Attenuating Glial Activation with Minocycline Reduces the Hyperthermic Response to 3, 4-Methylenedioxymethamphetamine (MDMA) In the Rat

P. Anderson*, M.R. Hutchinson, R.J. Irvine and A. Salem

Discipline of Pharmacology, School of Medical Sciences, University of Adelaide, SA 5005, Australia

Keywords: 3,4-Methylenedioxymethamphetamine, "ecstasy", hyperthermia, microglia, minocycline.

INTRODUCTION

Hyperthermia is a key clinical outcome from recreational use of MDMA and is the leading cause of MDMA related hospital admissions as well as being linked to enhanced neurotoxicity [1, 2]. Animal models of ischemia which also display hyperthermia have shown an inflammatory process mediated by microglia and the release of the pro-inflammatory cytokine interleukin 1-β (IL-1β) play a role in hyperthermicreactions [3]. Previous studies showed that microglia is prominently activated and IL-1β levels increased following MDMA administration [4], lending support to the hypothesis microglia play a role in MDMA induced hyperthermia. Minocycline is a tetracycline antibiotic with powerful anti-inflammatory properties, thought to be a result of its ability to attenuate glial activation [5]. This study examined whether preventing microglial activation through the administration of minocycline could limit or prevent the hyperthermia induced by MDMA.

METHODS

Male Sprague-Dawley rats were treated daily with 50 mg/kg i.p. of minocycline (or vehicle control) for two or three days (Fig. **1**). 30 min following the final dose they were administered 10 mg/kg i.p. of MDMA with core body temperature and behavioral measurements taken every half hour (from 2 hr prior to 4 hr post MDMA treatment). Experiments were conducted at a normal ambient temperature of 22°C. The animals were then anaesthetised with Chloral Hydrate (400mg/kg i.p.), core blood was taken and the brain quickly removed and stored at -70°C. Blood and brain levels of MDMA and its major metabolite 3,4-methylendioxyamphetamine (MDA) were measured using HPLC-ED and levels of IL-1β in the cortex and striatum were analysed using an ELISA assay. Temperature measurements and IL-1β levels were analysed using a two-way ANOVA with Bonferroni's post-hoc test. Plasma and brain levels of MDMA and MDA were analysed using one-way ANOVA with Tuckey's post-test. Behavioural data was compared using the Kruskal-Wallis test. $P < 0.05$ was taken as significant for all analyses.

*Address correspondence to this author at the Discipline of Pharmacology, School of Medical Sciences, University of Adelaide, SA 5005, Australia; Tel: +61 3 8344 0531; Fax: + 61 3 9347 1863;
E-mail: p.anderson2@pgrad.unimelb.edu.au

RESULTS

MDMA treated animals showed significant increases in core temperature compared with rats treated with saline ($p = 0.0001$, n=6). Minocycline alone had no significant effect on core temperature. Animals administered MDMA and minocycline had a significantly reduced rise in temperature compared to MDMA treated animals ($p<0.01$, n=6). Behavioural measures showed no significant differences between animals receiving minocycline and those not, but did between MDMA and saline treated animals (n=6, $P<0.0001$). Minocycline had no significant effect on either blood ($p =0.940$, n=8) or brain ($p =0.9296$, n=8) concentrationsof MDMA and MDA. An interleukin 1-beta assay was performed on cortex, this showed no significant differences between any of the treatment groups, ($p = 0.5235$, n=4).

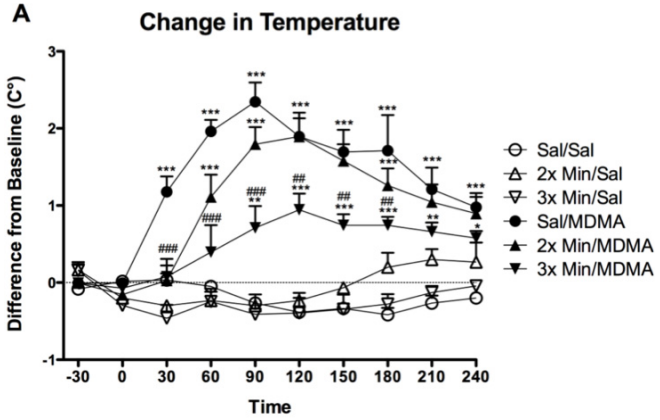

Fig. (1). Effect of MDMA co-administered with minocycline (2 day treatment [2x Min] or 3 day treatment [3x Min]) on core body temperature, represented as the change from baseline temperature (mean of temperature recorded at -60, -30 and 0 mins). Saline (Sal) or Min was administered at –30 min; Sal or MDMA (10 mg/kg, i.p.) was administered at 0 min. Data are given as mean + SEM (n = 6).

DISCUSSION

The major findings of this study are that the pre-treatment administration of minocycline significantly attenuates the hyperthermia induced by MDMA administration in rats. Minocycline also had no significant impact on MDMA-induced behavioural stimulation, supporting the hypothesis that an inflammatory response

1874-9410/11

plays a role in MDMA induced hyperthermia; independent of serotonin and dopamine mediated behavioural stimulation. Further evidence in support of this hypothesis is the finding of similar brain and plasma concentrations of MDMA and MDA with and without the co-administration of minocycline. Both compounds were detected at similar levels regardless of minocycline treatment indicating that minocycline's action is not due to changes in MDMA pharmacokinetics.

CONCLUSION

The results of this study indicate that the mechanisms underlying MDMA induced hyperthermia may include an inflammatory response mediated by microglia. These results also indicate that immune status may be a factor in the apparently idiosyncratic effects of MDMA on hyperthermia in some individuals and as such preventing or inhibiting glial activation may be a clinically relevant method of treating MDMA toxicity.

REFERENCES

[1] Malberg JE, Seiden LS. Small changes in ambient temperature cause large changes in 3,4- methylenedioxymethamphetamine (MDMA)-induced serotonin neurotoxicity and core body temperature in the rat. J Neurosci 1998; 18(13): 5086-94.

[2] Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI. The pharmacology and clinical pharmacology of 3, 4-methylenedioxymethamphetamine (MDMA, "ecstasy"). Pharmacol Rev 2003; 55(3): 463-508.

[3] Abraham H, Somogyvari-Vigh A, Maderdrut JL, Vigh S, Arimura A. Rapidly activated microglial cells in the preoptic area may play a role in the generation of hyperthermia following occlusion of the middle cerebral artery in the rat. Exp Brain Res 2003; 153(1): 84-91.

[4] Orio L, O'Shea E, Sanchez V, *et al*. 3, 4-Methylenedioxy-methamphetamine increases interleukin-1Œ≤ levels and activates microglia in rat brain: studies on the relationship with acute hyperthermia and 5-HT depletion. J Neurochem 2004; 89(6): 1445-53.

[5] Stirling DP, Koochesfahani KM, Steeves JD, Tetzlaff W. Minocycline as a neuroprotective agent. Neuroscientist 2005; 11(4): 308-22.

Received: November 4, 2010 Revised: November 13, 2010 Accepted: November 13, 2010