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High ambient temperature facilitates the acquisition of 3,4-methylenedioxymethamphetamine (MDMA) self-administration

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ABSTRACT

Rationale: MDMA alters body temperature in rats with a direction that depends on the ambient temperature (T_A). The thermoregulatory effects of MDMA and T_A may affect intravenous self-administration (IVSA) of MDMA but limited prior reports conflict.
Objective: To determine how body temperature responses under high and low T_A influence MDMA IVSA.
Methods: Male Sprague-Dawley rats were trained to IVSA MDMA (1.0 mg/kg/infusion; 2-h sessions; FR5 schedule of reinforcement) under T_A 20 °C or 30 °C. Radiotelemetry transmitters recorded body temperature and activity during IVSA.
Results: MDMA intake increased under both T_A during acquisition, but to a greater extent in the 30 °C group. The magnitude of hypothermia was initially equivalent between groups but diminished over training in the 30 °C group. Within-session activity was initially lower in the 30 °C group, but by the end of acquisition and maintenance, activity was similar for both groups. When T_A conditions were swapped, the hot-trained group increased MDMA IVSA under 20 °C T_A and a modest decrease in drug intake was observed in the cold-trained group under 30 °C T_A. Subsequent non-contingent MDMA (1.0–5.0 mg/kg, i.v.) found that rats with higher MDMA IVSA rates showed blunted hypothermia compared with rats with lower IVSA levels; however, within-session activity did not differ by group. High T_A increased intracranial self-stimulation thresholds in a different group of rats and MDMA reduced thresholds below baseline at low, but not high, T_A.
Conclusions: High T_A appears to enhance acquisition of MDMA IVSA through an aversive effect and not via thermoregulatory motivation.

1. Introduction

Recreational use of (±)3,4-methylenedioxymethamphetamine (MDMA; "Ecstasy") became increasingly popular in recent decades (Peroutka, 1987; Pope et al., 2001; Schuster et al., 1998). In the USA, annual prevalence rates have been around 5% of respondents for young adults in the past decade (Johnston et al., 2012a; Johnston et al., 2012b; Johnston et al., 2012c); *lifetime* prevalence for Ecstasy of 11–12% are reported in recent years. Annual prevalence of Ecstasy exposure is at least 3 fold higher than prevalence for heroin, crack (smokable cocaine), ice (smokable methamphetamine) or PCP. Thus, overall lifetime rates of exposure to Ecstasy are substantial and will continue to be so for some time, until these cohorts expire. It is further concerning that multiple Phase I clinical trials are underway to establish MDMA as an adjunctive treatment for psychotherapy (Kerbage and Richa, 2013; Oehen et al., 2013; Cukor et al., 2009; Doblin, 2002; Mithoefer et al., 2013; Mithoefer et al., 2011) because surveys of attitudes toward drug risk show that diverted pharmaceutical preparations (e.g., amphetamines) have a perception of safety which coincides with higher incident rates (Johnston et al., 2012a; Johnston et al., 2012b; Johnston et al., 2006). Increased population exposure is problematic because significant proportions of heavy Ecstasy users meet criteria for dependence at some point in their use history (Schuster et al., 1998; Thomasius et al., 2005; Cottler et al., 2001; de Almeida et al., 2009). There are also case reports of Ecstasy/MDMA use patterns that are daily or at least several times per week (Hurault de Ligny et al., 2005; Jansen, 1999; Kouimtsidis et al., 2006).

Laboratory studies of the abuse liability of MDMA have been curiously sporadic in comparison with many other drugs of abuse. MDMA will substitute for cocaine in baboons and rhesus monkeys trained for intravenous self-administration (Beardsley et al., 1986; Lamb and Griffiths, 1987; Fantegrossi et al., 2002; Fantegrossi et al., 2004; Lile et al., 2005) and it generates consistent, but low levels of self-administration in rats (De La Garza et al., 2007; Ratzenboeck et al., 2001; Reveron et al., 2010); one laboratory reports intakes at least several fold higher (Daniela et al., 2004; Daniela et al., 2006; Schenk et al.,

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2003). The Schenk lab has reported that only about 60% of rats reach acquisition criteria although additional animals may acquire after 21 + days of access (Schenk et al., 2007; Bird and Schenk, 2013; Colussi-Mas et al., 2010). There are also hints of increased MDMA intake with many sessions of access (De La Garza et al., 2007; Dalley et al., 2007; Reveron et al., 2006) or with longer daily access sessions (Vandewater et al., 2015).

A prior observation reported up to twice as many infusions of MDMA were self-administered in rats when ambient temperature was increased to 30 °C in single day challenges after initial training under normative (21 °C) ambient temperature (Cornish et al., 2003). A similar phenomenon may also occur in nonhuman primate models (Banks et al., 2008). This may be of critical translational importance since many human Ecstasy users ingest the drug in the context of a crowded dance club environment. This finding may also explain inconsistency in prior rodent investigations of MDMA self-administration. Rats' body temperature is decreased by MDMA at low ambient temperature and increased at high ambient temperature (Malberg and Seiden, 1998; Dafters, 1994; Dafters, 1995) which may be behaviorally motivational (Farrell and Alberts, 2007; Dymond and Fewell, 1998; Briese, 1986). The physiologically thermoneutral range for rats is around 30 °C, but behavioral preference in a thermocline may be some 6–8 °C lower (Gordon, 1990), although also see (Gordon et al., 1991) for behavioral preference for 27–29 °C. This raises the possibility that behavioral motivation may be altered by temperature decreases caused by self-administered MDMA at normal laboratory temperatures, typically below ~25 °C. Consequently the results of Cornish and colleagues (2003) could potentially be explained by an asymmetry in the aversion to body temperature responses to MDMA under different ambient temperatures.

This study was designed to determine if intravenous MDMA self-administration is increased in rats by training in a high ambient temperature and if so, if this is related to a change in the thermoregulatory response to intravenously self-administered MDMA. The threshold for thermoregulatory effect of acute MDMA appears to be 5 mg/kg (Dafters, 1994) and it is unknown if various intravenous self-administration patterns [0.5–1.0 mg/kg/inf is typical, resulting, e.g., in 4–7 mg/kg over 2 h (Reveron et al., 2010), 30 mg/kg over 6 h (Bird and Schenk, 2013) and 30 mg/kg over 2 h (Colussi-Mas et al., 2010)] alter body temperature. A minimally invasive implanted radiotelemetry system, previously shown sensitive to the temperature disrupting effects of non-contingent administration of Δ9-tetrahydrocannabinol, mephedrone (4-methylmethcathinone), 3,4-methylenedioxypyrovalerone (MDPV), α-pyrrolidinopentiophenone (α-PVP) and MDMA (Miller et al., 2013; Wright et al., 2012; Aarde et al., 2015a; Nguyen et al., 2016a) as well as the intravenous self-administration of 4-methylmethcathinone (Aarde et al., 2013a) in rats, and similar to that found sensitive to effects of MDMA, methamphetamine and THC in monkeys (Crean et al., 2007; Crean et al., 2006; Taffe, 2012; Taffe et al., 2006), was used to minimize behavioral disruption during the self-administration sessions. Finally, the effect of high and low ambient temperature on the effects of MDMA on intracranial self-stimulation reward was determined to test the hypothesis that high ambient interferes with the ability of MDMA to reduce brain reward thresholds.

2. Methods

2.1. Animals

Male Sprague-Dawley (Harlan, Livermore, CA; Experiment 1: $N = 24$) and Wistar rats (Charles River; Experiment 2, $N = 10$); were housed in humidity and temperature-controlled (23 ± 1 °C) vivaria on 12:12 h light:dark cycles. Animals entered the laboratory at 10–13 weeks of age and weighed 350–400 g at the start of the study. Animals had ad libitum access to food and water, except for during pellet training and drug self-administration sessions, (see below). Procedures were conducted under protocols approved by the Institutional Care and Use Committees of The Scripps Research Institute and consistent with the NIH Guide for the Care and Use of Laboratory Animals.

2.2. Drugs

Racemic MDMA (3,4-methylenedioxymethamphetamine HCl; provided by U.S. National Institute on Drug Abuse) was dissolved in physiological saline to a concentration of 1.0 or 0.5 mg/kg/inf per 0.1 ml of solution.

2.3. Surgeries

2.3.1. Intravenous catheterization

Rats were anesthetized with an isoflurane/oxygen vapor mixture (isoflurane 5% induction, 1–3% maintenance) and prepared with chronic intravenous catheters as previously described (Aarde et al., 2013b; Aarde et al., 2015b; Miller et al., 2012). Briefly, the catheters consisted of a 14-cm length of polyurethane based tubing (Micro-Renathane®, 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 tied gently with suture thread. A liquid tissue adhesive was used to close the incisions (3M™ Vetbond™ Tissue Adhesive; 1469SB).

A minimum of 7 days was allowed for surgical recovery. For the first three days of the recovery period, an antibiotic (cefazolin; 0.4 g/ml, 2.0 ml/kg, s.c.) and an analgesic (flunixin; 2.5 mg/ml, 2.0 ml/kg, s.c.) were administered daily. During testing and training the catheters were flushed with heparinized saline before sessions and heparinized saline containing cefazolin (100 mg/ml) after sessions.

Catheter patency was assessed nearly once a week after the last session of the week 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.

2.3.2. Radiotelemetry probe implantation

Sterile radiotelemetry transmitters (Data Sciences International; CTA-F40 or TA-F40) were implanted in the abdominal cavity thru an incision along the abdominal midline posterior to the xyphoid space (Wright et al., 2012). Absorbable sutures were used to close the abdominal muscle incision and the skin incision was closed with tissue adhesive. Post-operative care and recovery time was the same as that for i.v. catheterization. Body temperature and activity were measured as previously described (Miller et al., 2013; Wright et al., 2012; Aarde et al., 2015a). In brief, the temperature was sampled every 5 min and the activity reflects a rate (of arbitrary counts of movement per 5 min) of the transmitter across the receiver plate that is placed under the cage.

2.3.3. Intracranial self-stimulation electrode implantation

Rats were anesthetized with an isoflurane/oxygen vapor mixture (isoflurane 5% induction, 1–3% maintenance) and prepared with stimulation electrodes as described in (Markou and Koob, 1992). A small incision (approximately 1.5–4 cm) was made through the skin, the muscle carefully pushed aside using a blunt instrument, and the skull cleaned with sterile swabs or gauze. A stainless steel bipolar electrode (0.25 mm) was aimed at the medial forebrain bundle and implanted stereotaxically (in mm; + 5 incisor bar, − 0.5 AP from Bregma; ± 1.7 ML, − 9.5 DV from skull at Bregma). The electrode was anchored to the skull with four to six stainless-steel screws and dental cement. The