter cathinones are particularly powerful as reinforcing stimuli.

2. Methods

2.1 Subjects

Female (N=32) Wistar rats (Charles River, New York) entered the laboratory at 10 weeks of age and were housed in humidity and temperature-controlled (23±1 °C) vivaria on 12:12 hour light:dark cycles. Animals had ad libitum access to food and water in their home cages. All experimental procedures took place in scotophase and were conducted under protocols approved by the Institutional Care and Use Committees of The Scripps Research Institute and in a manner consistent with the Guide for the Care and Use of Laboratory Animals (National Research Council (U.S.). Committee for the Update of the Guide for the Care and Use of Laboratory Animals. et al., 2011).

2.2 Drugs

The α-pyrrolidinopentiophenone HCl (α-PVP) was obtained from Cayman Chemical and dissolved in physiological saline for the i.v. route of administration. Dosing is expressed as the salt.

2.3 Intravenous catheter implantation

Rats 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., 2015a; Aarde et al., 2013; Miller et al., 2013; Nguyen et al., 2017). Briefly, the catheters consisted of a 14-cm length polyurethane based tubing (MicroRenathane®, 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 secured gently with suture thread. A liquid tissue adhesive was used to close the incisions (3M™ Vetbond™ Tissue Adhesive; 1469S B). A minimum of 4 days was allowed for surgical recovery prior to starting an experiment. For the first 3 days of the recovery period, an antibiotic (cephazolin) and an analgesic (flunixin) were administered daily. During testing and training, intra-venous catheters were flushed with ~0 .2–0.3 ml heparinized (32.3 USP/ml) saline before sessions and ~0.2–0.3 ml heparinized saline containing cephazolin (100 mg/ml) after sessions. Catheter patency was assessed once a week, beginning in the third week of training, 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 s after infusion. Animals that failed to display these signs were considered to have faulty catheters and were discontinued from the study. Data that were collected after the previous passing of the test were excluded from analysis.

Operant conditioning chambers (Med Associates Model ENV-045; Med-PC IV software) enclosed in sound-attenuating cubicles were used for concurrent wheel access and self-administration as previously described (Aarde et al., 2015b). Chambers were equipped with slanted activity wheels (~100

cm inner circumference, 30 degree tilt of running surface relative to the disk/back), which allowed wheel access while tethered for self-administration. Eight total chambers were available thus animals were run in three sequential daily (M-F) cohorts with N=4 Wheel and N=4 No-Wheel per run.

2.4 Experiments

2.4.1 Acquisition and Wheel Switch: Female Wistar rats were prepared with intravenous catheters and trained to self-administer α-PVP (0.05 mg/kg per infusion) using a fixed-ratio 1 (FR1) response contingency. A pump pulse calculated to clear non-drug saline through the catheter started the session to ensure the first reinforcer delivery was not diluted, and a single priming infusion was delivered non-contingently if no response was made in the first 30 minutes of the session. The Wheel group (N=12) had the wheels unlocked and the No-Wheel group (N=12) had the wheels locked for the first 20 sessions. The wheel-access conditions were then switched for Sessions 21-27.

2.4.2 Dose Substitution: Thereafter, animals were subjected to dose substitution (0.0125, 0.025, 0.05, 0.1, 0.3 mg/kg/infusion) sessions in a randomized order. Half of the rats first completed a dose-substitution series with the wheel locked and half of the rats with the wheel unlocked (~half of each original wheel Group in each wheel condition). The dose-substitution was then repeated with the wheel-access conditions switched such that all rats completed one series with the wheel locked and one series with it unlocked.

2.5 Data Analysis

The number of infusions obtained in the acquisition and wheel switch intervals was analyzed by Analysis of Variance (ANOVA) with Sessions as a within-subjects factor and wheel access Group as a between-subjects factor. The dose-substitution data were analyzed with Dose and Wheel Access as within-subjects factors. Significant main effects from the ANOVAs were further analyzed with post hoc multiple comparisons analysis using the Tukey procedure for multi-level factor, and the Sidak procedure for two- level factor, comparisons. Survival analysis (Mantel-Cox log-rank) was used to compare

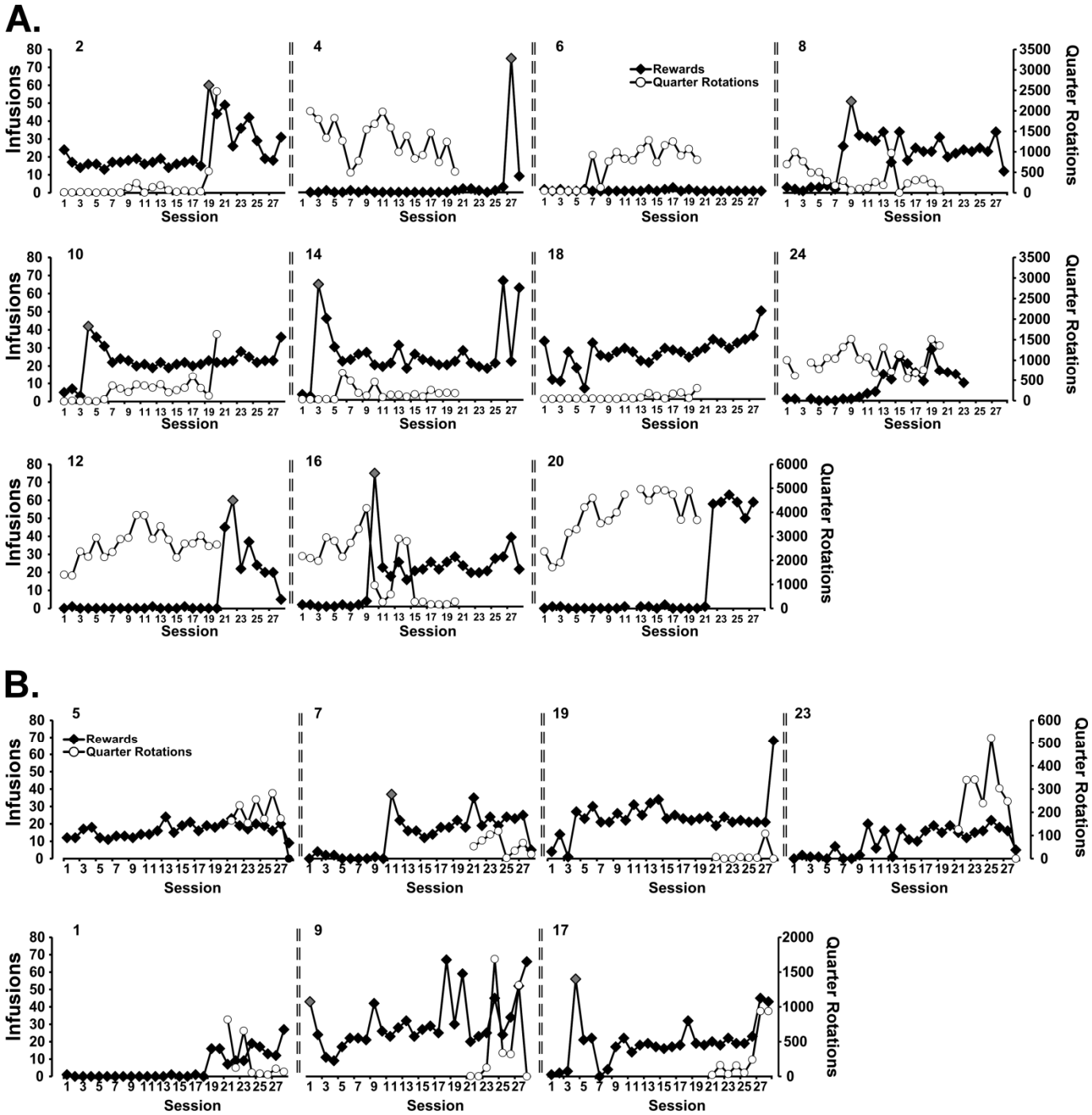

Figure 2: Individual infusions and wheel activity across the acquisition and wheel switch intervals for A) Wheel (N=11) and B) No-Wheel (N=7), acquisition groups. Grey symbols highlight the binge sessions.

the rate at which the Groups met an acquisition criterion of 3 sequential sessions with at least 6 infusions obtained; see (Aarde et al., 2015b). The criterion for significant results was at $P < 0.05$ and all analyses were conducted using Prism 7 for Windows (v. 7.03; GraphPad Software, Inc, San Diego CA).

3. Results

3.1 Acquisition

A total of N=18 (N=7 No-Wheel, N=11 Wheel) rats retained patent catheters throughout acquisition and the wheel switch part of the study. Examination of individual patterns of drug self-administration during the acquisition and wheel switch intervals under fixed per-infusion dose conditions confirmed the binge pattern in 6 / 11 Wheel animals and 3 / 7 No-Wheel animals (**Figure 2**). Two additional Wheel rats (#2, #4) also exhibited a spontaneous binge day however this followed 18 sessions of sustained high intake in one animal and occurred during the wheel switch interval in the other. The wheels in two of the operant boxes were found to be partially malfunctioning to the extent they did not move normally with an animal's weight and were adjusted after 6 sessions. This affected half of the "Wheel" group (#2, 6, 10, 14 and 18 of those that remained patent) and created a new Wheel group which effectively was a No-Wheel group for the initial 6 sessions. All of the wheels were moveable by rats after this point, however it appeared that one of them (affecting #2, 10 and 18) was not fully free and a lubrication on the final session led to further increased activity for all of the affected animals.

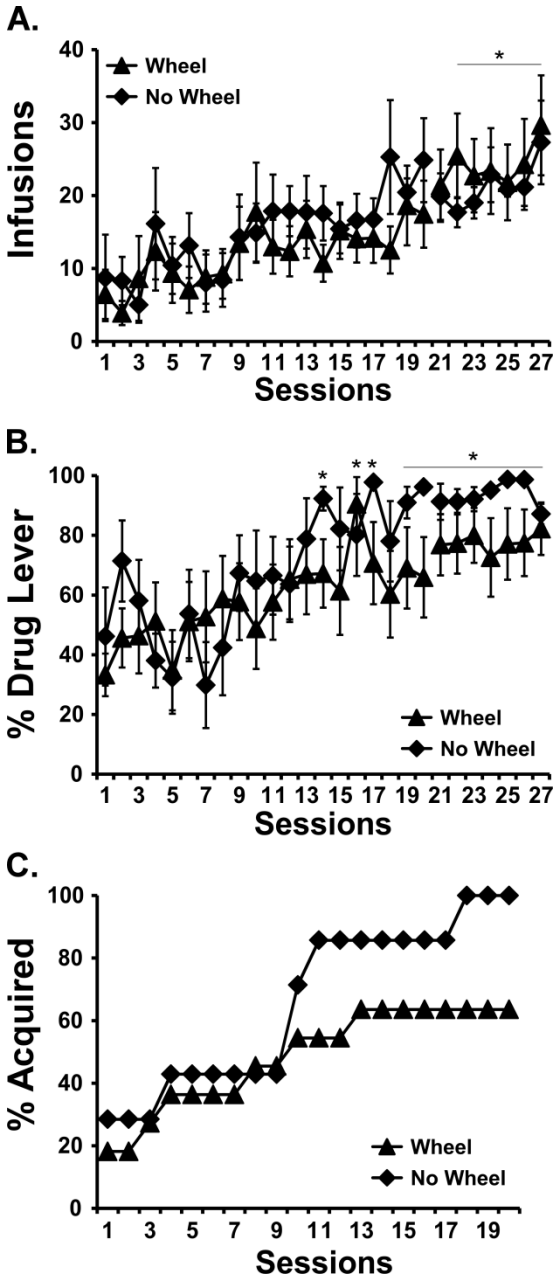

Figure 3: Mean (±SEM) infusions (A) and percent drug-associated lever responses (B) for Wheel (N=11) and No-Wheel (N=7) acquisition groups. C) Percent of each group meeting acquisition criteria. A significant difference from the first session, across groups, is indicated by *.

Overall, the two groups of rats self-administered similar numbers of infusions of α-PVP (0.05 mg/kg/inf) during both acquisition and the wheel switch (**Figure 3A**). The ANOVA confirmed a significant effect of Sessions of acquisition [F (26, 416) = 4.51; P<0.0001], but

not of Wheel access condition or of the interaction of factors. Similarly, the analysis of lever discrimination (**Figure 3B**) confirmed only a significant effect of Session [F (26, 416) = 6.72; P<0.0001].

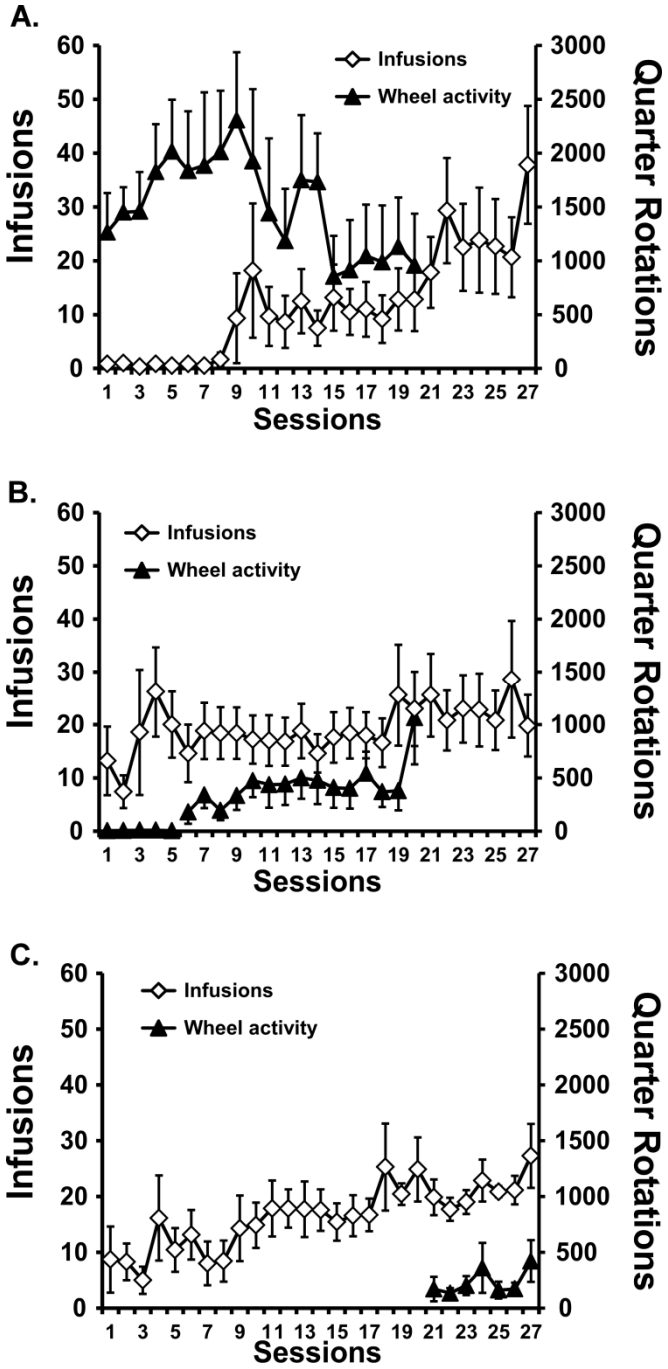

Figure 4: Mean (±SEM) infusions and wheel activity for A) Good Wheel (N=6); B) Bad Wheel (N=5); and C) No-Wheel (N=7) Groups.

The Mantel-Cox log-rank test failed to confirm (χ^2 = 2.34, df = 1, P = 0.127) any difference between the Groups in terms of the rate or proportion of subjects that reached acquisition criteria during the acquisition interval (**Figure 3C**). The rats in the Wheel group with functional wheel access from the start of acquisition were initially delayed in starting IVSA but ended up with a similar sustained mean intake compared with those which only had functional wheels after session 5 (**Figure 4A,B**). There was no systematic difference in wheel activity across acquisition sessions confirmed for either the entire Wheel cohort or for the subset that had fully functioning wheels from the beginning.

The Wheel switch produced no significant change in infusions obtained by the Wheel group upon fixing the wheels in place or by the No-Wheel group upon unlocking their wheels. Three of four Wheel individuals with essentially no IVSA intake during acquisition did start to self-administer drug (see **Figure 1**) but this produced no significant mean increase. Since wheel activity in the No-Wheel group was low after they gained access (**Figure 4C**), an additional experiment was conducted wherein a different group (N=8) of female Wistar rats were placed in the set of 8 operant boxes with unlocked wheels for four one-hour sessions. The rats were in different boxes each session, thus data for

each wheel were derived from 4 different rats. This study confirmed that the wheels in the operant chambers of the No-Wheel group were not dysfunctional, i.e., the test group produced mean activity levels in the No-Wheel chambers that was similar to the range for the Wheel group chambers. In addition, the No-Wheel chamber producing the lowest mean activity in this validation test was the one used for the No-Wheel rat that exhibited the most activity of that group in the wheel switch sessions.

3.2 Dose-Substitution

3.2.1 Self-Administration: A total of N=14 (N=7 No-Wheel, N=7 Wheel) rats retained patent catheters throughout the α-PVP dose-substitution studies. Wheel access had no effect on the dose-effect function for α-PVP IVSA (**Figure 5A**). The ANOVA confirmed a significant effect of Dose [F (4, 52) = 161.1; P<0.0001] but not of Wheel Access condition or the interaction of factors. The post-hoc test confirmed that each dose produced significantly different numbers of infusions compared with each of the other doses, collapsed across wheel-access condition. There was similarly no effect of Binge (N=8) / No Binge (N=6) phenotype (as expressed during acquisition) on the dose-effect relationship (**Figure 5B**). The ANOVAs confirmed a significant effect of Dose in the Wheel [F (4, 48) =

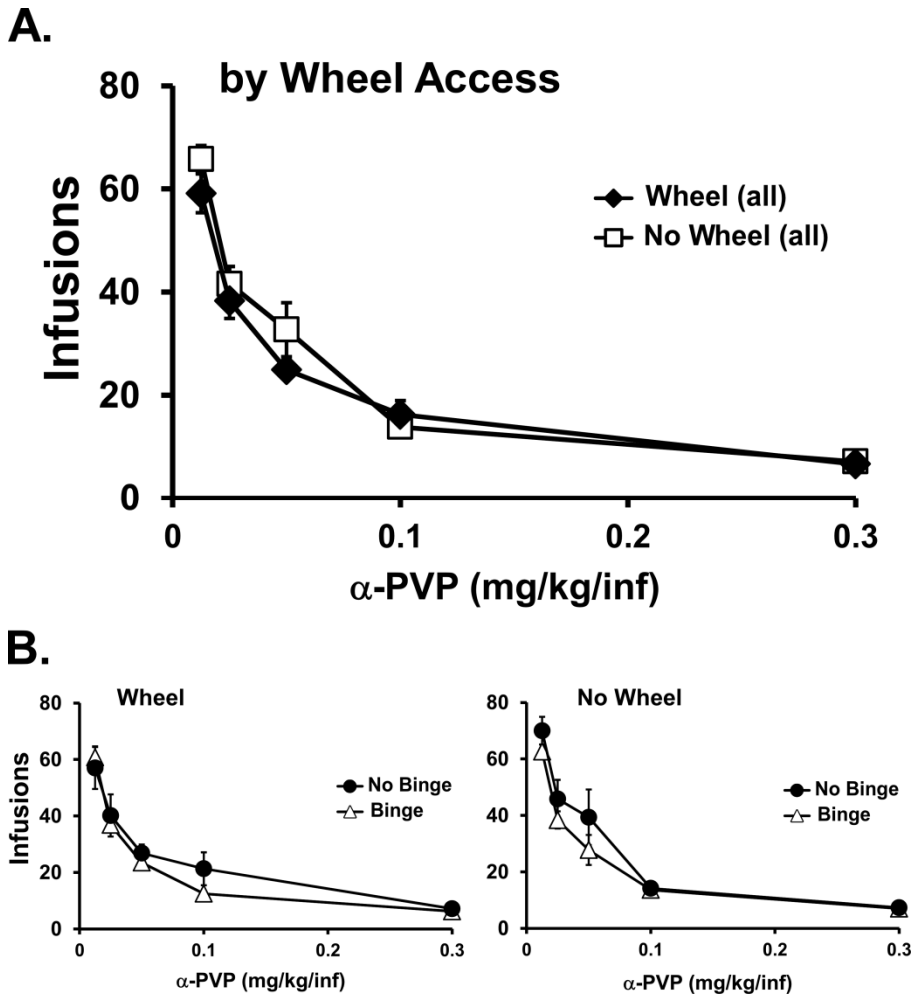

Figure 5: Mean (±SEM) infusions obtained during a dose-substitution. A) All rats with patent catheters (N=14) completed the dose series with the wheel unlocked (Wheel) or locked (No-Wheel). All doses differ significantly from all other doses. B) The results are divided by Binge (N=8) and No Binge (N=6) acquisition phenotype subgroups for the locked and unlocked wheel dose series.

85.25; P<0.0001] and No-Wheel [F (4, 48) = 83.85; P<0.0001] dose-effect series but no effect of Binge phenotype or the interaction. The post-hoc tests confirmed that, collapsed across Binge groups, all dose conditions differed from each other within Wheel conditions save that 0.05 mg/kg/inf did not differ from 0.1 mg/kg/inf in the Wheel condition and in the No-Wheel condition 0.025 did not differ from 0.05 mg/kg/inf and 0.1 mg/kg/inf did not differ from 0.3 mg/kg/inf.

3.2.2 Wheel Activity: Wheel activity during the dose-substitution with the unlocked wheel followed an approximately monotonic trend inversely related to self-administered dose in 13 of the animals (**Figure 6A**). One subject used the wheel substantially more than the other animals, despite cumulative drug intake that was similar to the group mean and was thus treated as a significant outlier (**Figure 6B**). Analysis for the activity of the remaining 13 animals confirmed a significant effect of dose [F (2.39, 28.72) = 8.43; P<0.001] with the post-hoc test confirming significantly more activity after the 0.0125 mg/kg/infusion dose compared with 0.05-0.3 mg/kg/infusion doses.

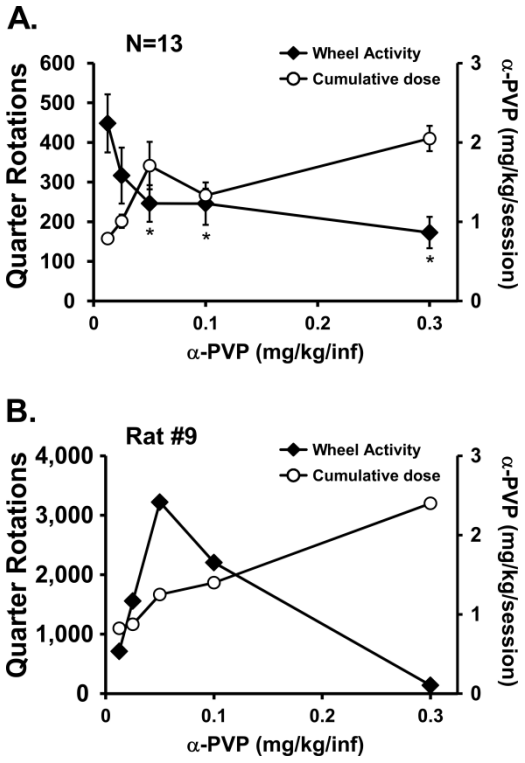

Figure 6: A) Mean (N=13; ±SEM) drug intake and wheel activity during the dose-substitution procedure. A significant difference from the 0.0125 mg/kg/inf condition is indicated by *. B) Cumulative drug intake and wheel activity for one individual rat.

4. Discussion

This study confirms that α-PVP is a potent reinforcer in female rats, just as has been previously shown in male rats (Aarde et al., 2015a; Gannon et al., 2017). Mean intakes after 13 sessions were also similar to those found in a single prior α-PVP IVSA study in which female rats were trained for 13 acquisition sessions (Javadi-Paydar et al., 2017). The amount of α-PVP that was self-administered by the female rats by the end of acquisition in this study was also very similar to the amount obtained by males in a prior study of α-PVP IVSA using similar methods (Aarde et al., 2015a), thus supporting a conclusion of minimal sex-differences in the IVSA of α-PVP. As with a prior study of MDPV

IVSA in male rats (Aarde et al., 2015b), the acquisition of IVSA of α-PVP in this study was not altered by concurrent access to an activity wheel. Correspondingly, the introduction of wheel access after the initial acquisition period did not decrease IVSA, similar to a prior result for methamphetamine IVSA (Miller et al., 2012). In addition, about half of the rats exhibited a binge-like session during acquisition after which intake subsided to a stable level that was higher than that observed prior to the binge day. As such, this study shows that the binge-like pattern of acquisition that was previously reported for MDPV IVSA in male rats (Aarde et al., 2015b) generalizes to female rats self-administering α-PVP. The binge session was observed in half of the Wheel and No-Wheel groups in the prior MDPV study (Aarde et al., 2015b) and this was matched by the relative proportions of binge-like acquisition female rats in the Wheel and No-Wheel groups in this study, further supporting the conclusion that this binging pattern is independent of wheel access during training.

Originally undetected issues with the movement of wheels in two of the operant chambers used for Wheel access animals precluded a robust test of the group mean reduction in wheel activity that was observed in prior studies of MDPV and methamphetamine IVSA in male rats (Aarde et al., 2015b; Miller et al., 2012). Nevertheless, it was the case that wheel activity declined in concert with the onset of sustained IVSA behavior for the 6 rats with wheels that functioned normally from the start of acquisition. In addition, the wheel activity of the No-Wheel group after the wheel switch and in the Wheel group with poorly adjusted wheels after adjustment was lower than the initial activity in the Wheel subgroup with functional wheels from the beginning of training. This finding parallels an outcome for groups given wheel access after 7 or 14 days of methamphetamine IVSA (Miller et al., 2012), and further underlines the phenomenon by which drug IVSA co-opts and devalues more naturalistic sources of reinforcement.

This study failed to find any effect of wheel access on established IVSA both in the switched condition for the original No-Wheel group and in the dose-effect functions generated with and without wheel access during the dose-substitution study. This outcome contrasts with the report of Cosgrove and colleagues in which cocaine IVSA and wheel activity were mutually inhibited (Cosgrove et al., 2002). The present finding confirms that our former finding, in which wheel access had no effect on established MA IVSA (Miller et al., 2012), was not a consequence of study in male rats. This is a critical confirmation

given that the effect of wheel on cocaine IVSA in Cosgrove et al. (2002) was present in female rats to a greater extent than in male rats. This study also shows the result is not likely attributable to pharmacological class, since α-PVP and cocaine are both restricted transporter inhibitors whereas methamphetamine is a transporter substrate and releaser.

There is one caveat to the overall conclusion that wheel access had minimal mean effect on the IVSA of α-PVP. Despite the fact that discontinuing wheel access had no significant mean effect on IVSA in the Wheel group (as in our prior study of methamphetamine IVSA), it was the case that three of four individuals who sustained high levels of wheel activity and minimal IVSA behavior during the 20 session acquisition interval started to respond for drug when the wheel was fixed. Thus it may be the case that a subset of rats would fail to ever acquire IVSA if wheel access was always available as an alternative.

In conclusion, this study further confirms the likely high abuse liability of α-PVP. The establishment of IVSA by female rats was similar to that of α-PVP or MDPV IVSA in male rats, including similar cumulative intake, a reduction in the value of wheel activity as an alternate reinforcer and a binge-like initial acquisition session in about half of the rats. Nevertheless, this study went on to show that the binge-like acquisition phenotype did not have lasting consequences for self-administration behavior, thus it may be the case that the pattern of acquisition is not predictive of individual differences in sustained drug seeking patterns of behavior.

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