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An Assessment of MDPV-induced Place Preference in Adult Sprague-Dawley Rats

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Abstract

OBJECTIVE—Most drugs of abuse have both aversive and rewarding effects, and the use and abuse potential of such drugs is thought to be a function of a balance of these affective properties. Characterizing these effects and their relative balance may provide insight into abuse vulnerability. One drug that has received recent attention is methylenedioxyparavalerone (MDPV), a monoamine transport inhibitor similar to, but significantly more potent than, cocaine. MDPV is self-administered and has been shown to produce aversive and rewarding effects in adult rats. The present study extended this characterization of the affective properties of MDPV by examining its ability to support place conditioning at a range of doses known to produce taste avoidance.

METHODS—Male Sprague-Dawley rats were injected with MDPV (1, 1.8 or 3.2 mg/kg) or saline and placed on the non-preferred side of a place conditioning apparatus for 30 min. On the next day, they were given an injection of saline and placed on the preferred side. This was repeated three times for a total of four conditioning cycles, and side preference was assessed on a final test.

RESULTS—All doses of MDPV produced significant increases in time spent in the drug-paired chamber, an effect not seen in vehicle-treated animals.

CONCLUSIONS—That the same doses of MDPV induced both taste avoidance and place preference allows assessments of how other factors might impact these effects and how they may, in turn, contribute to its abuse liability.

Keywords

MDPV; place preference; reward

1. Introduction

Since synthetic cathinones emerged in the United States in 2010, the subsequent rise in popularity and abuse poses a significant threat for public health (Bronstein et al., 2011; Rosenbaum et al., 2012; Spiller et al., 2011). These drugs have been marketed as “legal highs” and have been commonly sold in gas stations and “head shops”, as well as over the

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internet. Law enforcement in various countries has attempted to circumvent the use and distribution of the most common of these, namely 3, 4-methylenedioxypyrovalerone (MDPV), 3,4-methylenedioxymethcathinone (methylone) and 4-methylmethcathinone (mephedrone). For example, these compounds were given emergency Schedule I classification in the US in 2011 and now have permanent classification as such (Drug Enforcement Administration, 2011; Fass et al., 2012). These compounds, as well as several behaviorally active derivatives, however, are still being produced and distributed, thus their continued characterization is crucial (Araújo et al., 2014; Baumann, 2014; for a review, see German et al., 2014; Marusich et al., 2014).

One of the aforementioned parent compounds, MDPV, is the main substance found in patients presenting with bath salts overdose in the United States (see Baumann, 2014); it is a monoamine transport inhibitor similar to, but significantly more potent than, cocaine, with primary actions at dopamine and norepinephrine transporters (with minimal effects on serotonin) (Baumann et al., 2013; Baumann et al., 2012). Like cocaine, this compound has also been shown to maintain self-administration and promote escalation of intake across a range of doses in adult rats (Aarde et al., 2013; Watterson et al., 2014). Drug self-administration, in general, is thought to be a function of the balance of the drug's aversive and rewarding effects, thus understanding each of these affective properties of MDPV may provide some insight into its use and abuse vulnerability (for a review, see Riley, 2011; Verendeev and Riley, 2012; Verendeev and Riley, 2013). Independent assessments of MDPV's aversive and rewarding effects (and their relative contributions to drug self-administration), however, are limited.

In relation to its aversive effects, MDPV has recently been assessed for its ability to induce a conditioned taste avoidance in both adolescent and adult male Sprague Dawley rats (see Merluzzi et al., 2014), wherein MDPV (1.0, 1.8 or 3.2 mg/kg) produced dose-dependent avoidance of saccharin over trials. Further, Marusich et al. (2012) reported that MDPV produced significant increases in exploration, circling, hyperactivity and stereotypy (see also Aarde et al., 2013). In relation to its rewarding effects, MDPV has been shown to significantly lower ICSS thresholds across a range of doses in adult rats (comparable to those producing avoidance; see Watterson et al., 2014), an effect generally assumed to reflect the rewarding effects of the drug (Kornetsky and Bain, 1992; Wise, 1996). Additionally, Karlsson et. al. (2014) reported that in male C57BL/6J mice MDPV induced dose-dependent (0.5 – 20 mg/kg) conditioned place preference (CPP, a commonly used measure of a drug's rewarding effects; see Tzschentke, 1998; Tzschentke, 2007). Although this latter study illustrates that MDPV induces CPP (and at a range of doses), it utilized an inbred mouse strain that is particularly susceptible to the reinforcing effects of ethanol and other drugs (see Cunningham et al., 2009; Orsini et al., 2005; Risinger and Brown, 1996). Given that both strain (e.g., inbred versus outbred) and species (e.g., mice versus rats) have been shown to influence a host of effects induced by drugs other than MDPV, for example, D1 and D2 dopamine receptor activation (Ralph and Caine, 2005), alcohol-induced taste avoidance (Broadbent et al., 2002) and psychomotor stimulant effects of cocaine (Thomsen and Caine, 2011), it may be difficult to generalize results between strains and across species. Accordingly, the present study attempted to evaluate the ability of MDPV to induce CPP in adult male Sprague-Dawley rats, in which both MDPV's aversive effects and self-

administration of MDPV have been previously demonstrated. Characterizing the rewarding effects of MDPV in these rats allows for a baseline to assess how a range of factors might impact them and, in turn, the drug's abuse liability.

2. Materials and Methods

Forty-eight experimentally-naïve male Sprague-Dawley rats 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 rats per OptiRat Plus polycarbonate bins; 100 cm × 99 cm × 201 cm) and maintained on ad-libitum food and water until PND 90, 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 maximum, producing a biased apparatus (for a discussion on the impact of light in place conditioning, see Roma and Riley, 2005). 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 1.0, 1.8 or 3.2 mg/kg. Sterile isotonic saline was also filtered before being administered to saline controls, as well as to MDPV-treated subjects on non-drug paired days (see below). 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.

2.3 CPP Pre-test

On PND 90, each animal was allowed 15-min access to freely explore the entire place conditioning apparatus to obtain individual baseline times spent in each chamber. Immediately following the pre-test, animals were returned to their home cages. No injections

were given on this day. A biased conditioning procedure was used during CPP conditioning, i.e., each animal was subsequently given MDPV prior to placement on its own initially non-preferred side (see Cunningham et al., 2003; Davis et al., 2007; Schenk et al., 1986).

2.4 CPP Conditioning and Test

On PND 91 (Conditioning Day 1), animals were randomly assigned to receive an injection of either MDPV (1.0, 1.8 or 3.2 mg/kg; $n = 12$/dose) or saline ($n = 12$) and immediately confined to their respective non-preferred side (drug-paired side; DPS) of the CPP apparatus for 30 min. On the next day, all animals were given an injection of saline equivolume to the conditioning injections and then confined to the opposite chamber (non-drug paired side; NDPS). This two-day cycle of the drug given prior to animal's placement on the non-preferred side followed by vehicle given prior to its placement on the preferred side was repeated three additional times (for a 8 total conditioning days). Order of conditioning sessions (i.e., drug vs. saline) was not counterbalanced (see King and Riley, 2013; Lepore et al., 1995; Mayer and Parker, 1993). Following the final cycle, all of the animals were given a test for CPP during which they were placed in the middle gray compartment and allowed to freely explore the apparatus for 15 min, after which animals were returned to their home cages. No injections were given on this day.

2.5 Statistical Analyses

Percent time spent on the DPS on the pretest and final test was compared with a 2 × 4 repeated measures ANOVA, with a within-subjects variable of Trial (Pretest and Test) and a between-subjects variable of Drug (0, 1.0, 1.8 and 3.2). In the case of a significant interaction, simple effects of Trial for each Drug condition were assessed with multivariate analyses. All statistical analyses were based on a significance level of 0.05.

3. Results

Percent time spent on the DPS for all groups ($n = 12$ for each group) before (Pre) and following (Post) conditioning is presented in Figure 1. As illustrated, all doses of MDPV produced a significant increase in time spent on the DPS, with no such increase seen with vehicle-treated animals. The 2 × 4 repeated measures ANOVA revealed a main effect of Trial [$F(1, 44) = 64.517$], as well as a significant Trial × Drug interaction [$F(3, 44) = 4.906$]. There was no main effect of Drug. To further explore the Trial × Drug interaction, simple effects of Trial for each Drug condition were explored with multivariate analyses, which revealed significant increases for all MDPV-injected groups [1.0: $F(1, 44) = 34.737$; 1.8: $F(1, 44) = 17.213$; 3.2: $F(1, 44) = 26.526$], but no significant increase for vehicle-treated animals.

4. Discussion

The present study assessed the ability of MDPV to induce CPP in adult male Sprague-Dawley rats. As described, all doses of MDPV were shown to produce significant increases in time spent on the drug paired side (from pretest to test), suggesting that MDPV does produce rewarding effects (Brielmaier et al., 2008; Cunningham et al., 2003). It should be

noted, however, that actual preference was not produced, i.e., animals still spent a majority of time on the non-drug paired side. These relatively weak conditioning effects were likely a function of initial strong preference for the non-drug paired side (possibly a function of the chamber lights being set to maximum; see above). Additionally, these shifts in preference were not dose-dependent, contradictory to results seen with other stimulants (Costello et al., 1989; Durazzo et al., 1994). A meta-analysis of place conditioning studies with amphetamine and cocaine reported a significant effect of amphetamine dose on the magnitude of place conditioning effect, and a trend toward this same relationship with cocaine (Bardo et al., 1995). It is possible, however, that the doses used produced a ceiling effect, and that dose-dependent differences may have emerged at lower doses.

The fact that MDPV produces a positive shift in place conditioning is not surprising, given that other dopaminergic compounds have been shown to produce conditioned place preference (Bilsky et al., 1990; Calcagnetti and Schechter, 1993; Spyraki et al., 1982). Further, the present findings would be expected given that MDPV has been shown to lower ICSS thresholds (see introduction; Watterson et al., 2014), another common indicator of a drug's rewarding effects. The current findings are unique in that they demonstrate MDPV's rewarding effects in outbred rats, utilizing the same doses that have been shown to produce taste avoidance. That the same doses of MDPV are capable of producing both aversion and reward may seem paradoxical (Hunt and Amit, 1987; Riley, 2011), but it is consistent with data from a host of other drugs, including morphine (King and Riley, 2013; Simpson and Riley, 2005), amphetamine (Wang et al., 2010), and caffeine (Brockwell et al., 1991), that induce both taste avoidance and place preference at the same dose in the same animals in concurrent CTA/CPP assessments.

Further studies will be needed to determine how the balance of MDPV's subjective effects might impact self-administration. Additionally, given that both the aversive and rewarding effects likely contribute to drug taking, it will also be necessary to determine which factors may influence the strength of each of these and, thus, their overall balance. For example, age has already been shown to influence MDPV-induced aversions (Merluzzi et al., 2014), but a number of other experiential and subject factors such as sex, strain, dose and drug history should also be examined given their impact on the aversive and rewarding effects of other drugs of abuse (Freeman and Riley, 2009; Klosterhalfen and Klosterhalfen, 1985; Tzschentke, 1998). Determining how the balance between aversion and reward influences MDPV-induced self-administration, and the factors that can alter this balance, may provide valuable insight into possible risk factors for use and overall abuse potential.

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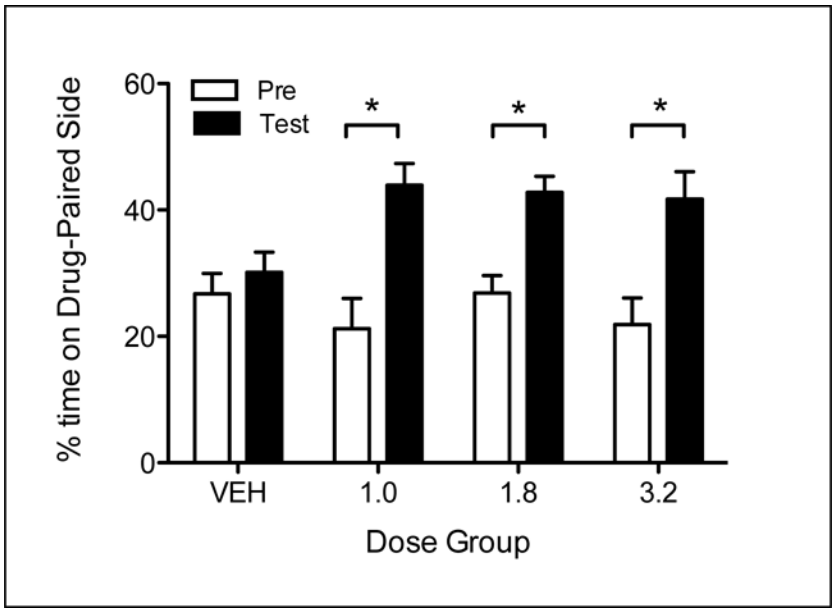

Figure 1.

Percent time spent on the DPS for all groups (n = 12 for each group) before (Pre) and following (Post) conditioning. Significant within-group changes from Pre-Test to Post-Test are denoted by asterisk ($p<.05$).