3,4-Methylenedioxymethamphetamine (MDMA) Induced Hyperthermia-The Role of Pro-Inflammatory Cytokines

A. Salem*, J. Gordon, M.R. Hutchinson and R.J. Irvine

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

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INTRODUCTION

The main 3, 4-methylenedioxymethamphetamine (MDMA)-induced adverse effect is disruption of normal thermoregulation leading to life threatening hyperthermia which is exacerbated by high ambient temperature and linked to chronic neurotoxicity [1-3]. Although the focus of the majority of research on MDMA-induced loss of thermoregulation has been on brain serotonergic and dopaminergic systems, results obtained from recent studies suggest that microglial activation and the subsequent release of the pyrogen interleukin-1β could also contribute to these effects [4, 5]. The aim of this study is to extend our understanding of the underlying mechanisms in the brain leading to the disruption of normal thermoregulation. We have examined the effect of interleukin 1 receptor antagonist **(**IL-1RA) on MDMA-induced hyperthermia and behavioural effects.

METHODS

Male Sprague Dawley rats maintained at normal ambient temperature (22 ± 1°C) were administered 10 mg/kg (i.p.) of MDMA and core body temperature and behavioural measurements were taken every 30 min for 4 hours. The interleukin 1 receptor antagonist (IL-1RA, 40 mg/kg i.p.) was administered 30 min prior to MDMA administration. Core body temperature measurements were analysed using a two-way ANOVA with Bonferroni's post-hoc test. Behavioural data were compared using the Kruskal-Wallis test. $P < 0.05$ was taken as significant for all analyses.

RESULTS

Fig. (**1**) illustrates the core body temperature response for each treatment group. No significant changes in core body temperature were recorded for Saline+Saline or IL-1RA+Saline treated rats ($P > 0.05$, n=5-9). After Saline+MDMA treatment, core body temperature increased by 2.4 °C and significant hyperthermic response was maintained from 30 min up to 240 min post MDMA compared to control group ($P < 0.05$, n=11). Although IL-1RA+MDMA treated animals showed similar hyperthermic response as MDMA+Saline group up to 120 min, all animals pre-treated with IL-1RA showed a significant decrease in body temperature at 180, 210 and 240 min. MDMA-treated animals had significantly increased behaviour scores over saline-only treated controls ($P < 0.05$, n=12). IL-1RA pre-treatment did not produce any significant effect on MDMA-induced behavioural effect.

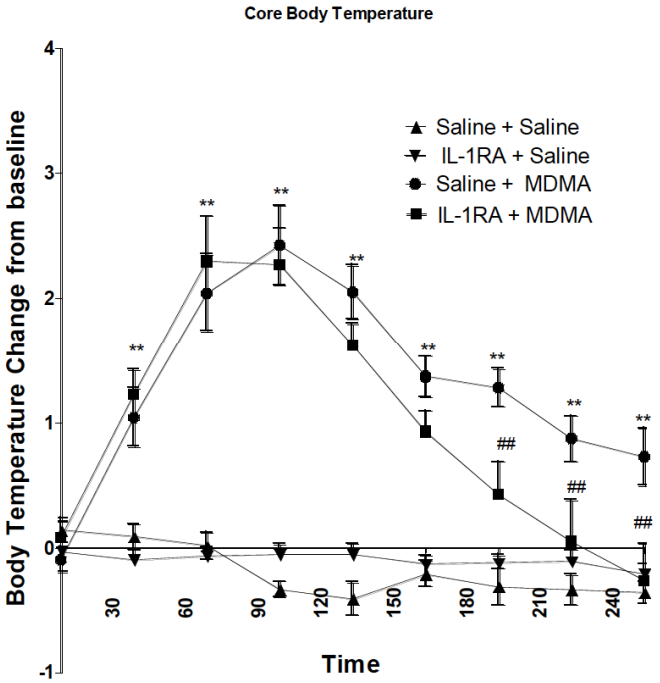

Fig. (1). Effect of MDMA on core body temperature, represented as the change from baseline temperature (mean of temperature recorded at -60 and -30 mins). Saline or IL-1RA was administered at –30 min; Saline or MDMA (10 mg/kg, i.p.) was administered at 0 min. Data are given as mean ± SEM (n = 4-12).

DISCUSSION

IL-1RA pre-treatment significantly attenuated the magnitude and duration of hyperthermia induced by MDMA administration. IL-1RA pre-treatment had no significant impact on MDMA-induced behavioural stimulation. The results of this study indicate that the mechanisms underlying MDMA induced hyperthermia may include the release of the endogenous pyrogen interleukin-1β in addition to serotonin

*Address correspondence to this author at the Discipline of Pharmacology, School of Medical Sciences, Univ of Adelaide, SA 5005, Australia;
Tel: 61 8 8303 4327; Fax: 61 8 8224 0685;
E-mail: abdallah.salem@adelaide.edu.au

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and dopamine mediated hyperthermic response and behavioural stimulation.

CONCLUSION

The present findings are consistent with the hypothesis that inflammatory processes play a role in MDMA induced adverse effects [3,5] and increase in expression of pro-inflammatory cytokines further exacerbate and sustain the hyperthermia caused by MDMA.

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: 5086-94.

[2] Green AR, O'Shea E, Colado MI. A review of the mechanisms involved in the acute MDMA (ecstasy)-induced hyperthermic response. Eur J Pharmacol 2004; 500: 3-13.

[3] Zhang L, Shirayama Y, Shimizu E, Iyo M, Hashimoto K. Protective effects of minocycline on 3, 4-methylenedioxy-methamphetamine-induced neurotoxicity in serotonergic and dopaminergic neurons of mouse brain. Eur J Pharmacol 2006; 544: 1-9.

[4] 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: 84-91.

[5] Orio L, Llopis N, Torres E, Izco M, O'Shea E, Colado MI. A study on the mechanisms by which minocycline protects against MDMA ('Ecstasy')-induced neurotoxicity of 5-HT cortical neurons. Neurotoxicity Research 2009: pp. 1-13.

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