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Changes in ambient temperature differentially alter the thermoregulatory, cardiac and locomotor stimulant effects of 4-methylmethcathinone (mephedrone)*

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Abstract

BACKGROUND—The substituted cathinone compound known as mephedrone (4-methylmethcathinone; 4-MMC) has become popular with recreational users of psychomotor-stimulant compounds. Only recently have the first preclinical studies provided information about this drug in the scientific literature; nevertheless, media reports have led to drug control actions in the UK and across several US states. Rodent studies indicate that 4-MMC exhibits neuropharmacological similarity to 3,4-methylenedioxymethamphetamine (MDMA) and prompt investigation of the thermoregulatory, cardiac and locomotor effects of 4-MMC. This study focuses on the role of ambient temperature, which has been shown to shift the effects of MDMA from *hyperthermic* to *hypothermic*.

METHODS—Male Sprague-Dawley rats were monitored after subcutaneous administration of 4-MMC (1.0–5.6 mg/kg) using an implantable radiotelemetry system under conditions of low (20°C) and high (30°C) ambient temperature. A pharmacokinetic study found a T_{max} of 0.25 h and a C_{max} of 1,206 ng/mL after 5.6 mg/kg 4-MMC. A dose-dependent reduction of body temperature was produced by 4-MMC at 20°C but there was no temperature change at 30°C.

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Contributors

M.A.T. and M.L.M. designed the telemetry studies within the context of a collaborative investigation into novel cathinone drugs including the laboratories of M.A.T., T.J.D. and K.L.H.

D.A. and T.J.D. designed routes, synthesized 4-methylmethcathinone and verified purity.

K.L.H. and D.J.B. conducted and analyzed the pharmacokinetic studies.

K.M.C. conducted the telemetry studies and performed initial data analysis.

Statistical analysis of the telemetry data, creation of figures and major manuscript drafting was conducted by M.A.T. with significant input from M.L.M.

All authors have approved the manuscript.

Conflict of Interest

The authors do not have any financial or other conflicts of interest to declare in relationship to this work.

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RESULTS—Increased locomotor activity was observed after 4-MMC administration under both ambient temperatures, however, significantly more activity was observed at 30°C. Heart rate was slowed by 1.0 and 5.6 mg/kg 4-MMC at 20°C, and was slower in the 30°C vs. 20°C condition across all treatments.

CONCLUSION—These results show that the cathinone analog 4-MMC exhibits *in vivo* thermoregulatory properties that are distinct from those produced by MDMA.

Keywords

stimulant; cathinone; thermoregulation; locomotor activity; heart rate; rat

1. INTRODUCTION

Despite a rapid increase in the popularity of the novel recreational drug 4-methylmethcathinone (4-MMC, mephedrone) over the past 4 years, scientific information remains scant (Iversen et al., 2010; Sedefov et al., 2010). Although 4-MMC is reported to have stimulant-typical subjective properties (Winstock et al., 2011), recent laboratory studies suggest that 4-MMC exhibits considerable similarity to the well-established recreational drug 3,4-methylenedioxymethamphetamine (MDMA; “Ecstasy”). Since MDMA can result in medical emergency involving acute thermoregulatory distress (Dar and McBrien, 1996; Mascola et al., 2010; Patel et al., 2004), it is critical to explore the thermoregulatory properties of 4-MMC in animal models to infer potential risks for humans.

Recent evidence shows that 4-MMC increases extracellular serotonin in the rat nucleus accumbens to the same extent as does MDMA, but to a greater extent than does methamphetamine (MA) or amphetamine (AMP); 4-MMC also increases extracellular dopamine to the same extent as the classical amphetamines, but to a greater extent than MDMA (Baumann et al., 2012; Kehr et al., 2011). Also, 4-MMC stimulated locomotion to the same extent as MDMA, yet to a lesser extent than MA/AMP in those studies. *In vitro* studies show slightly greater relative inhibition of the dopamine transporter (DAT) relative to the serotonin transporter by 4-MMC, and a 15-fold greater affinity for 5-HT₂ receptor subtypes than for D₂ receptors (Martinez-Clemente et al., 2011). Repeated, high-dose 4-MMC under high ambient temperature resulted in hyperthermia, decreased serotonin and SERT function in the hippocampus, but did not alter dopamine content or DAT function in the striatum (Hadlock et al., 2011). This latter effect is similar to the well-established effects of MDMA (Green et al., 2003). 4-MMC also suppressed wheel running in rats, similar to the effects of MDMA, whereas MA increases wheel activity (Huang et al., 2012).

Thermoregulatory responses to MDMA depend on ambient temperature (T_A), with hypothermia observed at 22–24°C T_A and hyperthermia above about 26°C in rats (Dafters, 1994; Malberg and Seiden, 1998), although this does not appear to be the case for monkeys or humans (Freedman et al., 2005; Von Huben et al., 2007). The current study was conducted to determine the effects of 4-MMC on thermoregulation, heart rate and locomotor activity in rats. The goal was to evaluate the impact of 4-MMC under high and low T_A , during the active (dark) part of the circadian cycle and in unrestrained animals. These approaches are critical since Baumann and colleagues (2012) and Kehr et al (2011) examined locomotor effects, during the light cycle, in animals that were constrained by a microdialysis tether- all of these might be predicted to modify drug responses. Furthermore, Hadlock and colleagues examined the thermoregulatory effects of repeated dosing with high doses (10.0 or 25.0 mg/kg, 4X per day at 2 h intervals) only at elevated (29°C) T_A and reported only the peak hyperthermia across the entire dosing interval (Hadlock et al., 2011). An initial pharmacokinetic study was performed to guide selection of the intervals of observation and data analysis for this study.

2. MATERIALS AND METHODS

2.1 Animals

Male Sprague-Dawley (N=7; Harlan; Livermore, California) were housed in a humidity- and temperature-controlled ($22^{\circ}\text{C} \pm 1$) vivarium on a reverse 12:12 light/dark cycle for the telemetry study. Rats were 27 weeks of age (mean ~500 grams) at the start of the study, and had previously received intermittent acute doses of 3,4-methylenedioxypyrovalerone in a treatment design similar to the one described below at normal ($22\text{--}23^{\circ}\text{C}$) T_A and with access to running wheels. Animals had *ad libitum* access to food and water in the home cage. Additional male Sprague-Dawley rats (N=3; Charles River; New York) were housed in a humidity and temperature-controlled ($22^{\circ}\text{C} \pm 1$) vivarium on a regular 12:12 light/dark cycle for the pharmacokinetic experiment. Procedures were conducted under protocols approved by the IACUCs of The Scripps Research Institute and University of New England and were consistent with the *NIH Guide* (Clark et al., 1996).

2.2 Surgery

Sterile radiotelemetry transmitters (Data Sciences International CTA-F40) were implanted under general anesthesia (isoflurane 5% induction, 1–3% maintenance). The hair from the subxyphoid space to the pelvis was shaved and disinfected with povidone-iodine solution and alcohol and a sterile drape positioned. An incision was made along the abdominal midline immediately posterior to the xyphoid space, just large enough to allow passage of the transmitter, which was placed in the abdominal cavity. Absorbable sutures were used to close the abdominal muscle incision and skin was closed with non-absorbable suture. A minimum of 7 days was allowed for surgical recovery.

2.3 Procedure

Each subject was transported to an experimental room for recordings made via placement of the telemetry receiver plate under a shoebox style cage. Ambient temperature conditions were established prior to and monitored throughout each session. Animals were recorded for at least 1 h prior to drug administration to establish a stable body temperature baseline. Recording continued for 3 h; thereafter, animals were returned to home cages in the vivarium. Drug challenges were administered no more frequently than twice per week, in a randomized order, with a minimum 3-day interval between challenges. All of the 4-MMC conditions were tested in a randomized order; thereafter the d-methamphetamine/3,4-methylenedioxymethamphetamine conditions were tested in a second randomized design.

2.4 Drugs

Drugs were diluted in physiological saline and injected subcutaneously in a volume of 1 ml/kg. The d-methamphetamine and 3,4-methylenedioxymethamphetamine were provided by NIDA drug supply. The 4-MMC used for this study was synthesized in gram quantities using a robust synthetic route based on literature precedent (Camilleri et al., 2010), with minor modifications (see Supplementary Materials¹). Compound purity was confirmed by LC-MS, HRMS, ^1H NMR and ^{13}C NMR.

2.5 Pharmacokinetics

Surgical placement of jugular vein catheters was conducted at the vendor prior to delivery at the laboratory (N=3). Blood was collected from awake, unrestrained animals at 5, 15, 30, 60, 120, 180 and 360 min after 5.6 mg/kg, 4-MMC, s.c. Plasma was stored at -80°C until analysis. Sample analysis was conducted using high-throughput liquid chromatography with tandem mass spectrometric detection (LC-MS/MS), with data analysis via the non-compartmental analysis model of PK Solutions (Summit Research Services; Montrose, CO).

2.6 Data analysis

Analysis of the 30-min averages (of 6 sequential samples) of body temperature, heart rate and activity data employed repeated measures analysis of variance (rmANOVA; GB-STATv7.0; Dynamic Microsystems, Silver Spring MD) with within-subjects factors of T_A , drug treatment condition and time post-injection. *Post-hoc* analyses of significant main effects for telemetry data were conducted using the Neuman-Keuls procedure including all pairwise comparisons; the criterion for significance was $p < 0.05$.

3. RESULTS

3.1 Pharmacokinetic study

Uptake and elimination of 5.6 mg/kg 4-MMC from Sprague Dawley rats after subcutaneous dosing was rapid. The peak concentration (C_{max}) observed following a 5.6 mg/kg subcutaneous dose was 1206 ng/mL of plasma with a T_{max} of 0.25 h and AUC^∞ of 1170 ng·h/mL.

3.2 Body Temperature

Body temperature decreased when rats were challenged with 4-MMC under 20°C, but not under 30 °C T_A conditions (Figure 1, top panel). The statistical analysis of the 30-min averages confirmed main effects of drug treatment ($F_{4,24}=7.57$; $p < 0.0005$), time post-injection ($F_{7,42}=11.61$; $p < 0.0001$), as well as the interaction of T_A with drug condition ($F_{4,24}= 4.11$; $p < 0.005$), T_A with time post-injection ($F_{7,42}= 65.01$; $p < 0.0001$), the interaction of drug condition with time post-injection ($F_{28,168}= 11.61$; $p < 0.0001$) and the interaction of all three factors ($F_{28,168}= 6.88$; $p < 0.0001$). *Post-hoc* comparisons confirmed that the body temperature of the rats under 20°C T_A was significantly lower compared with the time point prior to injection and the respective time point after vehicle following injection of 1.78 (30–90 min post-injection), 3.2 (30–120 min) and 5.6 (30–150 min) mg/kg 4-MMC. Body temperature was also reliably lower compared with the respective vehicle time points 30–60 minutes after injection with 1.0 mg/kg 4-MMC. The magnitude of effects differed significantly between doses (see Figure 1). In contrast, body temperature was unchanged relative to pre-treatment or the vehicle condition by the administration of 4-MMC under 30°C T_A . The only difference confirmed in the post-hoc test was between the 1.0 and 3.2 mg/kg doses 30–60 minutes after injection.

3.3 Activity

The activity rate was increased by 4-MMC when rats were challenged under both T_A conditions (Figure 1, middle panel). The statistical analysis of the 30-min averages confirmed main effects of drug treatment ($F_{4,24}=4.42$; $p < 0.01$), time post-injection ($F_{7,42}=49.78$; $p < 0.0001$), as well as the interaction of T_A with time post-injection ($F_{7,42}= 3.46$; $p < 0.01$) and the interaction of drug condition with time post-injection ($F_{28,168}= 6.95$; $p < 0.0001$). *Post-hoc* comparisons confirmed that under 20°C T_A , activity was significantly higher compared with the time point prior to injection and the respective time point after vehicle, and following injection of 1.78 (30 min post-injection), 3.2 (30–60 min) and 5.6 (30–60 min) mg/kg 4-MMC. Activity was also higher 30 min after 1.0 mg/kg compared with the pre-treatment baseline for that condition. The *post hoc* test further confirmed that activity was significantly higher than the 1.0 mg/kg condition following the administration of 1.78 mg/kg (30 min post-injection) or 3.2–5.6 mg/kg (60 min).

The *post-hoc* comparisons also confirmed that under 30°C T_A , activity was significantly higher compared with the time point prior to injection and the respective time point after vehicle, and following injection of 1.0–1.78 (30 min post-injection), 3.2 (30–60 min) and 5.6 (30–90 min) mg/kg 4-MMC. Furthermore, activity was higher 60–90 min following

administration of 5.6 mg/kg when compared with all other active doses and higher than the 3.2 mg/kg dose 30 min after injection.

3.4 Heart Rate

The heart rate (HR) was significantly affected by T_A conditions and by the administration of 4-MMC (Figure 1, bottom panel). The statistical analysis of the 30-min averages confirmed main effects of T_A ($F_{1,6}=46.67$; $p<0.001$), time post-injection ($F_{7,42}=2.39$; $p<0.05$), as well as the interaction of T_A with time post-injection ($F_{7,42}=3.64$; $p<0.005$) and the interaction of all three factors ($F_{28,168}=1.83$; $p<0.05$).

The post-hoc test confirmed that when administered at 20°C T_A , the 4-MMC resulted in lower HR after the 1.0 mg/kg (120 and 180 minutes after injection) and the 5.6 mg/kg (30–60 min) doses. The post-hoc test did not confirm any differences in HR post-injection relative to the pre-injection value within any treatment condition. Heart rate also did not differ relative to the vehicle condition for any time point after any dose of 4-MMC administered at 30°C T_A . Finally, mean HR was significantly lower in the 30°C versus 20°C T_A condition after vehicle (–60–180 min post-injection), 1.0 mg/kg (30–60 min), 1.78 mg/kg (60–120, 180 min), 3.2 mg/kg (–60–180 min) and 5.6 mg/kg (–60, –30, 120–180 min) 4-MMC.

3.5 MDMA and Methamphetamine

A control experiment was subsequently conducted in the animals to confirm that the 4-MMC temperature results at 30°C T_A were not due to unanticipated constraints of the experimental preparation and to provide reference for the magnitude of locomotor response. The results (Figure 2) confirm that 5.6 mg/kg 3,4-methylenedioxymethamphetamine (MDMA) elevated body temperature (main effect of treatment condition, $F_{2,7}=5.16$; $p<0.05$; interaction of time post-injection with treatment condition, $F_{14,84}=5.47$; $p<0.0001$) and both MDMA and 1.0 mg/kg d-methamphetamine increased locomotor activity (main effect of treatment condition, $F_{2,7}=33.13$; $p<0.0001$; main effect of time post-injection, $F_{7,42}=13.64$; $p<0.0001$; and the interaction of factors, $F_{14,84}=9.06$; $p<0.0001$). The post-hoc findings are illustrated in Figure 2. There were no changes in heart rate observed.

4. DISCUSSION

This study is the first to examine the thermoregulatory and cardiac properties of 4-methylmethcathinone (4-MMC; mephedrone) across high and low ambient temperature (T_A) conditions in a rodent model. Results show that 4-MMC decreases body temperature in rats under T_A at the low end of the range recommended in the NIH Guide and does not elevate body temperature under 30°C T_A . At 20°C T_A the highest dose of 4-MMC decreased heart rate (HR) in the first hour after administration and the lowest dose had a delayed suppressive effect. HR was unaffected by 4-MMC under 30°C T_A , but this may be due to the reduction that was observed across treatment conditions. The 4-MMC also increased ambulatory locomotion in unrestrained rats when they were evaluated in the active part of their circadian cycle. The telemetry data were consistent with the pharmacokinetic data, which identified peak plasma rates within 15 min of subcutaneous dosing and the majority of drug being cleared from plasma within 2 h.

The decrease in body temperature is similar to the effects of 3,4-methylenedioxymethamphetamine (Dafters, 1994; Malberg and Seiden, 1998) and N-ethyl-3,4-methylenedioxyamphetamine (Bexis and Docherty, 2006), both of which reduce the body temperature of rats under normal laboratory T_A (~22–24 °C). The results contrast with prior studies showing that methcathinone (Rockhold et al., 1997) and cathinone (Tariq et al., 1989) *increase* body temperature in male Sprague-Dawley and Wistar rats,

respectively. Thermoregulatory responses to 4-MMC were negligible at 30°C T_A, although this is a T_A under which MDMA *increases* temperature (Dafters, 1994; Malberg and Seiden, 1998) as verified for a 5.6 mg/kg dose in these animals (Figure 2). Thus, 4-MMC may have less potential to generate hyperthermia. This is important since the majority of human MDMA users that present to Emergency Medical Services with adverse reactions to MDMA have elevated body temperature as one of the symptoms (Liechti et al., 2005; Patel et al., 2005; Schifano et al., 2010).

The major caveat to the present finding is that the highest dose was limited to 5.6 mg/kg. This was the planned limit for this repeated-measures design because prior reports have found that high doses of MDMA can result in significant subject mortality. For example, 5/6 rats died after being administered 9.0 mg/kg MDMA at 29°C (Brown and Kiyatkin, 2004), 3/10 rats died after 10.0 mg/kg was administered at 22°C with wheel access (Gilpin et al., 2011) and 3/5 rats died after 20.0 mg/kg MDMA was administered at 25°C (Gordon et al., 1991). (In the follow-up study here, a single animal exceeded 42°C body temperature after MDMA and was exogenously cooled, per protocol, but did not survive.) It nevertheless remains possible that higher doses of 4-MMC may produce temperature effects where the present ones were negative.

Ambulation was increased by 4-MMC in rats that were unrestrained and evaluated in the dark part of the circadian cycle; this generalizes effects reported by Kehr, Baumann and their colleagues (Baumann et al., 2012; Kehr et al., 2011). Furthermore, the locomotor stimulant effect was greater, and more clearly dose-dependent, under 30°C vs. 20°C T_A. Locomotor stimulation was significantly higher after 5.6 mg/kg MDMA compared with 1.0 mg/kg methamphetamine under 30°C T_A in the follow-up study. These results contrast with a prior report of 4-MMC-induced suppression of wheel activity from this laboratory (Huang et al., 2012), which further underlines the difference between ambulatory and wheel-based measures of locomotor behavior (Bradbury et al., 1987; Della Maggiora and Ralph, 2000).

Although the effect of 4-MMC on HR was modest, it significantly reduced HR relative to the vehicle treatment for 1 h under the 20°C T_A (and a delayed reduction was also observed after the 1.0 mg/kg dose). This is consistent with a prior demonstration that a dose of 20.0 mg/kg MDMA lowered HR in Wistar rats by about 25–30 beats per minute (bpm), whereas 3,4-methylenedioxymphetamine reduced HR by over 100 bpm at 22°C T_A (Bexis and Docherty, 2006). Gordon and colleagues found that 20.0 mg/kg MDMA *elevated* HR of Long-Evans rats in association with hyperthermia that resulted in the death of 3/5 animals (Gordon et al., 1991), thus there may be strain differences in responses to 4-MMC, MDMA and related drugs that are not well characterized.

In summary, this study found that 4-MMC (1.0–5.6 mg/kg s.c.) produced significant locomotor stimulation in unrestrained rats when administered in the active cycle under low or high T_A. Similar to MDMA, 4-MMC lowered body temperature in low ambient conditions, but unlike MDMA there was no evidence of hyperthermia at 30°C T_A. The drug only significantly lowered heart rate in the 20°C T_A. Together, these data show that 4-MMC produces a unique constellation of effects amongst those produced by either MDMA or classical amphetamines. Correspondingly, drawing inferences about 4-MMC risks by reference only to other recreational drugs is likely to lead one astray and therefore additional investigations are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Mean ($N = 7 \pm \text{SEM}$) body temperature, activity rates and heart rate are presented for male Sprague-Dawley rats following challenge with 4-methylmethcathinone (1.0–5.6 mg/kg, s.c.) and vehicle under 20 °C and 30 °C T_A conditions. Open symbols indicate a significant difference from both the pre-treatment baseline, within condition, and the respective time point after vehicle. Shaded symbols indicate a significant difference from the pre-treatment baseline. Significant differences from vehicle only are indicated by # and from all other treatment conditions by @ (for temperature and activity; see text for heart rate details).

Figure 2. Mean ($N = 7 \pm \text{SEM}$) body temperature and activity rates following challenge with 1.0 mg/kg d-methamphetamine (MA), 5.6 mg/kg, 3,4-methylenedioxymethamphetamine (MDMA), s.c. or vehicle under 30 °C T_A conditions. Open symbols indicate a significant difference from both the pre-treatment baseline, within condition, and the respective time point after vehicle. Shaded symbols indicate a significant difference from the pre-treatment baseline. Significant differences from vehicle only are indicated by # and between MDMA and MA by *.