Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmacology 482 (2003) 339–341
www.elsevier.com/locate/ejphar

Short communication

Heat increases 3,4-methylenedioxymethamphetamine self-administration and social effects in rats

Jennifer L. Cornish, Zeeshan Shahnawaz, Murray R. Thompson, Suzanna Wong, Kirsten C. Morley, Glenn E. Hunt, Iain S. McGregor*

School of Psychology, University of Sydney, A19 NSW 2006, Australia

Received 22 September 2003; accepted 30 September 2003

Abstract

3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") is a drug frequently used under hot conditions in nightclubs. In rats tested in the social interaction paradigm, greater prosocial effects of MDMA (5.0 mg/kg) were seen at a hot temperature (30 °C) relative to normal laboratory temperature (21 °C). In the intravenous drug self-administration paradigm, hot temperature (30 °C) increased the number of MDMA infusions (0.1, 0.3 or 1.0 mg/kg/infusion) self-administered by rats. Hot temperatures thus appear to affect both the social and reinforcing effects of MDMA.
© 2003 Elsevier B.V. All rights reserved.

Keywords: MDMA (3,4-Methylenedioxymethamphetamine); Temperature; Self-administration

3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") is a popular drug that is frequently used in hot and sweaty nightclub conditions. The high ambient temperatures under which MDMA is often taken are of some concern as they may promote MDMA-induced hyperthermia and associated adverse reactions (Parrott, 2002). Moreover, taking the drug at high ambient temperatures may promote the long-term neurotoxic effects of MDMA (Malberg and Seiden, 1998). However, the influence of high temperatures on the acute social and reinforcing effects of MDMA are as yet unknown.

We previously reported that MDMA increases social interaction in pairs of rats meeting briefly for the first time (Morley and McGregor, 2000) and others have reported that MDMA is intravenously self-administered in rats (Ratzenboeck et al., 2001). Here we re-examined these phenomena at the normal temperature of our animal colony (21 ± 1 °C) and at a higher ambient temperature (30 ± 1 °C). All experiments were approved by the University of Sydney Animal Ethics Committee and adhered to both Australian and European Community guidelines for the use of experimental animals.

In the social interaction experiments, pairs of male Wistar rats were given either 5 mg/kg MDMA (IP), a dose that approximates typical human use (Boot et al., 2000), or vehicle. The rats were placed in a black Perspex box for 10 min where social interaction was assessed. MDMA caused an overall increase in social interaction, but the effect was significantly greater at 30 °C than at 21 °C (Fig. 1A). Under the same conditions, similar moderate stimulant doses of cocaine (15 mg/kg IP) and *d*-amphetamine (1 mg/kg IP) decreased social interaction (cocaine data shown in Fig. 1B) confirming the relatively unique prosocial properties of MDMA.

To examine whether intake of MDMA is also modified by ambient temperature, male Hooded Wistar rats were trained to self-administer MDMA or cocaine intravenously in daily 2-h sessions at 21 °C under a FR-1, 20-s time-out schedule in operant chambers equipped with two retractable levers (Norwood et al., 2003). Pressing one lever (the active lever) resulted in delivery of drug while pressing the other lever (the dummy lever) had no consequences.

As reported by others (Ratzenboeck et al., 2001), MDMA maintained lower rates of self-administration than cocaine (Fig. 1C, D). Once responding for a particular dose

* Corresponding author. Tel.: +61-2-9351-3571; fax: +61-2-9351-8023.
E-mail address: iain@psych.usyd.edu.au (I.S. McGregor).

0014-2999/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2003.09.060

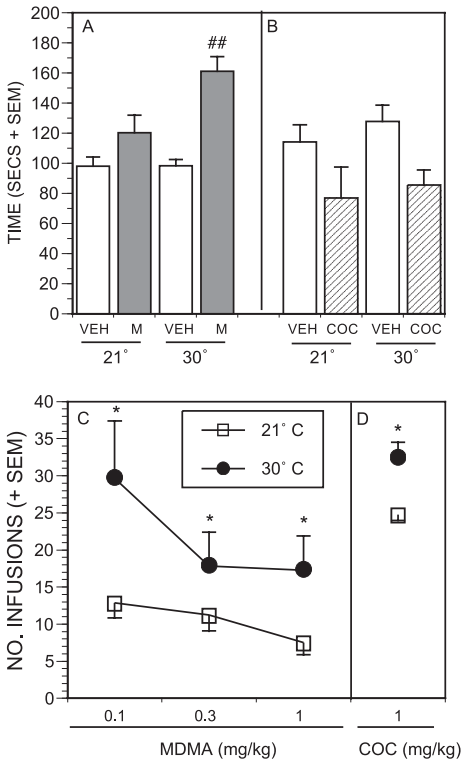

Fig. 1. (A) MDMA (5 mg/kg, $n=8$ pairs per condition) significantly increased social interaction ($P<0.001$) with a greater increase at 30 °C ($P<0.05$, $^{\#\#}$significant drug by temperature interaction, two-way ANOVA, M = MDMA, VEH = vehicle, COC = cocaine). (B) Cocaine (15 mg/kg, $n=4$ pairs per condition) significantly decreased social interaction regardless of temperature ($P<0.01$). (C) There were significantly more self-administered infusions of MDMA at 30 °C than 21 °C for the 0.1 ($n=13$), 0.3 ($n=17$) and 1 mg/kg/infusion ($n=10$) doses and (D) for the 1 mg/kg/infusion cocaine dose ($n=6$) (*$P<0.05$, for each dose tested a repeated measures ANOVA compared number of infusions on test day (30 °C) with number of infusions on the previous day (21 °C)).

had stabilised, rats were given a test session at an ambient temperature of 30 °C. Each rat was tested with at least two different doses of MDMA. Under higher ambient temperature, rats self-administered more MDMA at all doses tested (Fig. 1C). Responses on the dummy lever were not significantly affected by temperature.

Locomotor activity counts during MDMA self-administration, measured by the rat triggering passive infra-red detectors within the test chambers, declined by more than 50% at the 30 °C temperature (21 vs. 30 °C: MDMA (0.1 mg/kg/infusion) 2081 ± 175 vs. 814 ± 124 counts, $P<0.001$; MDMA (0.3 mg/kg/infusion) 2390 ± 161 vs. 817 ± 101 counts, $P<0.001$; MDMA (1 mg/kg/infusion) 1415 ± 193 vs. 610 ± 87 counts, $P<0.05$, repeated measures ANOVAs). This rules out hyperactivity as a cause of the self-administration results.

A moderate increase in cocaine self-administration (Fig. 1D) and decrease in locomotor activity (5114 ± 702 counts (21 °C) vs. 3108 ± 622 counts (30 °C), $P<0.05$) was also seen at 30 °C.

After completing testing with MDMA, a subset of rats ($n=7$) were run under extinction conditions (no infusions given) at 21 °C for 23–29 days. At the end of this extinction phase, a single extinction test at the high temperature (30 °C) failed to increase the number of "infusions" delivered (6.8 ± 1.26 at 21 °C vs. 4.00 ± 1.79 at 30 °C), but greatly decreased locomotor activity counts (1288 ± 205 at 21 °C vs. 384 ± 84 at 30 °C). This indicates that heat does not reinstate drug seeking behavior for MDMA and that heat does not increase responding when no MDMA is being delivered.

Overall, these results indicate that high ambient temperatures potentiate the prosocial effects of MDMA and encourage higher levels of MDMA self-administration in rodents. The increase in MDMA self-administration might conceivably involve temperature-induced facilitation of dopamine transporter function (Xie et al., 2000). The mechanisms underlying the modulation of social behavior are at present uncertain and are the subject of ongoing studies in our laboratory.

These results suggest that it may not be coincidental that MDMA is often used by humans under hot conditions. Hot conditions may accentuate the desirable social effects of the drug and encourage its consumption. It is therefore of concern to note that high temperatures may also exacerbate the long-term adverse effects of MDMA on brain serotonin systems (Malberg and Seiden, 1998) associated with increased anxiety and a seemingly permanent reduction in social interaction (McGregor et al., 2003).

Acknowledgements

This work was supported by a National Health and Medical Research Council grant to ISM and GEH. We are grateful to Garth Hargreaves and Julia Shrosbree for valuable discussions of MDMA-related matters.

References

Boot, B.P., McGregor, I.S., Hall, W., 2000. MDMA (Ecstasy) neurotoxicity: assessing and communicating the risks. Lancet 355, 1818–1821.

Malberg, J.E., Seiden, L.S., 1998. Small changes in ambient temperature cause large changes in 3,4-methylenedioxymethamphetamine (MDMA)-induced serotonin neurotoxicity and core body temperature in the rat. Journal of Neuroscience 18, 5086–5094.

McGregor, I.S., Clemens, K.C., Van der Plasse, G., Hunt, G.E., Chen, F., Lawrence, A.J., 2003. Increased anxiety 3 months after brief exposure to MDMA ('Ecstasy') in rats: association with altered 5-HT transporter and receptor density. Neuropsychopharmacology 28, 1472–1484.

Morley, K.C., McGregor, I.S., 2000. (±)-3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy') increases social interaction in rats. European Journal of Pharmacology 408, 41–49.

Norwood, C.S., Cornish, J.L., Mallet, P.E., McGregor, I.S., 2003. Pre-exposure to the cannabinoid receptor agonist CP 55,940 enhances morphine behavioral sensitization and alters morphine self-administration in Lewis rats. European Journal of Pharmacology 465, 105–114.

Parrott, A.C., 2002. Recreational Ecstasy/MDMA, the serotonin syndrome, and serotonergic neurotoxicity. Pharmacology, Biochemistry and Behavior 71, 837–844.

Ratzenboeck, E., Saria, A., Kriechbaum, N., Zernig, G., 2001. Reinforcing effects of MDMA ('Ecstasy') in drug-naive and cocaine-trained rats. Pharmacology 62, 138–144.

Xie, T., McCann, U.D., Kim, S., Yuan, J., Ricaurte, G.A., 2000. Effect of temperature on dopamine transporter function and intracellular accumulation of methamphetamine: implications for methamphetamine-induced dopaminergic neurotoxicity. Journal of Neuroscience 20, 7838–7845.