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Research article

Conditioned taste avoidance, conditioned place preference and hyperthermia induced by the second generation 'bath salt' α-pyrrolidinopentiophenone (α-PVP)

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ABSTRACT

Background: α-Pyrrolidinopentiophenone (α-PVP) has been reported to be rewarding in a variety of pre-clinical models. Given that a number of drugs of abuse have both rewarding and aversive effects, the balance of which influences addiction potential, the present study examined the aversive properties of α-PVP by assessing its ability to induce taste avoidance. This assessment was made in a combined taste avoidance/place conditioning design that also allowed an evaluation of the relationship between α-PVP's aversive and rewarding effects.

Methods: Male Sprague-Dawley rats were exposed to a novel saccharin solution, injected with one of four doses of α-PVP (0, 0.3, 1.0 and 3.0 mg/kg) (IP) and placed on one side of a place conditioning apparatus. The next day, they were injected with vehicle, given access to water and placed on the other side. Following four conditioning cycles, saccharin avoidance and place preferences were then assessed. The effects of α-PVP on body temperature were also examined.

Results: α-PVP induced dose-dependent taste avoidance as well as significant increases in time spent on the drug-paired side (although this effect was not dependent on dose). α-PVP also induced dose- and time-dependent hyperthermia.

Conclusions: α-PVP induced significant taste avoidance whose strength relative to the psychostimulants methylenedioxypyrovalerone (MDPV) and cocaine paralleled their relative binding to the dopamine transporter. Similar to other drugs of abuse, α-PVP has both aversive and rewarding effects. It will be important to assess how various experiential and subject variables impact these effects and their balance to predict abuse liability.

1. Introduction

Drugs of abuse have both rewarding and aversive effects (Cunningham, 1979; Turenne et al., 1996; Verendeev and Riley, 2011), and it is the balance of these two affective properties that impact their use and abuse (Colechio et al., 2014; Riley et al., 2009; Stolerman, 1985; Wise et al., 1976). One class of drugs only beginning to be examined in this context are the synthetic cathinones (Al-Juhaishi et al., 2012; Busardò et al., 2015; Kalix, 1992; Patel, 2000). Among these newly emerged compounds is α-pyrrolidinopentiophenone (α-PVP; aka "gravel"; "flakka" or "five dollar insanity"), one of the most popular "second-generation bath salts" (Marinetti and Antonides, 2013; Marusich et al., 2014). α-PVP, despite being known as a 'second-generation' bath salt, is actually the structural parent of the 'first generation' bath salt MDPV and has many characteristics in common (Aarde et al., 2015; Glennon and Young, 2016; Katselou et al., 2015; Marusich et al., 2014). Although α-PVP has not received the same attention as MDPV (for reviews on the behavioral and biochemical actions of MDPV, see Baumann et al., 2013; Glennon and Young, 2016; King and Riley, 2016; Meltzer et al., 2006; Simmler et al., 2013), some characterization has recently begun. For example, Aarde et al. (2015) reported that in rats α-PVP was similar to MDPV in both potency and efficacy in supporting intravenous self-administration (see also Schindler et al., 2015). Additionally, Watterson et al. (2014) demonstrated that in rats α-PVP dose-dependently decreased ICSS thresholds in a discrete trials current threshold procedure (Marusich et al., 2016). Consistent with this, Gatch et al. (2015) reported that in mice α-PVP induced significant dose-dependent conditioned place preferences.

As noted above, most drugs of abuse have both rewarding and aversive effects and their balance impacts abuse potential. Although α-

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PVP's rewarding effects have been examined, little is known of its aversive effects. Previous work has reported that a variety of CNS stimulants (including MDPV; see King et al., 2014, 2015; Merluzzi et al., 2013) are effective in inducing dose-dependent conditioned taste avoidance (CTA), a behavioral index of the aversive effects of drugs (Garcia and Ervin, 1968; Lin et al., 2016; Riley and Tuck, 1985). The taste avoidance procedure is one in which animals are given access to a novel taste and then injected with a drug. As a consequence of this pairing, consumption of the drug-paired taste is suppressed, a suppression generally described to be function of the drug's aversive effects (Garcia and Ervin, 1968; Revusky and Garcia, 1970; Riley and Tuck, 1985; Rozin and Kalat, 1971; for a review on the history of CTA, see Freeman and Riley, 2009). The present study began the initial characterization of the aversive effects of α-PVP by examining its ability to induce taste avoidance.

Although many drugs have been reported to induce taste avoidance, the mechanism underlying such effects in general remains unknown (Gamzu et al., 1985; Hunt and Amit, 1987; for reviews, see Lin et al., 2016; Verendeev and Riley, 2012). The limited work with cocaine suggests that dopamine activity may mediate, in part, its aversive effects. For example, a variety of dopamine antagonists block cocaine-induced taste avoidance (Freeman et al., 2005b; Hunt et al., 1985; Serafine et al., 2011, 2012) and cocaine's aversive effects are significantly attenuated by a prior history with other dopamine-reuptake inhibitors, an effect generally interpreted to be a function of cross-tolerance between the compounds (Berman and Cannon, 1974; Freeman et al., 2005b; LeBlanc and Cappell, 1974; Serafine and Riley, 2010; for a review, see Riley and Simpson, 2001). It is interesting in this context that MDPV appears to be roughly 10 times more potent than cocaine in inducing taste avoidance (Freeman et al., 2005a, b; King et al., 2014, 2015; Marusich et al., 2014; Merluzzi et al., 2013; Serafine et al., 2012; Woloshchuk et al., 2016). The relative potencies of MDPV and cocaine in inducing taste avoidance parallel their relative efficacy at blocking DA reuptake (MDPV: IC50 values of 4.1 ± 0.5 nM; cocaine: IC50 values of 211 ± 19 nM). Although α-PVP also inhibits the reuptake of dopamine, its relative efficacy is much more similar to MDPV than cocaine (α-PVP: IC50 values of 12.8 ± 1.2 nM; Marusich et al., 2014). If dopamine activity mediates the aversive effects of α-PVP in a manner similar to that for cocaine (and MDPV; see Woloshchuk et al., 2016), it might be expected to induce taste avoidance to a degree comparable to MDPV and at doses less than those needed to induce avoidance with cocaine and doing so with fewer conditioning trials.

As noted above, Gatch et al. (2015) have previously reported CPP with α-PVP in mice; however, species differences in place preference conditioning have been noted with other drugs (see Chaperon et al., 1998; Cunningham et al., 1993; Hempel et al., 2016; Hutcheson et al., 1998; Sañudo-Peña et al., 1997; Valjent and Maldonado, 2000). Accordingly, place preference conditioning was also assessed in the present experiment. Specifically, rats were allowed access to a novel saccharin solution and injected with one of four doses of α-PVP (0, 0.3, 1.0 and 3.0 mg/kg) prior to being placed in a distinct environment, a procedure used by our laboratory (Hempel et al., 2016; King et al., 2015; Pomfrey et al., 2015; Simpson and Riley, 2005; Verendeev and Riley, 2011) and others (Brockwell et al., 1991; Sherman et al., 1980; Wang et al., 2010) to simultaneously assess the aversive (CTA) and rewarding (CPP) effects of a host of drugs of abuse.

Core body temperature was also examined in response to α-PVP. Increases in body temperature is commonly observed with a number of psychostimulants (for MDMA, see Dafters and Lynch, 1998; for methamphetamine, see Fukumura et al., 1998; for cocaine, see Cappon et al., 1998; for MDPV, see Fantegrossi et al., 2013; King et al., 2014; Kiyatkin et al., 2015; Merluzzi et al., 2013). Interestingly, Aarde et al. (2015) have recently reported *hypothermia* in rats receiving 5.6 and 10.0 mg/kg of either α-PVP or MDPV. To extend these assessments of temperature changes with α-PVP, following the above-mentioned behavioral tests, subjects were injected with α-PVP and core body temperature was examined. This assessment also allowed for an initial examination of the relationship of taste avoidance conditioning to changes in temperature (see Cunningham et al., 1992; Merluzzi et al., 2013).

2. General methods

2.1. Subjects

The subjects were 33 experimentally naïve male Sprague-Dawley rats (Envigo, Indianapolis, IN). Rats entered the animal research facility at American University on postnatal day (PND) 23 and were allowed to mature undisturbed with the exception of weekly weight assessments from PND 23 though PND 83. Beginning on PND 83, animals were weighed daily to index health status and to reduce handling stress during the experimental procedures. Subjects were 90 days old and weighed between 321 and 445 g at the beginning of the study. All procedures adhered to the Guidelines for the Care and Use of Laboratory Animals (National Research Council, 2011) and the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council, 2003) and were approved by the Institutional Animal Care and Use Committee at American University.

2.2. Drugs and solutions

Racemic α-pyrrolidinopentiophenone HBr (α-PVP) (synthesized at the Drug Design and Synthesis Section, NIDA) was dissolved in isotonic saline (0.9%) and injected intraperitoneally (IP) at 0.3, 1.0 and 3.0 mg/kg. Concentration was held constant across dose groups (1 mg/ml), and animals were injected at a volume of 1 ml/kg. Isotonic saline (vehicle) was administered to controls at the same volume. Each drug (and vehicle) solution was prepared daily and was passed through a 0.2 um filter prior to injection. Saccharin (sodium saccharin, Sigma) was prepared as a 1 g/l (0.1%) solution in tap water.

2.3. Apparatus

Subjects were housed two per home-cage in OptiRat Plus cages (38.9 × 56.9 × 26.2 cm; 1181 cm^2). The room in which the cages were located was maintained on a 12-h light/dark cycle (0800–2000 h) at 23 °C. Unless stated otherwise, food and water were available ad libitum. During habituation, training and testing (see below), animals were transferred to individual hanging, stainless-steel wire mesh test cages (24.3 × 19 × 18 cm) on the front of which graduated Nalgene tubes could be placed for fluid presentation. Eight identical three-chambered conditioned place preference systems (San Diego Instruments Place Preference System, San Diego, CA) were employed for place preference conditioning (for a detailed description, see Hempel et al., 2016). During training and testing, the procedure room was lit with an 85-watt red light mounted in the ceiling.

2.4. Procedure

2.4.1. Habituation

On PND 90, subjects were deprived of water for 24 h and on the following day were given 20-min access to tap water in the test cages. Following this, the animals were returned to their home cages. This procedure was repeated for 10 days to allow water consumption to stabilize (drinking within 2 s with the average volume of water consumed not increasing or decreasing by > 2 ml for 3 consecutive days). Fluid was presented in graduated 50-ml Nalgene tubes, and intake was indexed by the difference between pre- and post-consumption volumes.