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Influences of activity wheel access on the body temperature response to MDMA and methamphetamine

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ABSTRACT

Recreational ingestion of the drug 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") can result in pathologically elevated body temperature and even death in humans. Such incidents are relatively rare which makes it difficult to identify the relative contributions of specific environmental and situational factors. Although animal models have been used to explore several aspects of MDMA-induced hyperthermia and it is regularly hypothesized that prolonged physical activity (e.g., dancing) in the nightclub environment increases risk, this has never been tested directly. In this study the rectal temperature of male Wistar rats was monitored after challenge with doses of MDMA and methamphetamine (MA), another drug frequently ingested in the rave/nightclub environment, either with or without access to an activity wheel. Results showed that wheel activity did not modify the hyperthermia produced by 10.0 mg/kg MDMA. However, individual correlations were observed in which wheel activity levels after a locomotor stimulant dose of MDMA were positively related to body temperature change and lethal outcome. A modest increase in the maximum body temperature observed after 5.6 mg/kg MA was caused by wheel access but this was mostly attributable to a drop in temperature relative to vehicle treatment in the absence of wheel activity. These results suggest that nightclub dancing in the human Ecstasy consumer may not be a significant factor in medical emergencies.

1. Introduction

Cases of human medical emergency and/or death which involve exposure to 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") are a continuing public health concern (Mascola et al., 2010) and are frequently associated with pathologically elevated body temperature (Dams et al., 2003; Gillman, 1997; Greene et al., 2003; Mallick and Bodenham, 1997). Such incidents are apparently rare as a percentage of all MDMA use episodes making it difficult to identify the relative contributions of specific environmental and situational factors. Although it is regularly hypothesized that prolonged physical activity (e.g., dancing) in the nightclub environment increases risk, deceased individuals may or may not (Libiseller et al., 2005; Patel et al., 2005) have been exposed to such conditions. It is well established that street Ecstasy tablets frequently contain the stimulant methamphetamine (MA) in addition to, or substitution for, MDMA (Baggott et al., 2000; Tanner-Smith, 2006). Furthermore qualitative evidence that users may differentially seek "speedy" versus "dopey" Ecstasy tablets (Levy et al., 2005) suggests that MA-containing tablets may be intentionally consumed by some users. Thus it is of significant interest to determine the thermoregulatory consequences of repetitive activity after treatment with either MDMA or MA.

MDMA-induced hyperthermia can be readily modeled in a variety of species. Hyperthermia has been reported in rats (Brown and Kiyatkin, 2004; Dafters, 1994; Malberg and Seiden, 1998), mice (Carvalho et al., 2002; Fantegrossi et al., 2003), guinea pigs (Saadat et al., 2004), pigs (Fiege et al., 2003; Rosa-Neto et al., 2004), rabbits (Pedersen and Blessing, 2001) and monkeys (Crean et al., 2006; Taffe et al., 2006; Von Huben et al., 2007). The role sustained motor activity plays in modulating the body temperature response of experimental animals remains nearly uninvestigated, despite prior work suggesting that increased muscle thermogenesis is an important contributor to MDMA-induced hyperthermia (Mills et al., 2004; Sprague et al., 2005). Despite the fact that MDMA has been shown repeatedly to increase open field locomotor behavior in rats at doses of about 10 mg/kg of either the racemic mixture or the S(+) stereoisomer (Bankson and Cunningham, 2002; Gold and Koob, 1988, 1989; Walker et al., 2007), the role of locomotor activity has not been explicitly manipulated in thermoregulatory studies. MDMA does not appear to be a locomotor or behavioral stimulant in macaque monkeys (Crean et al., 2007; 2006; Fantegrossi et al., 2009; Taffe et al., 2006), thus the rat is a preferred model for this purpose.

Many rodent species will spontaneously engage in considerable physical exercise, beyond that which animals would spontaneously perform in locomotion in a standard cage or an open field, when

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provided with a running wheel, as has been reviewed (Sherwin, 1998). In addition, concurrent access to a wheel suppresses the intravenous self-administration of cocaine (Cosgrove et al., 2002) and extended access results in an escalation of activity (Eikelboom and Lattanzio, 2003; Lattanzio and Eikelboom, 2003) akin to the escalation of drug taking under similar long-access conditions (Ahmed and Koob, 1998). Thus, this model offers a method to generate increased spontaneous activity levels with an onset that is controlled experimentally. The fact that activity is *spontaneous* confers some individual variability but it avoids the stress reaction (which may also have individual variance) that attends a forced-activity model such as a moving treadmill. Since the overall goal is to model the rave dance environment in which MDMA consumers *voluntarily* engage in a preferred repetitive locomotor behavior, selection of an activity wheel is an ideal choice.

Systematic (Smith and Clark, 1975; Squibb and Tilson, 1981) or intra-accumbens (Evans and Vaccarino, 1986) injections of d-amphetamine (AMP) can increase wheel running in rats. Since access to the running wheel can be experimentally varied, it can be used as an independent variable to model a high level of sustained physical activity (i.e., dancing) that is a feature of one prominent Ecstasy use environment. The present study was designed to determine if locomotor activity increased the degree of hyperthermia induced by MDMA or MA.

2. Methods

2.1. Animals

Eighteen male Wistar rats (Charles River, New York) were housed in a humidity and temperature-controlled (22 °C ± 1) vivarium on either a normal 12 h light/dark cycle (Experiment 2; N = 8) or a reverse cycle (Experiment 1; N = 10) depending on the experiment. Animals had *ad libitum* access to food and water throughout the course of the studies except during the acute challenge studies. All procedures were conducted under protocols approved by the Institutional Care and Use Committee of The Scripps Research Institute and consistent with the *National Institutes of Health Guide for the Care and Use of Laboratory Animals* (Clark et al., 1996).

2.2. Activity wheels

Two types of activity wheels were used. In Experiment 1, the wheels (Harvard Apparatus; ~33 cm runway diameter) fit into a shoebox style home cage; the No-Wheel condition was by removal of the entire wheel. In subsequent experiments, the wheels (Med Associates Model #ENV-046; ~35 cm diameter runway) were attached to the side of a shoebox style home cage modified with a door to provide wheel access. In these latter studies, access was prevented in the No-Wheel conditions by closing the door. In all studies animals access and activity was voluntary, they were not placed on the wheel at any time. Heating of the experimental rooms was by individual space heaters and verified by a portable thermometer (RadioShack). Variability of the ambient temperature was no greater than ± 1 °C from the target temperature for these studies.

2.3. Temperature

Rectal temperature was determined by inserting a lubricated thermistor (VWR Traceable™ Digital Thermometer) about 8 cm into the rectum of the rat. A stable reading was usually obtained within about 20 s. In all studies, temperature was determined 10 min prior to drug injection and then at 30, 60, 90 and 120 min after drug challenge. In all studies a response plan for managing excessive hyperthermia was in place. If an animal's temperature exceeded the allowable threshold (40 °C for the first study, 42 °C for the second) it was placed on a pad covering a layer of ice in a standard chamber until normative temperature range (36.5–39 °C) was restored for at least an hour. Animals were then monitored periodically up to ~6–8 h after the dosing time. Animals that were observed to be unresponsive, immobile and/or moribund this long after dosing were euthanized.

2.4. Drugs

The drugs for this study (*d*-methamphetamine, (±)3,4-methylendioxymethamphetamine), were provided by Research Triangle Institute under contract to the US National Institute on Drug Abuse Drug Supply program. Drug doses were diluted in physiological saline and injected in a volume of 1 ml/kg.

2.5. Data analysis

Analysis of the rectal temperature and wheel running data employed analysis of variance (ANOVA) with within-subjects factors of drug treatment condition, time post-injection and wheel access as outlined in the following experiments. Post hoc analyses of significant main effects were conducted using the Fisher's LSD test including all pairwise comparisons; the criterion for significance was $p<0.05$. The maximum temperature data were analyzed by pre-planned comparison to contrast the effects of drug treatment condition within each wheel-access condition and to contrast wheel-access condition within each drug treatment condition. Analyses were conducted with GB-STATv7.0; Dynamic Microsystems, Silver Spring MD.

2.6. Experiments

2.6.1. Experiment 1

Rectal temperature was determined in rats (N = 10; ~500 g) challenged with vehicle, 5 or 10 mg/kg MDMA i.p. under conditions of access to a freely moving or locked activity wheel in a repeated measures design. Prior to initiating the dosing, animals were habituated to the rectal temperature sequence with two unchallenged sessions and two sessions preceded by vehicle injection. Thereafter the animals were challenged every two days with a fixed dose order of 10 mg/kg, vehicle, 5 mg/kg, vehicle, 5 mg/kg, vehicle, 10 mg/kg. Within these drug treatment conditions, the wheel access was randomized across the group. All studies were conducted at 22 °C (± 1) T_A and during the animal's dark cycle.

2.6.2. Experiment 2

The locomotor suppression observed after 5 mg/kg MDMA in Experiment 1 appeared discordant with previous investigations of MDMA-induced hyperlocomotion (Baumann et al., 2008; Daniela et al., 2004; Gold and Koob, 1988, 1989; Herin et al., 2005), therefore a subsequent experiment was conducted that was hypothesized to produce greater drug-induced activity. Most of the prior studies with MDMA were conducted in the light portion of the daily cycle, presumably increasing the vehicle-drug differential, so this relatively inactive period was selected. This has the additional advantage of testing during the rats' subjective nighttime/inactive phase, similar to a typical nighttime dosing for the human Ecstasy consumer. This study examined the effects of d-methamphetamine (MA), a compound frequently found in putative "Ecstasy" and expected to result in robust locomotor stimulation in rats. Experiment 2 was conducted in a group of rats (N = 8; ~562 g, 20 weeks of age at start) to determine if wheel access altered the effects of 1.0 or 5.6 mg/kg MA, s.c., on rectal temperature in a repeated measures design. For this experiment the protocol required exogenous cooling if rectal temperature exceeded 42 °C; therefore the maximum temperature observed in the two hour interval following drug administration was included as an additional outcome measure. Animals were challenged no more frequently than twice per week with a minimum interval of three days between challenges.