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Sex differences in 3,4-methylenedioxypyrovalerone (MDPV)-induced taste avoidance and place preferences☆

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ABSTRACT

Synthetic cathinones, otherwise known as "bath salts", have gained significant attention in the last few years as a result of increased use and abuse. One such compound, 3,4-methylenedioxypyrovalerone (MDPV), is pharmacologically and behaviorally similar to cocaine and has been shown to possess both aversive and rewarding effects. For a host of other drugs, each of these effects (and their relative balance) can be influenced by a variety of factors, including sex, which in turn impacts drug taking behavior. In this context, the present assessment sought to determine whether males and females differed in MDPV-induced CTA and CPP. Both male and female Sprague–Dawley rats underwent a combined CTA/CPP procedure, in which an injection of one of three doses of MDPV (1.0, 1.8 or 3.2 mg/kg) was paired with both a novel saccharin solution and a novel environment and changes in preferences for these stimuli were examined. Taste avoidance was evident in both sexes, although this avoidance was weaker in females compared to males. MDPV also produced place preferences in all drug-treated animals, but these preferences did not vary as a function of sex. The fact that females showed a weaker avoidance response compared to males (despite comparable preferences) suggests that females may have a heightened susceptibility to use and abuse of MDPV, paralleling results seen with cocaine and other stimulants. The present findings extend the behavioral characterization of MDPV and the factors that may alter its aversive and rewarding effects.

1. Introduction

In recent years, "bath salts", or synthetic cathinones (stimulants derived from the khat plant; see Baumann, 2014), have become an increasingly visible public health concern. The rapidity with which these drugs have appeared in the general population and the magnitude of their adverse effects resulted in three of the primary parent cathinones [3,4 methylenedioxypyrovalerone (MDPV), 3,4-methylenedioxymethcathinone (methylone) and 4-methylmethcathinone (mephedrone)] being classified as Schedule I drugs by the DEA in 2012. Since this classification, reports from poison control centers involving bath salts have decreased significantly. However, the reduced availability of these has resulted in a wide array of "replacement" compounds, in which slight chemical modifications have been made in order to circumvent legal enforcement. Given that many of these replacements still involve derivatives of the original parent compounds, it is crucial to continue the behavioral and neurochemical research of these drugs in order to make a complete abuse risk assessment (Baumann, 2014). MDPV, specifically, has been the subject of increasing research, both in our laboratory and others (see Baumann et al., 2013a; Gatch et al., 2013; King et al., 2014; Merluzzi et al., 2014), and is the most frequently found cathinone in the United States (Spiller et al., 2011).

Products containing MDPV have been reported to produce paranoid psychotic behavior, agitation, hallucinations and delirium (see Brontein et al., 2010; Penders, 2012). MDPV has been compared both anecdotally and pharmacologically to cocaine (Baumann et al., 2013b); both drugs are dopamine reuptake inhibitors, with MDPV possessing 10 times the potency as cocaine at producing locomotor activity, hypertension and tachycardia in rats. Behaviorally, MDPV maintains self-administration in rats across a range of doses, induces escalated intake over long-access conditions and significantly lowers thresholds for brain stimulation reward (see Watterson et al., 2014) and has interoceptive effects similar to MDMA and methamphetamine in a drug discrimination procedure (Fantegrossi et al., 2013). Given that drug self-administration is

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often described as the result of a balance between the aversive and rewarding effects of a drug (see Riley, 2011; Stolerman and D'Mello, 1981; Verendeev and Riley, 2013), it is important to examine each of these effects in order to determine any factors that may influence them and, thus, their impact on abuse.

In one such examination of the aversive effects of MDPV, Merluzzi et al. (2014) reported that MDPV (1, 1.8 and 3.2 mg/kg) induced dose-dependent taste avoidance in adolescent and adult Sprague–Dawley rats (see also King et al., 2014, for a similar dose-dependent assessment with F344 and LEW rats). In relation to the rewarding effects of MDPV, King et al. (2015) reported that the same range of doses of MDPV induced significant non dose-dependent place preferences in adult male Sprague–Dawley rats (see also Karlsson et al., 2014 for a similar assessment in mice). That MDPV produces this reward at the same doses that produce avoidance parallels effects previously reported for a host of drugs of abuse (see Goudie, 1979; Riley, 2011; Wang et al., 2010; White et al., 1977).

Although these results have determined that MDPV is both pharmacologically and behaviorally similar to other abused stimulants and that it possesses both aversive and rewarding effects, much is still unknown about its abuse potential and what factors might serve to impact that potential. In this context, multiple experiential and subject variables have been shown to impact both the aversive and rewarding effects of drugs of abuse and, thus, may serve as predictive factors in determining propensity for abuse (for reviews, see Cunningham et al., 2006; Doremus-Fitzwater et al., 2010; Riley and Freeman, 2004; Tzschentke, 1998; Verendeev and Riley, 2012).

Sex in particular has been shown to influence both the aversive and rewarding effects of many drugs of abuse. Taste avoidance has been shown to produce differential effects in males and females, with the directionality of these differences dependent on a variety of factors, including drug, strain and route of administration (see Busse et al., 2005; Cailhol and Mormède, 2002; Foltin and Schuster, 1982; Goudie et al., 1978; Roma et al., 2008; Van Haaren and Hughes, 1990). Similarly, sex differences have also been reported in the rewarding effects of drugs, with the direction and magnitude of sex differences again showing considerable variance (see Cicero et al., 2000; Russo et al., 2003; Torres et al., 2009; Torres et al., 2014; Yararbas et al., 2010).

Given the fact that sex differences can potentially alter the interoceptive effects of drugs of abuse, the present experiments attempted to further characterize the subjective balance between the aversive and rewarding effects of MDPV. Specifically, both male and female adult Sprague–Dawley rats were run in a combined taste avoidance/place preference procedure, wherein three doses of MDPV (1, 1.8 or 3.2 mg/kg) were concurrently paired with both a novel taste and a novel place (this procedure has been previously shown to produce both avoidance of the drug-paired taste and increased preference for the drug-paired place with other drugs of abuse; see Brockwell et al., 1991; King and Riley, 2013; Simpson and Riley, 2005). Avoidance and preference, and any effect of dose, were compared between male and female rats in order to determine any effect of sex on the subjective effects of MDPV, which may provide insight into any sex-specific abuse vulnerability.

2. Materials and methods

Sixty-four experimentally-naïve male and female Sprague–Dawley rats ($n = 32$/sex) were obtained from Harlan Sprague–Dawley (Indianapolis, IN) on postnatal day (PND) 21. Procedures recommended by the National Research Council (1996), the Committee on Guidelines for the Care and Use of Animals in Neuroscience and Behavioral Research (2003) and the Institutional Animal Care and Use Committee at American University were followed at all times. Upon arrival to the animal facility on PND 21, subjects were group housed (three same sex rats per OptiRat Plus polycarbonate bins; 100 cm × 99 cm × 201 cm) and maintained on ad-libitum food and water until PND 71, when experimental procedures began. Animals remained drug- and experimentally-naïve until this time.

2.1. Apparatus

The place conditioning apparatus (San Diego Instruments Place Preference System, San Diego, CA) consisted of two main conditioning chambers (28 × 21 × 34.5 cm) joined by a smaller middle chamber (14 × 21 × 34.5 cm). One of the conditioning chambers featured a white aluminum diamond plate floor with white walls; the other conditioning chamber featured a haircell-textured black plastic floor with black walls; the smaller middle chamber was outfitted with a steel rod floor and gray walls. Each individual chamber in each apparatus had its own white LED lights, and the lights were set on minimum. A total of eight identical apparatuses were used; each apparatus featured a 16 × 4 photobeam array for recording time (in seconds) spent in each chamber. The CPP room was illuminated by a 25-W red light mounted to the ceiling, and a white noise generator was used to mask background noise.

2.2. Drugs and solutions

3,4-Methylenedioxypyrovalerone hydrochloride (synthesized at the Chemical Biology Research Branch of the National Institute on Drug Abuse) was dissolved in sterile isotonic saline (0.9%) at a concentration of 1 mg/ml and was subsequently filtered through a 0.2 mm filter to remove any contaminants before being administered intraperitoneally (IP) at a dose of 1, 1.8 or 3.2 mg/kg. The drug was delivered IP to ensure consistency with the existing literature in which assessments of MDPV's behavioral effects used this route of administration (see Fantegrossi et al., 2013; Gatch et al., 2013; Karlsson et al., 2014; King et al., 2015; Merluzzi et al., 2014). Sterile isotonic saline was also filtered before being administered to saline controls. Injections for vehicle controls were equivolume to the highest dose of MDPV (3.2 mg/kg). Volume of the injection was manipulated in favor of concentration, given the influence that concentration has on the absorption/distribution of the drug. Sodium saccharin (0.1%; Sigma-Aldrich, St. Louis, MO) was prepared daily as 1 g/L solution in tap water.

2.3. Phase I: habituation

Beginning on PND 71, animals were weighed and handled daily. Each subject's daily water consumption was recorded through PND 76. On the following day, subjects had their water removed for the next 24 h to encourage consumption during training and testing. On PND 78, animals were placed in hanging stainless-steel test cages (24.3 × 19 × 18 cm) where they received 20-min access to water in graduated 50-ml Nalgene tubes. Following removal of the water tubes, animals were returned to their group-housed bins. Daily 20-min water access was repeated until consumption was stable, i.e., subjects approached and drank from the tube within 2 s of its presentation, and water consumption was within 2 ml of that from the previous day for a minimum of 4 consecutive days with no consistent increase or decrease. Once consumption was stable, Phase II began.

2.4. Phase II: pre-test

Following stable water consumption, each animal was given 20-min access to water in the test cage and then allowed 15-min access to the two-compartment place conditioning apparatus to obtain individual baseline times spent on each side and to assess apparatus bias (Cunningham et al., 2003; Roma and Riley, 2005). Baseline side preferences were used during conditioning, i.e., animals were injected and then placed on their initially non-preferred side (see below).

2.5. Phase III: combined CTA/CPP

On the following day, animals received 20-min access to a novel saccharin solution during their daily fluid-access period after which they were immediately transported to a room adjacent to the CPP chambers. They were then assigned to one of eight groups such that consumption was comparable across groups and injected with vehicle or one of three doses of MDPV. Specifically, subjects were injected with 0 mg/kg (vehicle), 1 mg/kg, 1.8 mg/kg or 3.2 mg/kg of MDPV, yielding Groups M0, F0, M1, F1, M1.8, F1.8, M3.2 and F3.2 ($n = 8$ for each group). The letter in each group name denotes the sex of the animal (M for male; F for female), and the number denotes the dose of MDPV administered. After the injection, individuals were confined to their non-preferred side of the apparatus for 30 min (depending upon the initial side preference in Phase 2) and then returned to their home cages. On Day 2, the animals were given 20-min access to water, followed immediately by a saline injection and then confinement to the opposite (originally preferred) chamber of the previous day. This pattern of 20-min saccharin access, drug/vehicle injection and 30-min confinement to a CPP chamber on Day 1 followed by 20-min water access, saline injection and 30-min confinement to the other chamber on Day 2 constituted one conditioning cycle. The CTA/CPP procedure was carried out for a total of four consecutive cycles over 8 days. On Day 9, subjects were given water during the daily fluid access, followed by 15-min access to the entire place conditioning apparatus to determine any changes in time spent on the initially non-preferred side. On Day 10, subjects were given 20-min access to two Nalgene tubes (one containing tap water and the other containing saccharin solution) with placement counterbalanced to control for positioning effects, and saccharin/water consumption were measured. Immediately following this test, animals were returned to their home bins with ad libitum water access. No injections were given on the final two test days.

2.6. Statistical analyses

2.6.1. Conditioned taste avoidance

Saccharin consumption throughout conditioning was analyzed with a $2 \times 4 \times 4$ repeated measures ANOVA with between-subjects factors of sex (male and female) and dose (0, 1, 1.8 and 3.2) and a within-subjects factor of Trial (1–4). In the case of a three-way interaction, simple effects of dose for each sex and at each trial (univariate analysis), sex at each dose and trial (univariate analysis) and of trial at each dose and for each sex (multivariate analysis) were assessed, with Bonferroni-corrected multiple comparisons as warranted.

On the two-bottle CTA test, percent saccharin of total fluid consumption was analyzed with a 2×4 factorial ANOVA with factors of sex (male or female) and dose (0, 1, 1.8 and 3.2). A two-way interaction was followed by univariate analyses for simple effects at each level of sex and dose and followed by Bonferroni-corrected pairwise comparisons as warranted.

2.6.2. Conditioned place preference

Percent time spent on the drug-paired side (DPS) on pre-test and post-test was compared with a $2 \times 4 \times 2$ repeated measures ANOVA with between-subjects factors of sex (male and female) and dose (0, 1, 1.8 and 3.2 mg/kg MDPV) and a within-subjects factor of test (pre-test and post-test). In the case of a significant interaction, simple effects of test at each dose and for each sex were assessed with multivariate analyses.

2.6.3. CTA/CPP relationship

The relationship between changes in percent time spent on the DPS (post-test percentage subtracted from pre-test percentage) and changes in saccharin consumption (Trial 4 consumption subtracted from Trial 1 consumption) was determined for individual animals within each dose group and sex, using Pearson correlation coefficient.

For all comparisons, statistical significance was set at $\alpha = 0.05$.

3. Results

3.1. CTA

MDPV induced taste avoidance in all animals, an effect that was weaker in females compared to males. The $2 \times 4 \times 4$ mixed model ANOVA on saccharin consumption revealed significant effects of dose [$F(3, 55) = 22.987$] and trial [$F(3, 165) = 4.515$], as well as significant dose × trial [$F(9, 165) = 10.522$] and sex × dose × trial [$F(9, 165) = 1.989$] interactions (see Fig. 1). No other main effect or significant interactions were found.

Simple effects of dose for each sex and at each trial were assessed with a univariate analysis which revealed significant differences on Trials 2–4 for both males [Trial 2: $F(3, 55) = 7.544$; Trial 3: $F(3, 55) = 20.928$; Trial 4: $F(3, 55) = 21.026$] and females [Trial 2: $F(3, 55) = 4.776$; Trial 3: $F(3, 55) = 8.601$; Trial 4: $F(3, 55) = 4.0$]. Corrected multiple comparisons indicated that on Trial 2, Groups M1.8 and M3.2 drank significantly less than M0. Group F3.2 drank significantly less than Groups F0 and F1. On Trial 3, all male drug groups drank significantly less than Group M0 and Group M3.2 drank significantly less than Group M1. Groups F1.8 and F3.2 drank significantly less than Group F0. On Trial 4, all male drug groups again drank significantly less than Group M.0 and Group M3.2 drank significantly less than Groups M1 and M1.8. Groups F1.8 and F3.2 again drank significantly less than Group F0.

Simple effects of sex at each dose and trial were assessed with a univariate analysis which revealed significant differences at Trial 4 for Groups 3.2 [$F(1,55) = 7.92$] and vehicle [$F(1,55)$: 4.952]. Corrected multiple comparisons indicated that on Trial 4, Group M3.2 drank significantly less than Group F3.2, and Group F0 drank significantly less than Group M0.

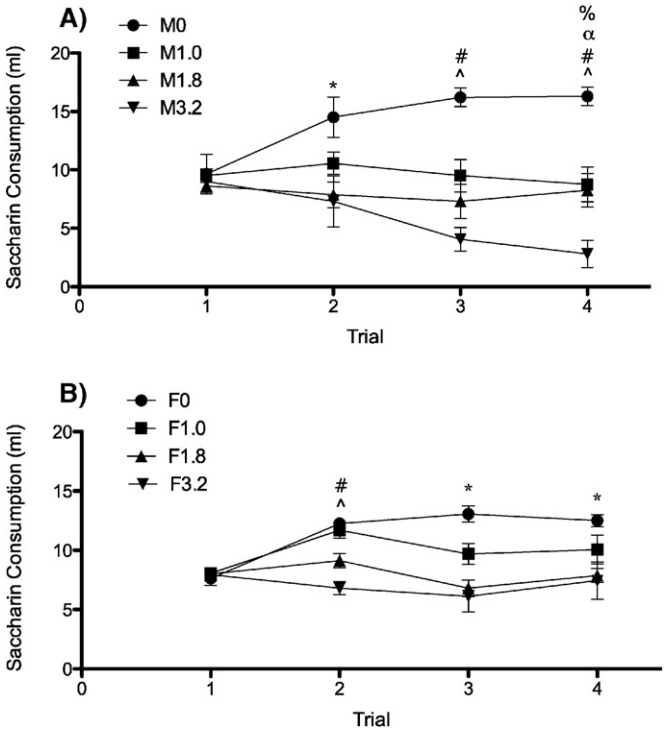

Fig. 1. Mean (±SEM) saccharin consumption in ml over all conditioning trials. Panel A (males): *M0 significantly greater than M1.8 and M3.2; ^M0 significantly greater than all drug-treated groups; %M1.0 and M1.8 significantly greater than M3.2; #M3.2 significant decrease from Trial 1; αM3.2 significant decrease from Trial 2. Panel B (females); *F0 significantly greater than F1.8 and F3.2; ^F0 and F1.0 significantly greater than F3.2; #F1.0 significant increase from Trial 1.

Simple effects of trial for each Sex and at each dose were assessed with a multivariate analysis which revealed significant differences for Groups M3.2 [$F(3,53) = 8.405$], F1 [$F(3,53) = 5.064$], M0 [$F(3,53) = 12.517$] and F0 [$F(3,53) = 10.53$] across trials. Corrected multiple comparisons indicated that Group M3.2 drank significantly less on Trials 3–4 than on Trial 1 and significantly less on Trial 4 than on Trial 2. Group F1 drank significantly more on Trial 2 than on Trial 1, but showed no differences at Trials 3–4. Both Groups M0 and F0 drank significantly more on Trials 2–4 than on Trial 1.

The 2×4 factorial ANOVA for percent saccharin consumption on the two-bottle test revealed a main effect of Dose [$F(3,55) = 19.395$], but no effect of sex and no dose X sex interaction (see Fig. 2A). Collapsed across sex, the percent saccharin consumed was significantly lower for animals treated with MDPV than for animals treated with vehicle (see Fig. 2B).

3.2. CPP

MDPV induced significant place preferences, although these were not sex-dependent. The $2 \times 4 \times 2$ repeated measures ANOVA on percent time spent on the DPS revealed main effects of dose [$F(3,55) = 2.799$] and test [$F(1,55) = 112.701$] as well as a test × dose [$F(3,55) = 4.296$] interaction, but no main effect of sex or any interactions with sex as a factor (see Fig. 3). To further explore the test × dose interaction, data were collapsed across sex and a 4×2 repeated measures ANOVA was run with a between-subjects factor of dose and a within-subjects factor of test. This revealed main effects of test [$F(1,59) = 115.98$], dose [$F(3,59) = 3.008$] and a test × dose [$F(3,59) = 4.447$] interaction.

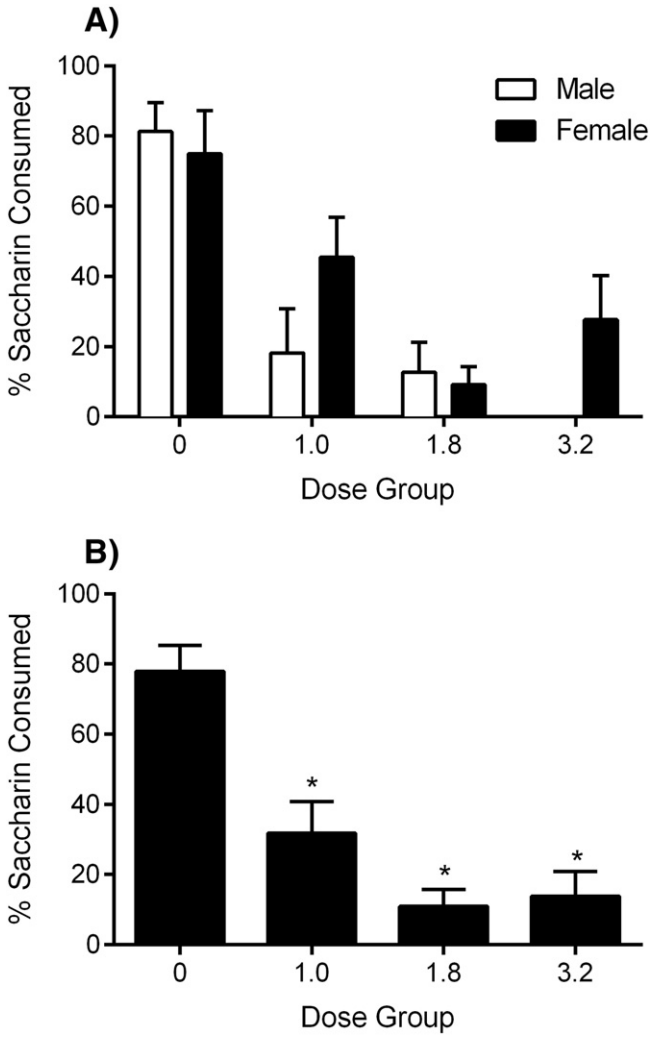

Fig. 2. Mean percent saccharin (±SEM) consumed on two-bottle avoidance test for males and females (A) and collapsed across sex (B). The analysis for the collapsed data showed that all drug-treated groups drank significantly less saccharin than the control animals. *Significant difference from Group 0.

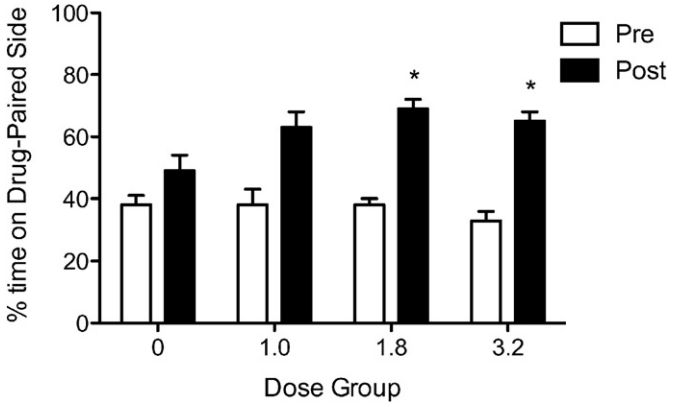

Fig. 3. Mean percent time spent on the drug-paired side (±SEM) for all groups at pre- and post-test, collapsed across sex. All groups (including vehicle) showed significant increase from pre-test to post-test. *Significant difference from Group 0.

Simple effects of test at each dose were assessed with a multivariate analysis, which revealed significant differences in all four groups [0: $F(1,59) = 5.245$; 1.0: $F(1, 59) = 30.052$; 1.8: $F(1, 59) = 47.051$; 3.2: $F(1, 59) = 5.245$]. Corrected multiple comparisons indicated that all groups, including vehicle, significantly increased time spent on the DPS from pre-test to post-test. Simple effects of dose at each test were assessed with a univariate analysis, which revealed no significant differences at pre-test, but did show significant differences at post-test [$F(3,59) = 4.564$]. Corrected multiple comparisons indicated that on the post-test, Groups 1.8 and 3.2 spent significantly more time on the DPS than did Group 0.

3.3. CTA/CPP relationship

Analysis of the change in the amount consumed over conditioning (Trial 4–Trial 1) and the change in percent time on the DPS (pre-test–post-test) (within each sex and dose group) revealed minimal correlations. No significant relationship was observed for Groups M0, M1, M1.8, M3.2, F0, F1 and F3.2 ($rs \leq .575$, $ps > .05$). The correlational analysis did reveal a significant relationship for subjects in Group F1.8, $r = .873$, $p = .005$. Specifically, animals with larger increases in percent time spent on the DPS showed larger increases in saccharin consumption (see Table 1/Fig. 4).

Table 1
The relationship between the change in the amount of saccharin consumed over conditioning (Trial 1–Trial 4) and the change in percent time on the DPS (pre-Test to post-Test). Each cell indicates the r and p values for the given relationship for each sex and dose group. Bold font indicates significant relationship (see text for more detail).

	Male	Female
Vehicle	$r = -.419$	$r = .316$
	$p = .350$	$p = .446$
1.0 mg/kg MDPV	$r = -.316$	$r = -.179$
	$p = .445$	$p = .672$
1.8 mg/kg MDPV	$r = .575$	$\mathbf{r = .873}$
	$p = .136$	$\mathbf{p = .005}$
3.2 mg/kg MDPV	$r = .457$	$r = .527$
	$p = .255$	$p = .180$

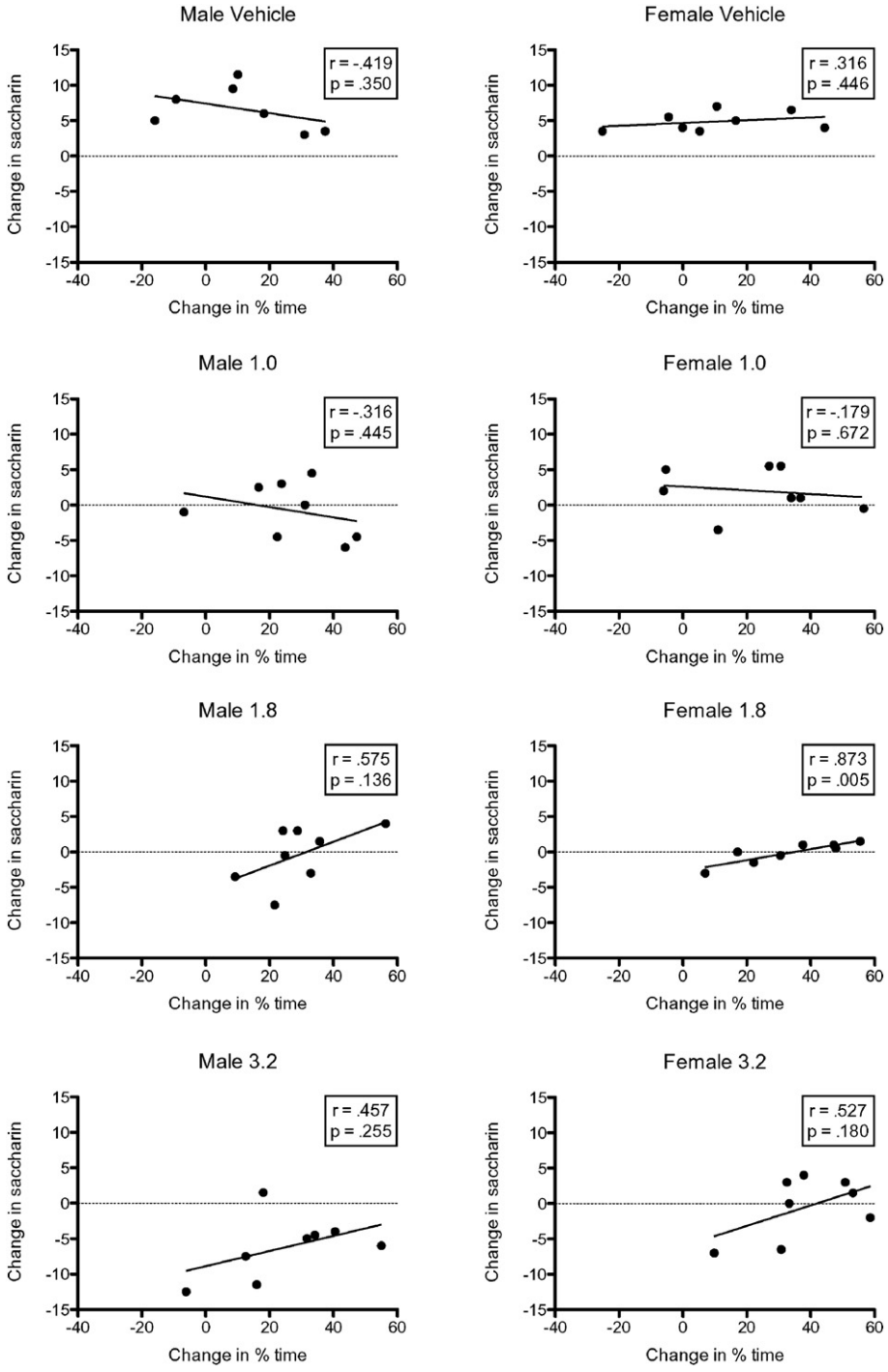

Fig. 4. Scatterplots (with best line of fit) showing the relationship between change in the amount of saccharin consumed over conditioning (Trial 4–Trial 1) and the change in percent time on the DPS (pre-test–post-test) for each sex and dose Group.

4. Discussion

MDPV has been shown to have both aversive and rewarding effects (King et al., 2014, 2015; Merluzzi et al., 2014), and in order to determine how these affective properties contribute to MDPV's relative abuse potential, it is critical to examine factors that might influence the balance between them (Gaiardi et al., 1991; Riley, 2011; Stolerman and D'Mello, 1981; Verendeev and Riley, 2013). Sex is of particular interest here, because while the data regarding the influence of sex on avoidance and reward are mixed (see above), work with a number of stimulants has demonstrated that, in general, females may be more likely to abuse these drugs (Lynch et al., 2002; Russo et al., 2003; Zakharova et al., 2009). Given the behavioral and pharmacological commonalities between MDPV and other classical stimulants, the same vulnerability might be predicted to occur with MDPV. In the present experiment, male and female rats underwent a combination taste avoidance/place preference procedure, where injections of a range of doses of MDPV (0–3.2 mg/kg) were paired with both a novel saccharin solution and a novel environment and changes in preference for these stimuli were examined. MDPV produced reductions in saccharin consumption for all drug-treated groups that did vary with sex. MDPV also induced significant place preferences that appeared independent of sex.

As noted, MDPV induced taste avoidance, an effect consistent with prior work with this compound in the taste avoidance

preparation in which male adolescent and adults were assessed (see Merluzzi et al., 2014). While MDPV induced avoidance, males and females differed in the acquisition and degree of this suppression. Specifically, males injected with MDPV displayed significant differences from control subjects at the two highest doses following only a single pairing of saccharin and MDPV. Avoidance was evident on this trial (Trial 2) for females only in the high dose group. This pattern was maintained over conditioning in that on Trials 3 and 4, all male subjects injected with MDPV drank less than controls, whereas only the two highest female groups displayed avoidance. Further, at no point over conditioning did any female dose group display a significant decrease from their own baseline consumption levels (Trial 1). In fact, female subjects in the low MDPV group increase consumption from Trial 1 to Trial 2. For males, Group M3.2 displayed a significant decrease from baseline consumption on Trials 3–4 and a significant decrease from Trial 2 to Trial 4. In a direct comparison between males and females, males injected with 3.2 mg/kg MDPV drank significantly less than females on Trial 4.

Based on both the within- and between-subjects analyses, MDPV-induced taste avoidance was weaker in females compared to males, demonstrating that MDPV's aversive effects are sex-dependent at the range of doses used. It is important to note that the fact that the differences between males and females were only evident on specific trials and with certain doses is consistent with results in other work on sex differences in taste avoidance (see Chambers and Sengstake, 1976; Roma et al., 2008; Torres et al., 2009). Given the similarities in the mechanisms of action of MDPV with cocaine, it might be expected that there would be parallels in some of their behavioral effects as well as how such effects might be impacted by factors such as sex. As noted above, work on sex differences with cocaine are somewhat mixed, with females displaying either stronger avoidance (Van Haaren and Hughes, 1990), weaker avoidance (Busse et al., 2005) or no differences than males (Foltin and Schuster, 1982). Such variability is likely a function of a host of factors including dose, species and route of administration, making it difficult to generalize the present findings to those with cocaine and other stimulants.

Although there were significant sex differences in acquisition of avoidance (M > F), these differences were not evident in the two-bottle assessment in which all drug-treated groups drank a smaller percentage of saccharin than control subjects. This is likely a reflection of the sensitivity of the two-bottle test relative to forced-choice consumption, i.e., when animals are given access to both the drug-associated taste and water in the two-bottle assessment, aversions are generally stronger (with no forced drinking) and differences among groups are not always evident in this more sensitive index of the drug's aversive effects (for discussion, see Dragoin et al., 1971; Grote and Brown, 1971). When collapsed across sex, MDPV-injected groups drank between 10 and 30% saccharin compared to controls that drank approximately 80%, suggesting that any sex effects in this test may have been masked by the strong degree of suppression.

MDPV also induced significant place preferences which are comparable to the results obtained by King et al. (2015) who assessed MDPV-induced CPP in male rats at the same range of doses (0, 1.0, 1.8 and 3.2 mg/kg) used in the present assessment. In the present assessment, although all groups (independent of drug treatment) significantly increased time on the DPS from pre-test to post-test, subjects injected with the two highest doses of MDPV, i.e., Groups 1.8 and 3.2, spent significantly more time on the DPS at post-test than did the vehicle animals, indicating that MDPV was rewarding in this preparation. Interestingly, these preferences did not vary as a function of sex. It might have been predicted that, given the pharmacological similarity to cocaine, MDPV might have produced stronger place preferences in females than males (see Russo et al., 2003; Zakharova et al., 2009). However, the prior studies showing larger preferences for cocaine in females compared to males utilized different strains (Russo et al., 2003) and initiated conditioning at different ages and under different experimental designs (Zakharova et al., 2009).

Given that the present assessment found that MDPV induced concurrent tastes avoidance and place preference, but that sex differences were only evident in taste avoidance, argues for a dissociation between these factors, i.e., these effects likely function independently (for a discussion, see Verendeev and Riley, 2013). This position is further supported by the correlational analyses between the MDPV-induced changes in saccharin consumed and side preferences over conditioning. As described, there was no consistent significant relationship between strength of taste avoidance and strength of place preference within sex and dose groups (Group F1.8 as the only exception; see above; see also Cunningham et al., 2002). The likelihood of obtaining one significant correlation in eight assessments is quite high by chance alone (.279) suggesting that such an effect is spurious. The fact that the significant correlation was not dose dependent supports this position. Interestingly, a similar correlational analysis between taste avoidance and place preferences conditioned with amphetamine and morphine found only one significant relationship (out of 16 total groups; see Verendeev et al., 2011).

Recently, it has been argued that preclinical and clinical work on drug effects necessitates the inclusion of sex as a variable. While historically, male subjects have primarily been used in biomedical research, recent years have seen an increased awareness of the fact that sex can influence the direction of findings in nearly all areas of brain research, including sensitivity to drugs of abuse (see introduction; see also Cahill, 2012; Goel et al., 2014; Stevens and Hamann, 2012; Wetherington, 2007). The fact that while MDPV produced a weakened avoidance response in females compared to males suggests that females may be more vulnerable to MDPV use and abuse (Becker et al., 2001; Chen and Kandel, 2002; Evans and Foltin, 2010; Lynch et al., 2002) and extends the behavioral characterization of MDPV and the conditions under which the aversive and rewarding effects might be impacted. Future work investigating the sex differences in MDPV-induced avoidance would benefit from controlling for hormone levels in ovariectomized animals/and or cycle phase in intact animals, in order to determine whether gonadal hormones have the same effect on MDPV-induced behavioral effects as they do with cocaine. Additionally, there is not yet data regarding sex differences in MDPV's behavioral or pharmacological effects in humans; the present study suggests it would be important to determine whether these differences exist and whether females may be more vulnerable to use and abuse of MDPV or other synthetic cathinones.

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