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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).